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Predictors and Consequences of Severe Hypoglycemia in Adults with Diabetes – A Systematic Review of the Evidence

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PREFACE

Quality Enhancement Research Initiative's (QUERI) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) managers and policymakers, as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout VA.

QUERI provides funding for four ESP Centers and each Center has an active VA affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence,
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of QUERI Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at nicole.floyd@va.gov.

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INTRODUCTION

Prevalence of type 2 diabetes is increasing at an alarming pace, fueled by the rising rates of overweight and obesity in many populations. A recent study estimated that the number of people with diabetes increased worldwide from 153 million in 1980 to 347 million in 2008.[1] This study estimated that from 1980 to 2008, the age standardized prevalence of diabetes in the United States increased from 6% to 12% in men and from 5% to 9% in women. In the VA, prevalence of diabetes is higher than in the general population and increasing over time. Miller et al. reported estimated rates of diabetes in VA of 17% in fiscal year (FY) 1998, 19% in FY99 and 20% in FY00.[2] More recently, it was estimated that nearly 25% of veterans receiving care in the VA have diabetes (http://www.va.gov/health/NewsFeatures/20110321a.asp, accessed April 3, 2012).

Although people with diabetes have a substantially increased risk of cardiovascular disease (CVD), three large well designed recent clinical trials testing intensive versus conventional glucose control strategies (ACCORD[3], ADVANCE[4] and VA-DT[5]), have found that intensive glucose control does not reduce the risk of CVD death or all-cause mortality although it reduces the risk of microvascular complications (nephropathy, retinopathy and neuropathy)[6] and possibly non-fatal myocardial infarction.[7] Intensive glucose control also increases the risk of hypoglycemic episodes. Several recent meta-analyses that included these large "intensive versus conventional control" trials have concluded that intensive control is associated with a 2-2.5 fold increased risk of severe hypoglycemia.[8-11] However, these reviews included only randomized controlled trials; we are unaware of a comprehensive systematic review examining incidence of and risk factors for severe hypoglycemia in adults with type 2 diabetes in both real-world and clinical trial settings.

Despite the increased risk of hypoglycemia with intensive glycemic control, influential national guidelines support an aggressive approach for patients with type 2 diabetes, recommending a target hemoglobin A1c level (HbA1c) of less than 7.[12] This recommendation implies that the benefits of tight control outweigh the risks even though the balance between these benefits and harms is not actually known. In particular, the effects of hypoglycemia on outcomes besides CVD events and all-cause mortality have not, to our knowledge, been rigorously evaluated. The VA/DoD guidelines recommend a more nuanced approach: target HbA1c levels are based on life expectancy and severity of microvascular complications. A level of < 7% is recommended only for those with no microvascular complications and a life expectancy of >10 years (http://www.healthquality.va.gov/diabetes_mellitus.asp, accessed January 27, 2012).

We conducted the current review to provide broader insight into the incidence of, the risk factors for, and the clinical impact of severe hypoglycemia in adults with type 2 diabetes treated with glucose lowering medications.

METHODS

TOPIC DEVELOPMENT

This project was nominated by Leonard Pogach, MD, National Program Director for Diabetes. The scope of the report and key questions were refined with input from a technical expert panel.

The key questions, as shown in the analytic framework in Figure 1, were as follows:

Key Question #1: What is the **incidence** of severe hypoglycemia in adults with type 2 diabetes on one or more hypoglycemic agents?

Key Question #2: What are the **risk factors** for severe hypoglycemia in adults with type 2 diabetes on one or more hypoglycemic agents (e.g., demographics, co-morbidities, diabetes treatment regimen, other medication use, goal and achieved HbA1c)?

Key Question #3: What is the effect of severe hypoglycemia on other **outcomes** in adults with type 2 diabetes on one or more hypoglycemic agents (e.g., quality of life, mortality, morbidity, utilization)?

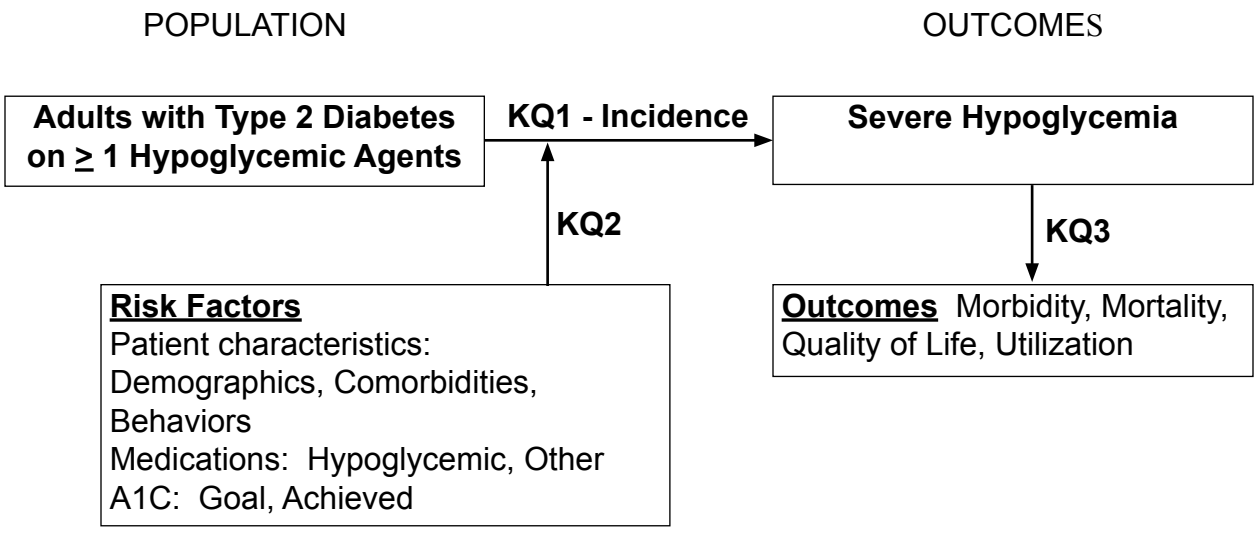
Extension of Key Question #1: In order to gain a more population-based perspective on hypoglycemia incidence (as recommended by our technical expert panel November 1, 2011) we re-reviewed all the abstracts identified through the initial search strategy (through November, 2011) to find articles that might contain data from more representative groups that had not met the initial inclusion criteria.

SEARCH STRATEGY

We searched MEDLINE (OVID) for clinical trials and systematic reviews from 1950 to December 2010 using standard search terms. The search was updated in November 2011. We limited the search to articles involving adult, human subjects and published in the English language. Search terms included: hypoglycemia, hypoglycaemia, and diabetes mellitus, type 2. The full MEDLINE search strategy is presented in Appendix A.

We obtained additional articles from a search of the Cochrane Library, other systematic reviews, reference lists of pertinent studies, reviews, editorials, and by consulting experts. We also searched the following Web sites: Centers for Disease Control, ClinicalTrials.gov, Department of Transportation, Framingham Heart Study, National Health and Nutrition Examination Survey, National Institute of Diabetes and Digestive and Kidney Diseases, and Occupational Safety and Health Administration.

Figure 1. Analytic Framework



STUDY SELECTION

Investigators and research assistants trained in the critical analysis of literature assessed for relevance the abstracts of citations identified from literature searches. Full-text articles of potentially relevant abstracts were retrieved for further review.

Specific exclusion criteria for Key Questions #1 and #2 were as follows:

1. Population: exclude if animal study, age less than 18 years, inpatients, type 1 diabetes, patient on dialysis, gestational diabetes, or fasting populations.
2. Publication type: exclude case reports, narrative reviews, case series, letters, editorials, commentaries, book chapters, dissertations, other summaries, duplicate publications.
3. Outcomes: exclude if no outcomes of interest. Outcomes of interest are incidence of severe hypoglycemia and risk factors for severe hypoglycemia. Exclude if severe hypoglycemia not reported or defined.
4. Study duration: exclude if study is less than 6 months in duration.
5. Sample size: exclude if study enrolled fewer than 500 patients.
6. Intervention: exclude if study only includes patients on one or more non-FDA approved hypoglycemic agent (vildagliptin, algogliptin, taspoglutide, giclazide, troglitazone, exubera, any inhaled insulin) or on continuous insulin infusion.

For Key Question #1 – Extension, we employed the same exclusion criteria with the following modifications: we included population or clinic-based studies that may have enrolled fewer than 500 patients or had fewer than 6 months of follow-up; in which the definition of severe hypoglycemia may not have been rigorously defined but included some definition of symptomatic hypoglycemia; and in which there may not have been true incidence data (e.g.,

cross-sectional patient surveys). From this search we identified 16 articles (see Figure 2, shaded boxes).

For Key Question #3, we placed no restriction on sample size or study duration. The study had to report an association between severe hypoglycemia and outcomes of interest. Outcomes of interest included all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, neurological events (other than stroke), hospitalizations, emergency department visits, accidents/trauma, quality of life, cognitive function, productivity, and other health resource utilization.

DATA ABSTRACTION

We abstracted the following data for each included study (as appropriate based on study design): study design, definition of severe hypoglycemia, length of follow-up, population characteristics, subject inclusion and exclusion criteria, intervention(s), comparison(s), length of follow-up, and outcome(s).

QUALITY ASSESSMENT

We assessed study quality for randomized controlled trials using the criteria recommended by the Cochrane Collaboration to assess the risk of bias of studies included in a systematic review:[13] 1) adequate allocation concealment, based on the approach by Schulz and Grimes;[14] 2) blinding methods (participant, investigator, or outcome assessor); 3) how incomplete data were addressed (did the study analyze the data based on the intention-to-treat principle, i.e., were all subjects who were randomized included in the outcomes analyses), 4) reasons for dropouts/attrition reported. Studies were rated good, fair or of poor quality. A rating of good generally indicated that the trial reported adequate allocation concealment, blinding, analysis by intent-to-treat, and reasons for dropouts/attrition were reported. Studies were generally rated poor if the method of allocation concealment was inadequate, blinding was not defined, analysis by intent-to-treat was not utilized and reasons for dropouts/attrition were not reported and/or there was a high rate of attrition.

Quality assessment for non-randomized studies was based on: 1) population, 2) outcomes, 3) measurement, 4) confounding, and 5) intervention (if applicable). We assessed whether the study fulfilled the descriptive characteristics for each element (see Appendix B). Studies were considered to be of higher quality and more applicable if they were prospective, explicitly defined severe hypoglycemia, used multivariate analysis and included patients representative of typical patients with type 2 diabetes.

DATA SYNTHESIS

We constructed evidence tables showing the study characteristics for all included studies. Outcomes tables were organized by key question. We critically analyzed studies to compare their characteristics, methods, and findings. We compiled a summary of findings for each key question and drew conclusions based on qualitative synthesis of the findings or pooled results, where appropriate.

For Key Question #1, data were pooled and analyzed in Comprehensive Meta-Analysis software© (Biostat, Inc., Englewood, NJ). Risk ratios (RR) were calculated using a random-effects model if substantial heterogeneity was present. Statistical heterogeneity between trials was assessed using the I^2 test with a score of 50% or greater suggesting moderate to substantial heterogeneity among studies.

PEER REVIEW

A draft version of this report was reviewed by technical experts as well as clinical leadership. Their comments and our responses are shown in Appendix C.

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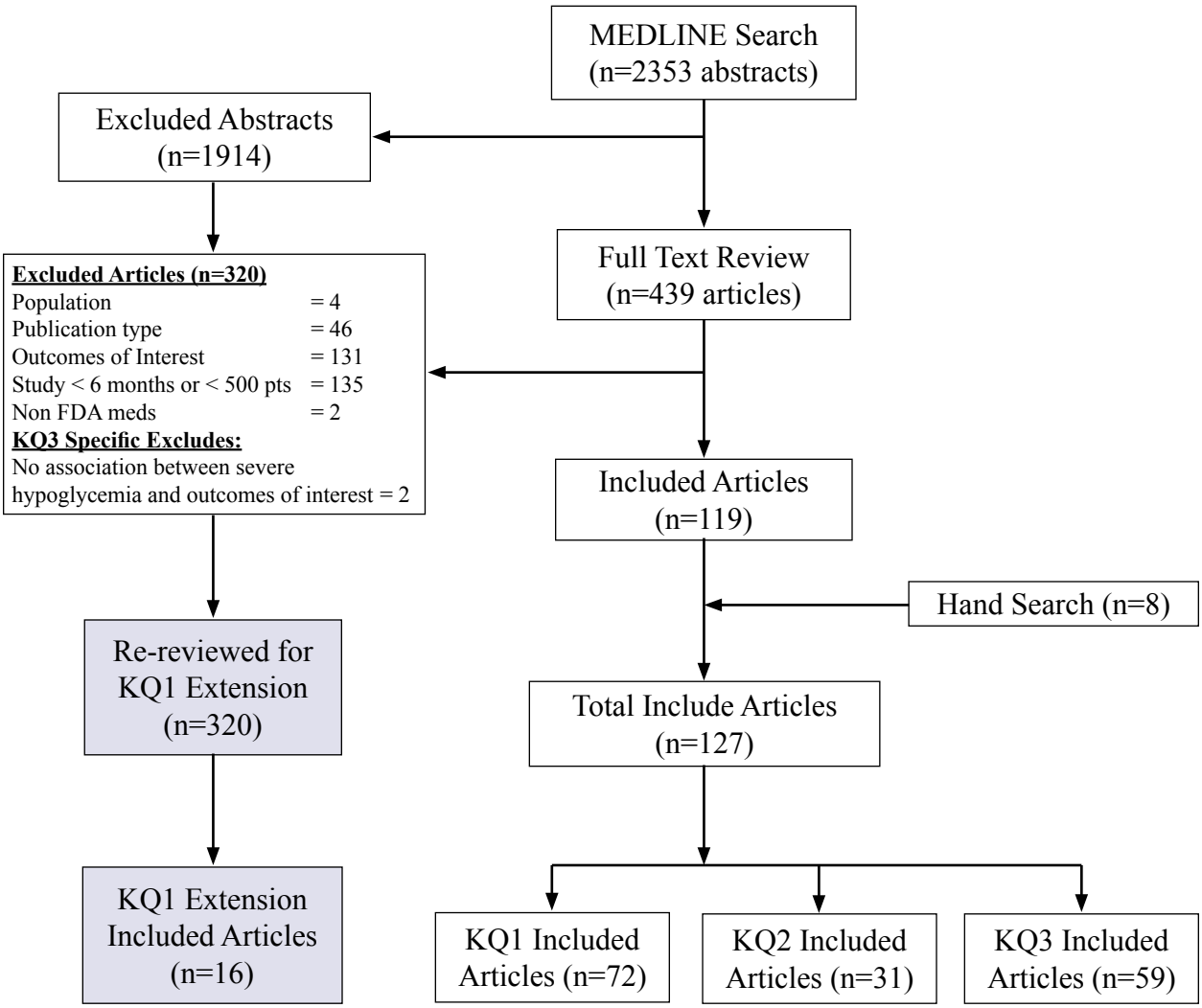
RESULTS

LITERATURE FLOW

We reviewed 2353 titles and abstracts from the electronic search. After applying inclusion/exclusion criteria at the abstract level, 1914 references were excluded. We retrieved 439 full-text articles for further review and another 320 references were excluded. We identified 8 references by hand searching reference lists of relevant publications resulting in a total of 127 references for inclusion in the current review. We grouped the studies by key question. We re-reviewed excluded studies to identify studies that might address a more population-based perspective on hypoglycemia incidence (Key Question #1-Extension). Sixteen articles were included in this extended view of incidence. Figure 1 details the exclusion criteria and the number of references related to each of the key questions.

Figure 2. Literature Flow Diagram



*A number of articles provided data for more than one KQ. Therefore, the total number of included articles does not equal the sum of the articles for each key question.

KEY QUESTION #1. What is the incidence of severe hypoglycemia in adults with type 2 diabetes on one or more hypoglycemic agents?

We identified 72 articles on 60 studies that provided data to address Key Question #1. We also identified 21 systematic reviews that were not funded by industry and provided severe hypoglycemia data. Four of the reviews included only the "intensive versus conventional" studies while 17 reviewed specific drugs or drug combinations.

Overview of Included Studies (Appendix E, Table 1)

The 60 studies included 46 RCTs (N>75,000), eight prospective observational studies,[15-22] and six retrospective studies.[23-28] Five of the RCTs randomized participants to an intensive versus a conventional treatment strategy, and not to specific drug regimens.[3-5, 21, 29, 30] Thirty were multinational, eighteen were conducted in the US and/or Canada, six in the United Kingdom, five elsewhere, and in one it was unclear.[31] Forty-seven were funded exclusively by pharmaceutical companies, ten by government research institutes with or without supplementary pharmaceutical support, and funding for three studies was not reported.[28, 32, 33] All studies enrolled both men and women except one VA study which enrolled only men.[30] Among the RCTs, most enrolled a broad age range of patients from age 18 to no upper age limit; only three had a lower age limit of 40.[3, 5, 30] As shown in Appendix E, Table 1 there was a wide spectrum of hypoglycemic treatment regimens and of other inclusion criteria.

Definition of Severe Hypoglycemia

All 60 studies met our pre-specified minimal definition of severe hypoglycemia: an episode with typical symptoms (e.g., sweating, dizziness, tremor, visual disturbance) that resolves after treatment (oral carbohydrate, intramuscular glucagon, or intravenous glucose) administered by another person. Adopting the language used in ACCORD,[3] we refer to this type of episode as **HA—Hypoglycemia** needing any **A**ssistance. Thirty-seven studies used this definition exclusively. Six studies required that the episode be treated by medical personnel to qualify as "severe"—referred to as **HMA** (**H**ypoglycemia requiring **M**edical **A**ssistance); ten studies used other definitions (see Appendix E, Table 1); and seven studies categorized events by more than one definition.

Study Quality

As shown in Appendix D, Table 1, only 26% (n=12) of the 46 unique randomized studies were rated as a good quality study or having a low risk of bias based on adequate allocation concealment, blinding, analysis by intent-to-treat, and adequate study withdrawal reporting. The remaining studies were assessed as fair quality with an unclear risk of bias. Adequate methods used to conceal allocation was reported in 41% (n=19) of the studies, and any blinding (participants, personnel, and/or outcome assessors) was reported in 63% (n=29) of studies. Most studies analyzed data based on randomized subjects who had taken at least one dose of study medication (modified intent-to-treat). Reasons for dropouts/attrition were generally reported. Nearly all studies reported funding from pharmaceutical industries.

Among the 14 unique non-randomized studies for Key Question #1, eight were prospective cohort studies, five were retrospective cohort studies and one was a case series (Appendix D, Table 2). Although our intent was to exclude case series, this study was originally misclassified

and was retained in our analysis. Most studies used a study sample that pertained to the population of interest, included inclusion/ exclusion criteria, and used appropriate sampling methods. Outcomes reporting and measurement assessment were considered appropriate in nearly all studies. Methods for minimizing confounding were reported in seven of the studies.

Results

We tabulated frequency of severe hypoglycemia by treatment regimen (Appendix E, Table 3). Overall incidence of severe hypoglycemia was low in most studies, particularly studies of metformin monotherapy(<1%), GLP-1 analogs (< 1%), DPP-4 inhibitors (<1%), glinides (0%), detemir (<1%) and TZDs (<1%). In the single study evaluating pramlintide, the incidence of severe hypoglycemia was less than 2%, the same as the placebo incidence.[34] We pooled incidence data for specific treatment regimens as detailed below.

Long-acting Insulins

There were eight studies of insulin glargine,[35-42] three long term (pooled incidence 4.1%, 95% CI 1.9 to 8.4%, N=1223) and five short-term (pooled incidence 1.6%, 95% CI 0.8 to 3.2%, N=13,088) (Appendix F, Figure 1). There were three insulin detemir studies[18, 40, 43] (Appendix F, Figure 2), two long-term (incidence 1.4%, 95% CI 0.7 to 2.9%, N=525) and one moderate term (incidence 0.4%, 95% CI 0.1 to 0.9%, N=1129). NPH insulin monotherapy was studied in two trials[35, 39] (Appendix F, Figure 3), with a pooled incidence of 9.3% (95% CI 7.3 to 11.8%, N=763) over a weighted average follow-up time of 3.5 years. Six studies with eight treatment arms evaluated NPH insulin in combination with other glucose lowering medications[35, 39, 41, 44-46] (Appendix F, Figure 4). Five of the six studies were short-term and one was long-term. Pooled incidence was 5.0% (95% CI 4.1 to 6.1%, N=3150) over a weighted average follow-up time of 1.2 years. We also pooled relative risks for NPH versus glargine (Appendix F, Figure 5). For this comparison there were three trials,[35, 39, 41] one long term and two short-term. There was no difference in risk over a weighted average follow-up time of 2.5 years, (RR 1.37, 95% CI 0.66 to 2.81, N=2291)

Fast-acting Insulin Analogues

In the two lispro studies,[36, 47] the pooled incidence of severe hypoglycemia was 3.6% (95% CI 2.3 to 5.4%, N=1198, Appendix F, Figure 6) over a weighted average follow-up time of 1.3 years. In the four studies of aspart,[15, 22, 43, 48] the pooled incidence of severe hypoglycemia was 0.2% (95% CI 0.2% to 0.2%, N=54,225, Appendix F, Figure 7) over a weighted average follow-up time of 0.5 years. In the 2 studies of glulisine (combined with NPH insulin),[45, 46] the incidence of severe hypoglycemia was 1.0% (95% CI 0.5 % to 2.1%, N=883, Appendix F, Figure 8) over a weighted average follow-up time of 0.5 years.

In the 13 sulfonylurea studies (Appendix F, Figure 9), the pooled incidence of severe hypoglycemia was 1.2% (95% CI 0.9 to 1.5%, N=9081) over a weighted average follow-up time of 2.3 years.[17, 18, 21, 32, 49-57]

Insulin Provision versus Insulin Sensitization

One multinational factorial trial enrolled 2307 patients with type 2 diabetes and coronary heart disease and randomized them to either a percutaneous or surgical revascularization procedure and to either

an insulin sensitization (metformin and TZDs most commonly used) or an insulin provision strategy (insulin and sulfonylureas most commonly used). The target HbA1c in both groups was less than 7%. The average length of follow-up was 5.3 years. The incidence of severe hypoglycemia was 5.9% in the insulin sensitization group and 9.2% in the insulin provision group[58] (Appendix F, Figure 10).

Placebo

Two short-term (24 weeks) studies had a placebo only arm[59, 60] and one long-term (10 years) study had a diet-only arm[21, 29] with a total of 1312 subjects followed for a weighted average time of 7 years. The incidence of severe hypoglycemia was 0.6% (95% CI 0.3 to 1.2%). The two studies with placebo arms had rates of 0%.

Trials of Intensive versus Conventional Glycemic Control

Five trials randomized participants to intensive glycemic control versus conventional control[3-5, 21, 29, 30] (Table 1, below). Length of follow-up ranged from 2.3 to 10 years, with a weighted average follow-up time of 5.2 years. The pooled incidence of severe hypoglycemia in these 5 trials was 7.6% in the intensive group and 3.1% in the conventional group (RR 2.4, 95% CI 1.8 to 3.1, N= 27,644, Appendix F, Figure 11).

The largest of these trials was ACCORD[3] which enrolled over 10,000 patients in the US and Canada and randomized them to receive intensive (target HbA1c <6%) or conventional (target HbA1c 7-7.9%) treatment. This trial was stopped early due to an increase in all-cause mortality in the intensively treated group. Although this group had a higher incidence of serious hypoglycemia requiring medical assistance (which might have explained the increased mortality), subsequent analyses did not confirm an association between hypoglycemia and increased mortality.[61] The other four trials did not find increased all-cause mortality in the intensively treated arms. This discrepancy may be explained by the fact that ACCORD[3] was the largest of these trials and enrolled a higher risk population. For example, in ADVANCE,[4] the next largest trial, fewer than 2% of subjects were on insulin at baseline compared to 35% of subjects in ACCORD. Similarly, average duration of diabetes and baseline level of HbA1c were higher in ACCORD than ADVANCE.

Table 1. Incidence of Severe Hypoglycemia – Trials of Intensive vs. Conventional Glycemic Control

Study	Standard	Intensive	Average Follow-up (Years)	Definition	Glycemic Targets (conventional /intense)
ACCORD[3]	261/5123 (5.1%)	830/5128 (16.2%)	3.5	HA	HbA1c 7.0 – 7.9/ HbA1c < 6.0
ADVANCE[4]	81/5569 (1.5%)	150/5571 (2.7%)	5.0	HA	Local standards/HbA1c ≤ 6.5
VA-DT[5]	28/899 (3.1%)	76/892 (8.5%)	5.6	**	HbA1c < 9/HbA1c < 6
VA-CSDM[30]	2/78 (2.6%)	5/75 (6.6%)	2.3	HA	HbA1c < 13/HbA1c 4.0 – 6.1
UKPDS#[21, 29]	8/1138 (0.7%)	33/3071 (1.1%)	10.0	HA	FPG 6.1 – 15.0 mmol/l/ FPG < 6.0 mmol/l

*** life threatening or resulted in death, hospitalization, disability or incapacity*
 # data for the 2 UKPDS studies are combined as per Hemmingsen 2011[9]
HA—episode of hypoglycemia requiring assistance of another person

Other Meta-Analyses

We identified four high quality meta-analyses comparing intensive versus conventional control strategies.[8-11] These reviews reported a 2- to 2.5- fold increased risk of severe hypoglycemia in intensively treated patients, with 5 year incidence rates of 2-3% with conventional control and 5-7% with intensive control. In addition, several high quality reviews have pooled data on specific diabetes treatments including exenatide,[62, 63] sitagliptin,[64] long-acting insulin analogs,[65, 66] fast acting insulin analogs,[67, 68] liragultide,[63] insulin with or without oral hypoglycemic agents (OHAs),[69] insulin with pioglitzone[70] and glinides.[71] As shown in Table 2, the frequency of severe hypoglycemia was less than1% in all these reviews.

Table 2. Frequency of Severe Hypoglycemia in Prior Reviews

Treatment	Reference	# of Studies*	Frequency of Severe Hypoglycemia
Exenatide	Waugh[62]	7	Rare episodes, mostly when combined with sulfonylureas
	Shyangdan[63]	3	1 episode
Sitagliptin	Richter[64]	11	0 episodes
Glargine, Detemir (long acting insulin analogs)	Swinnen[65]	4	No difference between determir and glargine
	Horvath[66]	4	No difference between analogs and NPH
Lispro, Glulisine, Aspart (fast acting insulin analogs)	Siebenhofer[67]	14	Incidence ranged from 0 to 30.3 (median 0.3) episodes per 100 pt-yrs compared to 0-50.4 (median 1.4) per 100 pt-yrs for people on regular insulin
	Tran[68]	2	No difference between Lispro 2/811 (0.1%) and Human Insulin 5/811 (0.6%)
Liragultide	Shyangdan[63]	3 (1.2 mg) 4 (1.8 mg)	1.2 mg dose: 0 episodes; 1.8 mg dose: 6 episodes
Insulin with or without OHA	Goudsward[69]	14	1 episode
Insulin with Pioglitazone	Clar[70]	6	"severe hypoglycemia rarely seen"
Glinides	Black[71]	5	4 studies had 0 episodes; 1 study (repaglinide) had 3 episodes (1%)

** reporting severe hypoglycemia*

Extension of Key Question #1

In order to gain a more population-based perspective on hypoglycemia incidence, we re-reviewed all the abstracts identified through the initial search strategy (through November 2011) to find articles that might contain data from more representative groups that had not met the initial inclusion criteria (see Methods). From this search we identified 16 additional studies.

Overview of Included Studies

The 16 studies included 13 cross-sectional patient surveys, retrospective analyses of administrative data, and 1 prospective cohort study.[72] Six of the studies were from the US, nine from Europe, and one from Asia.[73] Ten were funded in whole or in part by industry, two by the VA,[74, 75] three by foundations or other government agencies,[76-78] and funding was not reported for one study.[79] For more details on these studies see Appendix E, Table 2.

Patient Surveys (n=13)

Six reported events from the previous 6 months,[73, 74, 78, 80-83] five from the previous year,[76-79, 84] one from the previous 5 years[85] and one from the previous 2 weeks.[86] Seven studies included patients on any OHA, three on insulin only, two on a SU with or without metformin, and one on any combination of medications.[79] Eleven studies categorized hypoglycemic events as requiring assistance from another person (six further categorized events as requiring medical (HMA) or non-medical assistance (HA)) and two had other definitions.[80, 86] Sample sizes ranged from 215 to 5965.

All the survey studies which had 6 months of follow-up and reported severe hypoglycemia included patients on OHA only.[73, 74, 82, 83, 87] In these five studies rates of HA were 1%, 2%, 4%, 9%, and 13% and of HMA were 2%,[83] 1%,[82] 4%,[87] and 3%.[73] In the three of the four studies with 1 year of follow-up,[76, 77, 84] all of which included patients on insulin only, rates of HA were 12, 15 and 17 % and of HMA 2% (Honkasalo et al.[77] only study to report). The four remaining survey studies included one in which 14% of 2074 patients on OHA only reported one or more symptomatic episodes (not necessarily severe) in past 2 weeks;[86] one in which 27% of 1709 patients on OHA reported HA and 5% reported HMA over past 5 years;[85] one in which symptomatic hypoglycemia (not necessarily severe) occurred in the previous 6 months in 20% of 203 patients;[80] and one in which 27% of 635 people on insulin and 6% of 2689 people on OHA only reported HA in one year.[79]

Results from Other Studies (n=3)

- In a community based study in Scotland, a random sample of 173 adults with type 2 diabetes prospectively recorded hypoglycemic episodes over 1 month. Five (3%) experienced one or more severe episodes (required the assistance of another person).[72]
- In a US study using claims data from a privately insured population of adults age less than 65 with type 2 diabetes on either glargine (N=400) or NPH (N=400), 0.75% in each group had one or more hypoglycemia related outpatient claims during 1 year.[88]
- In a retrospective cohort analysis of 243,222 VA patients, diabetic patients with chronic kidney disease (CKD) had an average of 2.99 hypoglycemic events (glucose < 50) per 100 patient-months compared to 1.45 events in those without chronic kidney disease.[75]

Summary of Key Question #1

Overall incidence of severe hypoglycemia was less than 1% in the majority of the 60 reviewed studies, particularly those of metformin monotherapy (<1%), GLP-1 analogs (<1%), DPP-4 inhibitors (<1%), insulin detemir (<1%), insulin aspart (<1%), glinides (0%) and TZDs (<1%). The data suggest annual rates of severe hypoglycemia greater than 1% for NPH, glargine, lispro, glulisine and sulfonylureas. Some of the highest rates of severe hypoglycemia were observed in the intensive control arms of large trials comparing this treatment to conventional control (e.g., ACCORD).

Of the additional 16 studies reviewed to gain a broader population-based perspective on incidence of symptomatic hypoglycemia, 13 were survey studies reporting patient-recalled rates. Eleven of these 13 asked patients to report on events in the past 6 months (N=6) to one year (N=5). In these 11 studies patient reported incidences of hypoglycemia varied widely from 1% to 17%.

KEY QUESTION #2. What are the risk factors for severe hypoglycemia in adults with type 2 diabetes on one or more hypoglycemic agents (e.g., demographics, co-morbidities, diabetes treatment regimen, other medication use, goal and achieved HbA1c)?

We identified 31 articles on 28 studies that provided information about risk factors for severe hypoglycemia.

Overview of Included Studies (Appendix E, Table 1)

An overview of the 31 included articles is shown in Appendix E, Table 1. These 31 articles represent 28 unique studies, including four randomized controlled trials,[43, 89-91] three prospective cohort studies (in five articles),[16, 17, 92-94] five retrospective cohort studies, [25, 95-98] seven cross sectional studies,[76, 78, 84, 85, 99-101]seven case control studies,[24, 27, 102-106] and three case series,[107, 108] one of which was related to a prospective cohort study.[17] Although we excluded case series, two studies were originally misclassified and retained in our analyses. Four studies were multinational,[3, 4, 85, 107] seven were performed in the United States, three in Germany, three in Scotland, three in the UK, and eight in other countries (Australia, Denmark, Mexico, Sweden, Italy, Japan, Greece, Poland). All of the studies enrolled both men and women. Average age ranged from the mid 50s to the low 80s, with 14 of the studies having an average age in the 60s. Six studies[17, 24, 25, 27, 43, 85, 109] were entirely funded by a pharmaceutical company. Funding for nine studies was supplied by government agencies with or without supplementary pharmaceutical company support. Funding for 13 studies was not reported.

Although all 28 studies are included in Appendix E, Tables 4 and 5, in the text below we summarize 14 articles on 12 unique study populations. Sixteen articles were not included in this summary because they did not report multivariate analyses of risk factors. One additional article was excluded since the multivariate analysis evaluated any (not severe) hypoglycemia.[24] The 12 studies included two RCTs, one prospective and one retrospective cohort, four cross sectional, and four case control studies.

Definition of Severe Hypoglycemia

All 28 studies met our pre-specified minimal definition of severe hypoglycemia as defined in Key Question #1. Of the 12 multivariate adjusted studies, four used HA (**H**ypoglycemia needing any **A**ssistance), three used HMA (**H**ypoglycemia requiring **M**edical **A**ssistance), three used administration of IV glucose, and two studies categorized events by more than one definition.[3, 92]

Quality

The quality of both RCTs was good. Of the non-randomized studies, 9 of 12 met criteria for three or more of the quality metrics (Appendix D, Table 3).

Results (See Table 3 and Appendix E, Table 6)

Since the studies varied considerably with respect to risk factors evaluated (and their definitions), populations studied, and lengths of follow-up, the data were considered unsuitable for pooling. We present, instead, a narrative summary. Although *impaired hypoglycemia awareness* was

evaluated in only one study, it is frequently listed as a well-established risk factor so we include it here as well. The single study that met our criteria was a cross sectional survey of 401 subjects, in which impaired awareness was associated with an increased risk of hypoglycemia (OR 2.66, 95% CI 1.55 to 4.56).[84] The risk factor *intensive glycemic control* is discussed above under Key Question #1.

Gender was evaluated as a risk factor in seven studies,[16, 27, 89, 90, 97, 100, 102] with mixed findings. Most studies, including the large ADVANCE trial, showed no association between gender and risk for severe hypoglycemia.[16, 90, 102] One large retrospective cohort study showed that men were at higher risk than women, but the 95% confidence interval extended to 1.0.[97] In ACCORD, women were more likely than men to experience a hypoglycemic event requiring medical assistance (HR 1.21, 95% CI 1.02 to 1.43). Similarly, in a nested case-control study using a claims database, men on at least one OHA had a 16% lower risk of hypoglycemia-associated hospitalization than women (OR 0.84, 95% CI 0.73 to 0.96).[27]

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Table 3. Significant Risk Factors for Severe Hypoglycemia

Study, year	Older Age	Male Gender	Nonwhite Race	Married	Advanced Education	Impaired Awareness	Alcohol	Smoking	Lower BMI	Longer Diabetes Duration	Higher HbA1c	Previous Hypoglycemia	Polypharmacy	Renal Disease	Microvascular Complications	Macrovascular complications	Dementia or cogniftive impairment	Intense control	Insulin or insulin dose	Time on insulin	Metformin	Sulfonlyurea or dose	Other
Akram 2006[84]****	x			↑		↑		x		↑					↑	x			x		x		↓
Bruce 2009[92]**	x			x					↑	x		↑		↑	x	x	↑		↑				↑
Davis 2010[16],*****	x	x			↑		x		x	x	↑	↑		↑	↑				↑	↑		x	↑
Davis 2011[93]**	x	x			↑		x		x	x	x	↑	x	↑	↑				x	↑		x	↑
Duran-Nah 2008[104]	↓				↓					↑		↑	x	↑									↑
Holstein 2009[102]	↓	x							x	x	x		x	x							x	↑	
Holstein 2011[103]											↓					↑	x		x			x	↑
Miller 2001[100]******	x	x	x						x	x	x	x		x					x			x	x
Miller 2010[89]	↑	↓	↓↑*****		↓		x		↑	↑*	↑			↑	↑	x		↑	↑		x	x	↓
Quilliam 2011[27]	x	↓										↑		↑	↑	↑			↑		↓	↑	↑
Sarkar 2010[78]*******	x	x	x		↓		x		x	x	x			x	x		x		x		x	x	
Shen 2008[101]*******	x	x	↑													x	x						
Shorr 1997[97]	↑	↑	↑				↑						↑						↑			↑	↑
Zoungas 2010[90]	↑	x			↓			↑	↑	↑	x			↑	↑	x	↑	↑			x		↑

↑ = significantly increase the risk of hypoglycemia in multivariate analysis
↓ = significantly decrease the risk of hypoglycemia in multivariate analysis
X = risk factors included in the multivariate model AND non significant risk factors
Microvascular Disease: microalbuminuria, diabetic eye disease, peripheral neuropathy
Macrovascular Disease: stroke, transient ischemic attack, myocardial infarction, angina, coronary or peripheral revascularization, leg amputation
* Total time since diagnosis of diabetes not significant, but 16+ years ↑
**Data from Fremantle Diabetes Study
*** compiled data from all multivariate models
**** includes both any event and repeated events
***** ↑ for African American, ↓ for "Other"
****** Includes intensive, standard, and combined
*******Only evaluated one risk factor as independent variable

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Race was evaluated in four studies, three of which found that blacks are at higher risk for severe hypoglycemia than whites. These studies included one large RCT,[89] two retrospective cohort studies,[97, 100] and one cross-sectional study.[101] ACCORD reported that, compared to non-Hispanic whites, blacks had a 43% increased risk of HMA (HR 1.43, 95% CI 1.2 to 1.7) and that people in racial groups other than Hispanic or black had a lower risk of HMA than whites (HR 0.64, 95% CI 0.47 to 0.88).[89] An increased risk for African Americans was also seen in a large population-based retrospective cohort study of 20,000 Medicaid enrollees over age 65 in Tennessee. Specifically, blacks on OHAs had a two-fold increased risk of hypoglycemia-related hospitalization, ED visit or death compared to whites (RR 2.0, 95% CI 1.7 to 2.4).[97] A cross-sectional analysis of hospitalizations among people with type 2 diabetes in US community hospitals indicated that blacks were more likely than whites to have a diagnosis of acute hypoglycemic condition (OR 1.62, 95% CI 1.55 to 1.69).[101]

Body mass index was evaluated in five studies, including two large RCTS,[89, 90] both of which found that a higher BMI was associated with a lower risk of severe hypoglycemia. In ACCORD,[89] a BMI of 30 or higher was associated with a 35% lower incidence of HMA than a BMI of less than 25 (HR 0.65, 95% CI 0.5 to 0.85). Similarly, in ADVANCE[90] for each unit (kg/m^2) increase in BMI there was a 5% decrease in risk of HA (HR 0.95, 95% CI 0.93 to 0.98). BMI was not found to be associated with risk in three smaller studies.[16, 100, 102]

Age was evaluated as a risk factor for severe hypoglycemia in nine studies (two RCTs, one prospective and one retrospective cohort, one cross sectional, and four case control). The two largest trials (ACCORD[89] and ADVANCE[90]) both reported significant associations between older age and risk of severe hypoglycemia. In ACCORD,[89] the risk of HMA increased by 3% for each additional year of age (HR 1.03, 95% CI 1.02 to 1.05). ADVANCE[90] reported almost identical results (HR 1.05, 95% CI 1.03 to 1.07). Confirming these findings, a population-based retrospective cohort study of 20,000 Medicaid enrollees over age 65 in Tennessee, found that compared to enrollees age 65-69, older age groups had significantly increased risk (age 70-74: RR 1.1, 95% CI 0.9 to 1.4; age 75-79: RR 1.5, 95% CI 1.2 to 1.9; age $\geq$ 80: RR 1.8, 95% CI 1.4 to 2.3).[97] Six smaller studies showed either no significant association between age and risk of severe hypoglycemia[16, 27, 84, 100] or a significant inverse association.[102, 104]

Diabetes duration was evaluated as a risk factor in seven studies (two RCTs, one prospective and one retrospective cohort, two case control, one cross sectional). In ACCORD, compared to people with diabetes duration of 5 years or less, the risk for those with diabetes duration of 11-15 years increased by a non-significant 6% (HR 1.06, 95% CI 0.83 to 1.37) and by 37% for those with diabetes of 16 or more years (HR 1.37, 95% CI 1.09 to 1.73).[89] In ADVANCE each year of diabetes was associated with a 2% increase in risk of severe hypoglycemia (HR 1.02, 95% CI 1.00 to 1.04).[90] Similar results were reported by the cross sectional[84] and one of the case control studies.[104] The other three studies did not find statistically significant associations between duration of diabetes and incidence of severe hypoglycemia.[16, 100, 102]

Previous hypoglycemia was evaluated as a risk factor in four studies, two case control,[27, 104] one prospective,[16] and one retrospective cohort.[100] Three studies found that a history of past hypoglycemia was a strong predictor of future episodes, and one did not.[100] In a large case control study based on administrative data, a prior emergency room (ER) visit for hypoglycemia

increased the odds of a subsequent inpatient admission for hypoglycemia by more than nine-fold (OR 9.5, 95% CI 5 to 18).[27] In the other case control study a reported history of hypoglycemia, not further defined, in the previous year was associated with a three-fold increase risk of hypoglycemia associated hospitalization or ER visit (OR 2.9, 95% CI 1.3 to 6.5).[104] History of previous episode requiring health services use was associated with a six-fold increase for another episode over the next 8 years (HR 5.7, 95% CI 2.2 to 15) in the prospective cohort study.[16]

Education was evaluated as a risk factor in five studies, two RCTS,[89, 90]one cross sectional,[78] one case control[104] and one prospective cohort study.[16] Four of the five studies found significant but modest associations between level of education and risk for severe hypoglycemia. ADVANCE found a marginally significant inverse association between the age at completion of formal education and risk of severe hypoglycemia (HR 0.98 95% CI 0.96 to 1.0).[90] Similarly, in ACCORD, subjects with less than a high school education were at an increased risk for severe hypoglycemia (conventional control: HR 1.74, 95% CI 1.02 to 2.95; intensive control: HR 1.38, 95% CI 1.06 to 1.81) compared to those with more education.[89] In the case control study, illiteracy was associated with an increased risk (OR 3.7, 95% CI 1.4 to 10).[104] In a cross sectional study in a community population, Sarkar et al. found that subjects who indicated that they had "problems learning," "needed help reading," or "lacked confidence with forms" were about 30-40% more likely to have reported an HA in the previous year.[78] Finally, in the prospective cohort study, "education level higher than primary level" was associated with an increased risk of severe hypoglycemia (HR 2.3, 95% CI 1.09 to 5.04, N=616).[16]

Renal disease was evaluated as a risk factor in seven studies, two RCTs,[89, 90] one prospective,[16] one retrospective cohort[100] study, and three case control studies.[27, 102, 104] Five of these studies found that renal insufficiency (defined as elevated serum creatinine level or elevated estimated glomerular filtration rate) was significantly associated with increased risk of severe hypoglycemia. The only studies that did not find a significant association were a very small study,[102] and the retrospective cohort study that was conducted in a single institution with a predominantly African American population.[100] In ACCORD, a urine albumin:creatinine ratio greater than 300 or a serum creatinine greater than 115 umol/L were each associated with a significantly increased risk of about 70%. In ADVANCE, for each umol/L increase in serum creatinine, the risk of a severe hypoglycemic event increased by 1%.[90]

Other (non-renal) microvascular disease was assessed in five studies.[16, 27, 84, 89, 90] In four of the five there were significant positive associations; in one relatively small study (N=415), which evaluated untreated retinopathy and symptomatic or asymptomatic peripheral neuropathy, there were no statistically significant associations for any event, but peripheral neuropathy was found in increase the risk of repeated events of severe hypoglycemia.[84] In ACCORD a history of peripheral neuropathy conferred a modest but significant increased risk (HR 1.2, 95% CI 1.1 to 1.4).[89] In ADVANCE a "history of microvascular disease" conferred a twofold increased risk of severe hypoglycemia (HR 2.1, 95% CI 1.5 to 3.).[90] In a nested case-control database study, peripheral ulceration was found to be positively associated with risk of inpatient hospital admission for hypoglycemia (OR 1.71, 95% CI 1.2 to 2.44).[27] Finally a population based but relatively small study (N=616) found that a history of peripheral neuropathy was significantly associated with severe hypoglycemia (HR 2.4, 95% CI 1.3 to 4.5).[16]

Dementia was evaluated as a risk factor for severe hypoglycemia in three studies.[90, 92, 103] In ADVANCE, higher cognitive function as measured by the Mini Mental Status Examination was significantly associated with a modest decreased risk of severe hypoglycemia (HR 0.93, 95% CI 0.87 to 0.99).[90] In the second study, which was population based and prospectively followed 302 patients age 70 years and older, patients with dementia at baseline had a significantly higher risk for hypoglycemia requiring medical attention than those who did not have dementia (HR 3.0, 95% CI 1.1 to 8.5).[92] In a small case control study, dementia was not found to be a significant risk factor.[103]

Other risk factors evaluated in the 12 studies included genetic markers, marital status, smoking, alcohol consumption, polypharmacy, recent discharge from the hospital, and use of ACE inhibitors. All were found, in one or more studies, to be associated with increased risk of hypoglycemia (See Appendix D, Table 6). However, these findings were generally sparse, often conflicting, and ultimately inconclusive.

Summary of Key Question #2

Factors most consistently and independently associated with risk for severe hypoglycemia in adult patients with type 2 diabetes on hypoglycemic medication include: intensive glycemic control (discussed above under Key Question #1), history of hypoglycemia, renal insufficiency, history of microvascular complications, longer diabetes duration, lower education level, African American race and history of dementia. History of hypoglycemia unawareness was evaluated in only one study. Gender, age and lower BMI were not consistently associated with risk, although higher age and lower BMI were associated with higher risk in the two largest studies.

KEY QUESTION #3. What is the effect of severe hypoglycemia on other outcomes in adults with type 2 diabetes on one or more hypoglycemic agents (e.g., quality of life, mortality, morbidity, utilization)?

We identified 59 articles on 53 studies that provided information about outcomes in patients who experienced severe hypoglycemia.

Overview of Included Studies (Appendix E, Table 1)

An overview of the 59 included articles is provided in Appendix E, Table 1. Among the 53 studies were 14 randomized controlled trials,[3-5, 21, 30, 41, 42, 46, 52, 54, 110-113] 16 cohort studies,[17, 19, 25, 26, 75, 92, 94-97, 114-118] 12 cross sectional studies,[78, 81, 82, 99, 119-126] and 11 case control or case series studies.[9, 28, 105, 107-109, 127-131] Twelve studies were multinational; additionally, twelve were performed in the United States, four in Germany, three in the UK, three in Scotland, three in Sweden, and the remainder in other countries (Canada, Australia, Singapore, India, Israel, Netherlands, Turkey, Switzerland, France, Italy, Greece, and Poland). All but one of the studies[30] enrolled both men and women. Average age ranged from 30 to 85 years with most studies reporting a mean age in the 50 or 60 year range. Twenty one studies were entirely funded by a pharmaceutical company while eight studies were funded by government agencies, three by private foundations, and five by multiple funding sources. No source of funding was listed for 16 studies.

All-Cause Mortality

All-cause mortality associated with severe hypoglycemia was reported in three large randomized trials that compared intensive control to conventional control.[3, 4, 21, 61, 90] Mortality ranged from zero to 12.5 percent in intensively treated people who became hypoglycemic; in two of these three studies mortality in this group was 0.1% or less and in the third there was one death in eight study subjects (12.5%). In all three randomized trials, mortality in the conventional control groups ranged from 0% to 1.2%.

Six additional randomized trials (typically fewer than 1,000 patients enrolled with follow-up less than 30 weeks) compared different treatment regimens, including oral medications and different forms of insulin.[42, 43, 46, 52, 111-113] No deaths related to severe hypoglycemia were reported in these studies.

Eight cohort studies reported mortality outcomes, typically in patients seen in an ER or hospitalized for severe hypoglycemia. There were no deaths in three studies.[16, 17, 116] In four other studies, between 0.3% and 8.3% of the patients died following severe hypoglycemic events.[95-97,98] One study of veterans with and without CKD did not report number of deaths but reported odds ratios for outpatient risk of death within one day of a hypoglycemic event (defined as glucose <50 mg/dl) compared to individuals with glucose of ≥70 mg/dl.[75] For patients without CKD, the odds ratio was 13.28 (95% CI 9.30 to 19.18). For patients with CKD, the odds ratio was 6.84 (95% CI 4.41 to 10.62).

Mortality was also assessed in six case series. As with the cohort studies, these studies also enrolled patients seen in an emergency room or admitted to a hospital as a result of severe hypoglycemia. Four studies reported no deaths.[28, 108, 109, 128] Three other studies reported that between 3.2% and 11% of the enrolled patients died after severe hypoglycemia.[105, 127, 131]

Three studies reported long-term follow-up mortality data. Participants in the ADVANCE trial were followed for a median of 5 years.[90] The mortality rate was 19.5% in those who had experienced at least one episode of severe hypoglycemia and 9.0% in those who had not (adjusted HR 3.27, 95% CI 2.29 to 4.65). The median time to death was 1.05 years. In a prospective cohort study, there were no deaths at the time of the event but 16 of the 45 patients (35.6%) died during the mean follow-up period of 22.8 months.[17] The third study, a retrospective cohort study that observed in-hospital mortality of 1.6% (2 of 126 patients), reported long-term mortality of 42.1% (53 of 126 patients) during a median follow-up of 23.2 months. Of the 53 total deaths, 20 were in the group of patients treated with oral medications and 33 were in the group treated with insulin (univariate analysis, p=0.02).[95] The authors reported that median annual mortality in the study population was 22% and compared that to 5.2% in the general population (patients with and without diabetes, age 80 years).

Non-fatal Myocardial Infarction

Three randomized trials, one cohort study, and one case series provided information about non-fatal myocardial infarctions among patients with severe hypoglycemia. Two randomized trials reported no events.[30, 113] The third reported that one patient (4.5%) experienced severe hypoglycemia with cardiac arrest.[110] The authors did not say how much time elapsed between the hypoglycemic episodes and the cardiac arrests. A cohort study that enrolled individuals

who experienced severe hypoglycemia reported three cases (0.5%) with myocardial infarction as a complication of the hypoglycemia.[97] A case series reported two cases (2%) of transient asymptomatic myocardial ischemia associated with severe hypoglycemia.[127]

Non-fatal Stroke

Non-fatal stroke outcomes were reported in four studies. A randomized trial of several hypoglycemic therapies reported no stroke events.[113] A cohort study with 586 patients reported seven patients (1.2%) experiencing stroke as a complication of severe hypoglycemia.[97] A case series of 207 patients admitted to a hospital with severe hypoglycemia during a three year period, included two patients (0.97%) who experienced cerebrovascular ischemic stroke.[108] In a case series of 19 patients with severe hypoglycemia associated with glipizide use (over a 7 year period), one patient (5.3%) who had a stroke prior to the hypoglycemic event experienced further functional impairment. The patient died 23 days after the event.[105]

Other Neurologic Events

Two randomized trials with veterans assigned to either intensive or conventional control reported data on other neurologic events associated with severe hypoglycemia. In one trial, loss of consciousness was reported for both of the conventional control group patients who experienced severe hypoglycemia (2.6% of the conventional control group) and none of the five intensive control patients who experienced severe hypoglycemia (0% of the intensive control group).[30] In the second trial, severe hypoglycemia with impaired consciousness was reported in three episodes/100 patient-years in the conventional control group compared to nine episodes/100 patient-years in the intensive control group. In addition, complete loss of consciousness was reported in one episode/100 patient-years and three episodes/100 patient-years, respectively. Both differences were significant ($p<0.001$). The median follow-up in the trial was 5.6 years.[5]

Five randomized trials of different treatment regimens also reported neurologic outcomes. Two trials reported zero events.[41, 54] In another trial, at the three year follow-up, loss of consciousness associated with severe hypoglycemia was reported by four patients – one in the biphasic aspart group (0.4%) and three in the basal detemir group (1.3%).[43] One trial reported one patient with a coma (0.5%) among 199 treated with NPH plus regular human insulin.[112] In the last trial, seven episodes in four patients either required medical assistance or were accompanied by neurological symptoms.[52]

Three cohort studies provided data on neurologic outcomes. One study reported that, at presentation to a hospital, 51% were in a coma, 18% were disoriented, 11% experienced somnolence, 9% experienced paralysis, 7% had cerebral seizures and 5% had psychological disturbances.[17] In another study, among 126 patients admitted for severe hypoglycemia, 54% of oral hypoglycemic agent users experienced coma compared to 30.2% of insulin users.[95] A third study reported transient ischemic attack as a complication of severe hypoglycemia in four patients (0.7%).[97] At presentation, a loss of consciousness was observed in 49% of episodes, seizures in 5% of episodes and irrational behavior in 6% of episodes.[97]

Seven other studies reported on this outcome. A cross-sectional study reported that 4% of patients experienced convulsions associated with episodes of severe hypoglycemia in the past year.[99] In five case series, coma was reported in 19% to 71% of individuals with severe

hypoglycemia.[105, 107, 108, 128] "Semi-coma" (30%),[108] coma or stupor (21%),[28] somnolence (51%),[128] decreased consciousness (16%),[105] seizures (8-10%),[107, 127] disorientation (81%),[107] and transient right hemiplegia (1%)[127] were also reported. One study documented seizures and/or psychological disturbances in 30% of patients with severe hypoglycemia.[128]

Hospitalization

Five randomized trials reported hospitalization data. One trial of intensive versus conventional control among veterans reported no hypoglycemia-associated hospitalizations.[30] Four trials of different treatment regimens found between 0%[41, 42, 113, 132] and 0.8%[112] were hospitalized for hypoglycemia.

Hospitalizations were also reported in nine cohort studies (10 papers). Among patients starting insulin, there were no hospitalizations in 9970 patient years of observation.[26] A study of 344 veterans followed for one year identified 55 severe hypoglycemic episodes in 19 subjects; two of these (3.6%) required hospitalization.[19] A mean hospitalization rate of 0.15 episode/patient/year was reported for type 2 patients based on data from 21 patients with 29 severe hypoglycemic episodes.[116] A hospitalization rate of 47 per 1000 person-years was reported based on data from all discharges from Navajo Area Indian Health Service hospitals during a 5 year period with an estimated 26,125 person-years of observation.[96] A study that included both type 1 and type 2 patients reported that over a mean follow-up of 2.5 years, insulin-treated individuals with diabetes who had hypoglycemic episodes had more overall hospital admissions (0.97 per year vs. 0.48 per year in insulin-treated individuals without hypoglycemic episodes, $p<0.01$). Forty percent of the excess hospital admissions were due to hypoglycemia.[118]

Three other cohort studies (four papers) reported hospitalization associated with 17% to 33% of hypoglycemic events[25, 114, 133] or 7.1% of patients experiencing hypoglycemia.[117] Another study reported that 16% of patients seen in the emergency department were subsequently admitted to the hospital.[115]

In a cross-sectional study of patients with type 2 diabetes from a large diabetes registry, 8% of the patients with a self-reported significant hypoglycemia episode had a documented emergency room visit or hospitalization. The odds of an emergency room visit or hospitalization were significantly higher in patients who reported having at least one significant hypoglycemia episode (OR 19.0, 95% CI 13.0 to 26.0) compared to those without a significant hypoglycemia episode.[78] One other cross-sectional study reported no hospitalizations[125] while a second reported that 5.5% of patients were treated in an emergency department or hospitalized following severe hypoglycemia.[124]

Length of hospital stay, reported in two case series, ranged from a median of 5.5 days[128] to means of 9.8 days for patients on oral medications and 8.0 days for patients taking insulin.[95]

Emergency Department Visits

Two randomized trials reported that no patients with severe hypoglycemia required an emergency department visit.[42, 113] A third randomized trial reported that either 0% (insulin glargine group) or 15.4% (NPH group) of those with severe hypoglycemia were seen in the emergency department.[41, 132]

Four cohort studies reported emergency department use. One study reported that between 14% and 23% of severe hypoglycemic episodes were treated in the emergency room.[114, 133] Another cohort study reported that 31% of the patients enrolled, all of whom were eventually hospitalized, were treated first in the emergency department[17] while a third found that 8% of patients were treated in either the emergency or primary care service, 36% were treated by an ambulance service and 55% required both ambulance and emergency or clinic service.[25] Finally, over a mean follow-up of 2.5 years, insulin-treated diabetic individuals who experienced hypoglycemic episodes had higher rates of overall emergency department use (0.85 visits per year vs. 0.40 visits per year in insulin-treated diabetic individuals who did not have a hypoglycemic episode, $p<0.01$) with 53% of the excess visits due to hypoglycemia.[118]

Two cross-sectional studies (noted above) reported on rates of either hospitalization or emergency department visit (5.5% to 8%).[78, 124] An additional cross-sectional study reported that six of the seven patients with severe hypoglycemia during a one month period required medical services including three emergency room visits.[125]

Accident/Trauma

An evidence report prepared for the Federal Motor Carrier Safety Administration (FMCSA)[134] focused on the risk of motor vehicle crashes in drivers with diabetes and the relationship with hypoglycemia. Based on data from 13 case-control studies of low to moderate quality, the conclusion was that the risk for crash among drivers with diabetes was higher than for those without diabetes (RR 1.19, 95% CI 1.08 to 1.31). Many of the studies enrolled only patients with type 1 diabetes and all but two were published before 2000. The strength of evidence was rated as weak. To look at the effect of hypoglycemia on driving ability, the review identified three studies of moderate quality, all with type 1 patients. All three involved induced hypoglycemia and simulated driving ability. Although driving ability was impaired, it was unclear which aspects of driving ability were most affected or at what level of hypoglycemia the impairments were evident. It is unknown whether data from driving simulators are predictive of crash risk in actual driving conditions.

We identified several other studies related to motor vehicle operation that were either not included in the FMCSA review or were published after the review was completed. A case-control study identified 795 drivers who were reported (typically because of a motor vehicle crash, mandatory annual review for commercial vehicle license, license suspension appeal, or notifiable medical condition) to the Ontario Ministry of Transportation Medical Advisory Board and who had an underlying diagnosis of diabetes mellitus. The type of diabetes was not reported. Among the cases (57 drivers who had a crash), 60% reported experiencing severe hypoglycemia in the past 2 years compared to 27% of the controls (738 drivers with no crash) (OR 4.07, 95% CI 2.35 to 7.04). A lower HbA1c was also associated with an increased risk of crash even after adjusting for severe hypoglycemia (OR 1.25, 95% CI 1.02 to 1.55).[129] A cross-sectional study of diabetic patients taking hypoglycemia-inducing medications found that among the 122 patients talking oral-antidiabetics (116 with type 2 diabetes, mean age 64.2 years), subjects reported two hypoglycemia-induced accidents per year driven. Among the 151 patients receiving conventional insulin therapy (109 with type 2 diabetes, mean age 59.0 years, treated with one or two injections of premixed insulin and may also be taking other oral antidiabetics), there were three

hypoglycemia-induced accidents per year driven. When asked if they refrained from driving due to fear of hypoglycemia events during driving, 0.8% of the oral medication group and 4.0% of the conventional insulin therapy group responded "yes."[121]

Several studies reported on motor vehicle accidents but did not specifically relate the outcome to severe hypoglycemia. In the ACCORD study, there was no difference in incidence of motor vehicle accidents in which the patient was the driver (0.2% in intensive therapy, 0.3% in standard therapy, p=0.40).[3] A nested case-control study used an insurance registry of all eligible drivers ages 67 to 84 years, an accident report file, and a prescription drug database. The type of diabetes was not reported. Several medication regimens were associated with a borderline significant risk of an accident. A combination of sulfonylureas and metformin was used during the preceding month by 1.6% of those involved in a crash and 1.2% of the controls (adjusted rate ratio 1.3, 95% CI 1.0 to 1.7). The adjusted rate ratio for any insulin use was 1.3 (95% CI 1.0 to 1.8). A dose-response effect was noted for users of a combination of sulfonylureas and metformin over the year preceding the index event.[135]

Six studies reported falls and bone injury data.[17, 95, 97-99, 127] A cohort study of 45 patients with sulfonylurea-induced hypoglycemia requiring hospitalization reported that six (13%) had soft tissue injuries or fractures as a result of falls associated with hypoglycemia.[17] A second cohort study of 126 type 2 diabetic patients hospitalized for severe hypoglycemia found that the percentage of patients who had experienced a fall was 21.5% with no difference between oral medication and insulin users.[95] In a third cohort study, among patients hospitalized for severe hypoglycemia, bone injuries were reported in 7.3% of patients (9.9% of the insulin users, 0% of the oral medication users).[98] A cohort study[97] and a cross-sectional study[99] reported "injury" in 1.7% to 5% of patients who experienced severe hypoglycemia. In a case series brain trauma and skeletal injury were reported in 7% of patients.[127]

Quality of Life

Nine cross-sectional studies reported measures of quality of life. One study assessed health-related quality of life with the SF-36 and reported that scores for all domains were lowest for patients reporting severe hypoglycemia.[120]

Five studies (reported in six papers) assessed health utility/quality of life with the EuroQol-5 Dimensions (EQ-5D). EQ-5D scores were lower for patients reporting severe hypoglycemia.[81, 82, 87, 119, 120, 126] Three studies reported data from the worry subscale of the Hypoglycemia Fear Survey-II (HFS-II). In two studies worry scores were highest for patients who reported severe/very severe symptoms compared to those with lesser symptoms[81, 126] while in the third study, there were no differences in worry score as severity increased.[82] Both the quality of life and the worry scores were impacted by the frequency of severe hypoglycemia episodes.[87]

Two studies looked at anxiety and depression associated with severe hypoglycemia.[122, 123] In one study, affective disorder, but not anxiety disorder, was found to be associated with a history of severe hypoglycemia in the prior 12 months.[122] The second study found that a lifetime history of at least one episode of severe hypoglycemia was associated with symptoms of anxiety ($p<0.001$) but not depression.[123]

Lifestyle changes made following an episode of severe hypoglycemia were the focus of one study.[124] Patients reported more frequent testing of blood glucose, changes to insulin doses, greater fear of hypoglycemia, requests to have someone check on them, and additional concerns about driving.

Other Outcomes

Cognitive Decline

Cognitive decline was reported in two cohort studies. One of the studies followed patients to determine if the risk of dementia was increased in those with at least one episode of hypoglycemia requiring hospitalization or an emergency room visit.[94] Patients who had experienced at least one episode of hypoglycemia during a 22 year period were evaluated for an additional mean of 3.8 years to determine whether they developed dementia. No patient had a diagnosis of dementia, mild cognitive impairment or general symptom memory loss at the time of the hypoglycemic episode(s). Among 1465 patients, the incidence of dementia was higher for patients who had at least one episode of hypoglycemia than for those who had no episodes (17% vs. 10%, $p<0.001$). The attributable risk of dementia in patients with one or more episodes of hypoglycemia was 2.4% per year (95% CI 1.7 to 3.0). In the adjusted model all patients with at least one episode of severe hypoglycemia were at increased risk for dementia (hazard ratio 1.4, 95% CI 1.3 to 1.7 for one or more episodes).

In the second prospective study, a baseline assessment (the Mini-Mental State Examination and the Informant Questionnaire for Cognitive Decline in the Elderly) was completed on 302 patients age 70 and over. At 18 months, a repeat assessment was done on 205 patients (29 had died, 27 had developed dementia and 41 declined the assessment). Thirty-three new cases of cognitive decline were identified (four cases of dementia and 29 cases of cognitive impairment without dementia). There was no significant difference in prior severe hypoglycemia (either self-reported or requiring medical assistance) between those who developed cognitive decline and those who did not.[92]

Productivity

One cohort study and two cross-sectional studies reported on productivity. In the cohort study, insulin-treated patients with a medical claim coded for hypoglycemia were more likely to use short-term disability (47% vs. 32%, $p<0.01$) and to use more sick days (19.5 vs. 11.0, $p<0.01$) than insulin-treated patients with no claim for hypoglycemia. The analysis included patients with either type 1 or type 2 diabetes.[118] In one cross-sectional study, a mean loss of 8.6 productive days following hypoglycemia was reported for patients who experienced severe hypoglycemia; for those with mild or moderate hypoglycemia, the mean days lost was 2.7. In multivariate modeling, severity of hypoglycemia (along with frequency) was a significant predictor of productivity.[120] A second study reported that 32% of patients who experienced severe hypoglycemia went home from school, work or other activities and 26% stayed home the next day.[124]

Medical Resource Use

Several studies reported on medical service use other than hospitalization or emergency room visits. A randomized trial reported that one of five patients on liraglutide (20%) who experienced severe hypoglycemia required medical assistance of some type.[54] One cohort study reported that 1.9% of the 2,417 patients studied required medical contact for hypoglycemia during the first year of insulin use. The number decreased to 0.4% by the fourth year of use.[26] A cross-sectional study reported mean total resource use of 13.2 contacts with a health service provider among patients who reported severe hypoglycemia. For patients with mild or moderate hypoglycemia, the mean was 11.5 contacts.[120] A second cross-sectional study reported eight nurse visits, three physician visits and one telephone contact with medical care among six patients who experienced severe hypoglycemia in a one-month period (number of events not reported).[125] Another cross-sectional study reported that 2.5% of the patients experiencing severe hypoglycemia had additional visits to their physicians while 0.4% had additional communication (non-visit).[124] Two studies[114, 133] that reported hypoglycemic events before and after conversion to a pen device reported significantly fewer physician visits (37.7% of hypoglycemic events before, 28.1% after; OR 0.39, 95% CI 0.24 to 0.64), no significant difference in outpatient visits (7.8% before, 12.2% after, OR 0.79, 95% CI 0.31 to 2.01), and significantly lower use of "other" (not emergency department, hospitalization, physician visits, or outpatient visits) health care resources (22.1% before, 16.5% after, OR 0.38, 95% CI 0.20 to 0.71) after conversion to the pen device.

Summary of Key Question #3

We found good evidence for an increased risk of the following outcomes in patients who have experienced severe hypoglycemia: all-cause mortality, neurological events (other than non-fatal stroke), hospital and emergency department utilization and decreased quality of life. Severe hypoglycemia does not appear to be associated with short-term mortality. However, a history of severe hypoglycemia may contribute to increased long-term mortality. Neurological events, including coma, impaired consciousness, seizures and paralysis, were reported in seven randomized trials, three cohort studies and seven other studies. Few patients in the randomized trials experienced coma or loss of consciousness. However, in observational studies of patients presenting to an emergency department or admitted to a hospital, between 19% and 71% were in a coma. Hospitalization and emergency department utilization was reported in five randomized trials, nine cohort studies and three other studies with wide variation across studies. Although many of these studies lacked control groups, there is some evidence of increased emergency department visits and hospital admissions among patients who experience severe hypoglycemia. Data from eight cross-sectional studies suggest that patients who experience severe hypoglycemia generally report a lower quality of life and higher worry.

We found limited data about many of our outcomes of interest including non-fatal MI, non-fatal stroke, cognitive decline, motor vehicle accidents, falls and traumatic injuries, work productivity and other medical service utilization. The available evidence suggests that non-fatal MI and stroke are unlikely consequences of severe hypoglycemia. There are mixed findings from two studies on development of cognitive decline or dementia in individuals with a history of severe hypoglycemia. Few studies have reported motor vehicle accident data specifically related to severe hypoglycemia. Falls and injuries are common consequences of severe hypoglycemia but

given the absence of appropriate control groups it is unclear if these outcomes are hypoglycemia-related or simply reflect the age and co-morbidity burden of the population. The evidence suggests that individuals who experience episodes of severe hypoglycemia are more likely to miss days at work. Medical resource utilization findings are difficult to interpret without appropriate control group data.

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SUMMARY AND DISCUSSION

SUMMARY OF EVIDENCE BY KEY QUESTION

Key Question #1: What is the incidence of severe hypoglycemia in adults with type 2 diabetes on one or more hypoglycemic agents?

Overall incidence of severe hypoglycemia was less than 1% in the majority of the 60 reviewed studies, particularly those of metformin (0-1.5%), GLP-1 analogs (< 1%), DPP-4 inhibitors (<1%), insulin detemir (<1%), glinides (0%) and TZDs (<1%). These rates are similar to the placebo or diet-only rates which were measured in three studies[21, 29, 59, 136] with a pooled incidence of severe hypoglycemia of 0.6% (95% CI 0.3 to 1.2%) over a weighted mean follow-up time of 7 years. These results are consistent with other high quality systematic reviews of exenatide,[62, 63] liragultide,[63] sitagliptin,[64] glinides[71] and pioglitazone.[70] These results are also consistent with a recent meta-analysis of a wide variety of OHAs that concluded that severe hypoglycemia did not "occur more often with any particular monotherapy or combination therapy" but that the sulfonylureas were the most likely to increase the risk.[137] However, Bennett did not include insulins or intensive versus conventional control trials.

The treatment regimens with the highest risk were sulfonylureas, those targeting intensive control of HbA1c levels and insulin (in particular NPH, glargine, lispro, and glulisine). For the *sulfonylureas* the pooled incidence of severe hypoglycemia was 1.2% (95% CI 0.9 to 1.5%) over a weighted average follow-up time of 2.4 years. Due to limited data we were unable to determine incidence rates associated with individual sulfonylureas.

In the five trials that randomized participants to *intensive versus conventional glycemic control*[3-5, 21, 29, 30] the pooled incidence of severe hypoglycemia was 7.6% in the intensive group and 3.1% in the conventional group (RR 2.4, 95% CI 1.8 to 3.1, N= 27,644) over a weighted average follow up of 5.2 years. This is consistent with four other high quality meta-analyses that included these RCTs and other studies and that reported a 2- to 2.5- fold increased risk of severe hypoglycemia in intensively treated patients, with 5 year incidence rates of 2-3% with conventional control and 5-7% with intensive control.[8-11] A post-hoc analysis of the ACCORD data indicated that participants whose HbA1c did not drop to target levels promptly were at the highest risk. The authors concluded that clinicians should not continue to intensify glucose lowering regimens when initial efforts are unsuccessful.[89]

Insulin

There were only two trials of *NPH monotherapy*, one of which reported a 5 year incidence of 11.1%[35] and one a 6 month incidence of 2.3%.[39] These results are consistent with two meta-analyses, one which identified no cases of severe hypoglycemia in 14 RCTs with an average follow-up of 40 weeks.[69] The second reported an incidence of severe hypoglycemia of 2.6% in six studies with 1532 subjects followed for 6 months to 1 year.[66] Overall, it appears that the annual incidence of severe hypoglycemia in persons on NPH monotherapy is about 0-3%.

For *NPH with* OHAs we documented a pooled incidence of severe hypoglycemia of 5% (95% CI 4.1 to 6.1%, N=3150), over a weighted average followup time of 1.2 years. This is consistent with the results of a large trial in which an insulin-based strategy to lower HbA1c to

less than 7% was associated with a 9.2% 5-year incidence rate[58] and another systematic review which compared long-acting insulin analogues to NPH insulin with or without concomitant OHAs and reported a 6 month 2.7% incidence of severe hypoglycemia[66] However, a review by Goudswaard,[69] which investigated either insulin monotherapy or combinations of insulin plus OHAs, identified only one severe hypoglycemic episode in a patient on morning NPH plus a sulfonylurea. In this review, 12 unique studies reported rates of hypoglycemia, none of which were included in our review because either they enrolled fewer than 500 subjects, were not published in English or were less than 6 months in duration.

Insulin detemir, a long-acting insulin analogue, was associated with a low incidence (<1%) of severe hypoglycemia, consistent with another systematic review (also including only studies of at least 6 months duration) which reported an incidence of 1.2% (7/578) in two studies.[66] However, a third review reported an incidence of severe hypoglycemia of 3.0% in four RCTs with a total of 1247 patients.[65] Since this review included studies as short as 12 weeks in duration and hypoglycemic episodes are known to occur more frequently during initiation of therapy, this may explain the discrepancy between the reviews.

Insulin glargine was evaluated in eight studies. Results from three long term studies (pooled incidence 4.1%, 95% CI 1.9 to 8.4%, N=1223) and five short-term studies (pooled incidence 1.6%, 95% CI 0.8 to 3.2%, N=13,088) are consistent with the findings of two other recent meta-analyses in which risk of severe hypoglycemia with glargine was found to be 3.2%[65] and 1.9%.[66]

Among the s*hort (or fast) acting insulin analogues (lispro, aspart, glulisine)*, for *lispro*, the pooled incidence of severe hypoglycemia was 3.6% (95% CI 2.3 to 5.4%, N=1198) over a weighted average follow-up time of 1.3 years. For *aspart*, the pooled incidence of severe hypoglycemia was 0.2% (95% CI 0.2% to 0.2%, N=54,425) over a weighted average follow-up time of 6 months; this analysis however was dominated by a very large observational study conducted in physician offices in 11 countries and funded by a pharmaceutical company.[22] If the analysis is repeated without this study the incidence is 1.5% (95% CI 0.9 to 2.5%) over a weighted mean average follow-up of years 1.2 years. For *glulisine* (combined with NPH insulin) the incidence of severe hypoglycemia was 1.0% (95% CI 0.5 % to 2.1%, N=883) over a weighted average follow-up time of 6 months.

In a meta-analysis comparing these insulins with either non-insulin agents, premixed human insulin, or long-acting insulin analogues in adults with type 2 diabetes, Qayyum found that there was no significant difference in risk of serious hypoglycemia.[138] A Canadian health technology report came to a similar conclusion, stating that there was no significant difference in severe hypoglycemia between treatment with human insulin or the insulin analogues.[68] A Cochrane review reported a median incidence of 0.3 severe hypoglycemic episodes (range 0 to 30.3) per 100 patient-years.[67] The authors attributed the wide range to the inclusion of a single study with a very short duration of follow-up.

Key Question #1 Extension

Of the additional 16 studies reviewed to gain a broader population-based perspective on incidence of severe hypoglycemia, 13 were survey studies reporting patient-recalled rates. Eleven of these asked patients to report on events in the past 6 months (N=6) to 1 year (N=5). In these 11 studies,

patient reported incidences of HA varied widely from 1% to 17%. Although hypoglycemic agents are among the most commonly implicated drugs in adverse event reports and ER visits (see Key Question #3 discussion), these data do not cast any light on incidence. In the two studies least likely to be affected by recall bias, one which recorded events within the past 2 weeks[86] and the prospective study in Scotland,[72] the incidence of symptomatic hypoglycemia was 14% over 2 weeks in the former and 3% over one month in the latter. The discrepancy is likely due to Donnelly et al.'s more restrictive definition of hypoglycemia (HA as opposed to symptomatic only).

VA Specific Data

Among the studies included herein, four reported specifically on VA patients.[5, 30, 74, 75] In addition we identified two VA publications which did not meet our inclusion criteria. One was an unpublished abstract examining VA administrative data reporting that 22% of 1.4 million veterans with diabetes had a hypoglycemic associated medical encounter over 5 years. It is unclear from the abstract how the diagnoses were confirmed and what the severity of the episodes were. The second, published after our search was concluded, evaluated the incidence of hypoglycemia as determined by administrative records in 497,900 veterans aged 65 or older.[139] That study found that 7.5% of subjects had one or more inpatient or outpatient visits in which a code for hypoglycemia was recorded over 24 months.

Although suggestive of increased rates of hypoglycemia among veterans with diabetes, it is difficult to derive definitive conclusions from these VA studies since there is substantial heterogeneity with respect to definitions of hypoglycemia, study design, subject inclusion criteria, treatment regimens and lengths of follow-up.

Limitations of Available Studies

Much of the evidence comes from reports of RCTs funded by pharmaceutical companies which enroll highly selected populations and generally do not include those at highest risk for hypoglycemia. Second, the definitions of severe hypoglycemia varied among studies and there is likely substantial ascertainment bias, especially in the RCTs designed primarily to measure the benefits of specific drug regimens. Finally, there are few studies that investigated regular insulin, generally thought to be associated with high rates of hypoglycemia.

Conclusion for Key Question #1

The incidence of severe hypoglycemia is about 0-3% per year for adults with type 2 diabetes on hypoglycemic medications. Risk is highest for insulins, sulfonylureas and regimens targeting intensive control of HbA1c levels. Risk is lowest for metformin, GLP-1 analogs, DPP-4 inhibitors, glinides and TZDs. Since most of these data are derived from pharmaceutical company funded RCTS which enrolled highly selected populations, the generalizability of the results is unclear. Indeed, one small population based prospective study suggests that the incidence may be as high as 3% per month in community based subjects treated with insulin.[72] Furthermore, several studies performed in VA suggest that incidence of hypoglycemia may be higher in this population. Larger population-based prospective studies of people on a variety of hypoglycemic agents that employ accurate methods for ascertaining incidence of severe hypoglycemia should be performed.

Even with this relatively low incidence of severe hypoglycemia, given the high prevalence of diabetes in the general population[1] and in the VA, there are likely tens of thousands of people in the US experiencing severe hypoglycemia every year. These episodes tend to be frightening, and may lead to more severe consequences (see Key Question #3 below) and to reluctance to pursue optimal blood sugar control.[140] They may also be associated with significant costs to the health care system.[141]

Key Question #2: What are the risk factors for severe hypoglycemia in adults with type 2 diabetes on one or more hypoglycemic agents (e.g., demographics, co-morbidities, diabetes treatment regimen, other medication use, goal and achieved HbA1c)?

We identified 14 articles from 12 studies that reported multivariate adjusted risk factor analyses for severe hypoglycemia in adults with type 2 diabetes on hypoglycemic mediations. Since these varied considerably with respect to risk factors evaluated (and their definitions), populations studied, and lengths of follow-up, the data were considered unsuitable for pooling. Transient causes (e.g., missed meal, excess exercise, alcohol use, acute infection) were not included.[142]

The factors evaluated in the 12 multivariate analyses are discussed below. In addition, genetic markers, marital status, smoking, alcohol consumption, polypharmacy, recent discharge from the hospital, congestive heart failure and use of ACE inhibitors were all identified in at least one of these 12 studies as independent risk factors for severe hypoglycemia. However, the findings for these risk factors were generally sparse, often conflicting, and ultimately inconclusive.

Independent Risk Factors

Factors most consistently and independently associated with risk include: intensive glycemic control (discussed above under Key Question #1), history of hypoglycemia, renal insufficiency, history of microvascular complications, longer diabetes duration, lower education level, African American race and history of dementia. History of hypoglycemia unawareness, gender, age and BMI are not consistently associated with risk, although higher age and lower BMI were associated with higher risk in the two largest studies.

Previous hypoglycemia which was evaluated in four studies, appears to be one of the strongest risk factors for a severe hypoglycemic event (three to nine-fold increased risk) and is often listed as a well known risk factor in reviews of this topic.[142, 143] Repeated episodes of hypoglycemia are thought to lead to autonomic insufficiency, a state in which patients become unaware of the common symptoms of low blood sugar, such as palpitations and lightheadedness. This unawareness may then lead to failure to take corrective action resulting in more episodes, thus establishing a vicious cycle.[144]

Renal insufficiency was evaluated in seven studies, five of which found it to be a significant independent risk factor for severe hypoglycemia. The two studies that did not find a significant association were either very small[102] or recorded very few episodes of severe hypoglycemia.[100] Renal insufficiency is a well known risk factor for hypoglycemia; the reduced clearance of insulin in the diseased kidney causes relative hyperinsulinemia which can lead to hypoglycemia.[141, 143] Hypoglycemia in renal insufficiency may also be due to reduced clearance of antidiabetic agents[145] and a decrease in renal gluconeogenesis.[146]

The relationship between renal insufficiency, hypoglycemic agents and incidence of severe hypoglycemia, however, is complicated. A nested case control study of 558 people with diabetes over the age of 65 on insulin, metformin or glyburide investigated whether renal function was an effect modifier for the association between glyburide or insulin use and hypoglycemia.[147] Since the study did not distinguish between severe and other forms of hypoglycemia, it was not included in our review. Results indicated that while renal function did not significantly modify risk of glyburide associated hypoglycemia, risk of insulin-associated hypoglycemia was, unexpectedly, attenuated by renal dysfunction.

The relationship between *non-renal microvascular disease* and severe hypoglycemia was evaluated in five studies. In three of the five studies, there were significant positive associations between peripheral neuropathy (or its manifestation, leg ulcerations) and risk of severe hypoglycemia with risk ratios in the 1.2 to 2.4 range; the largest of these three studies, ACCORD,[3] found the lowest risk. In a fourth study, "history of microvascular disease," which also included renal disease, conferred a twofold increased risk of severe hypoglycemia (HR 2.1, 95% CI 1.5 to 3).[4] The pathophysiologic mechanism underlying this association is unclear. Although microvascular complications are an indicator of longstanding diabetes, duration of diabetes was often controlled for in these analyses.

Diabetes duration was associated with a modestly increased risk for severe hypoglycemia in studies (with odds ratios of less than 2) and is thought to be due to the compromised ability of people with advanced type 2 diabetes to mount an appropriate counter-regulatory hormonal (insulin, epinephrine, and glucagon) response to low blood sugar.[141, 143]

Demographic variables such as *African American race* and *lower education level* were both independently associated with a modestly increased risk of severe hypoglycemia. In the studies that evaluated race, blacks were significantly more likely than whites to experience severe hypoglycemia, with relative risks of 1.4 to 2.0. This association was independent of other known risk factors, such as education, that may track with race.[89]

Four of five studies that evaluated education, reported significant positive associations between lower education level and risk of severe hypoglycemia. One of these found the risk associated with low literacy rates, a more specific construct than education level, was associated with close to a four-fold increased risk. However this study was a case-control study that included fewer than 300 subjects leading to wide confidence intervals around the odds ratio.[104] It has been speculated that persons with low levels of education and literacy may not fully understand how to take their hypoglycemic medications or how to treat incipient hypoglycemia.

Dementia was found to be an independent risk factor for severe hypoglycemia in two of three studies. As is expected based on sample size, the much larger of these two studies (N=11,140)[4] found a modestly increased risk with a very tight confidence interval, whereas the smaller study (N=302),[92] found a larger risk with a very wide confidence interval. The only study that did not find an association was very small.[103] In addition, an article from ACCORD that was not included in our review because it was published in 2012, also found a significant association between poor cognitive function and risk of HMA.[148] Dementia may increase the likelihood of errors in self-medication and of inability to recognize and treat incipient hypoglycemia.[141]

Risk Factors NOT Found to be Independently Associated with Risk

Gender, age and low BMI were not consistently associated with risk, although age and low BMI were significantly predictive of risk of severe hypoglycemia in the two largest trials.[3, 4] It has been suggested that older people may be at increased risk due to diminished counter-regulatory and autonomic system responses to low blood sugar[149] and may be more likely to suffer from hypoglycemia unawareness.[150] Low BMI may contribute to hypoglycemia because of poor nutrition, decreased glucose absorption, or erratic meal plans. In contrast to age and BMI, the results for gender were conflicting in the two large trials: ACCORD found that women were at modestly increased risk compared with men whereas ADVANCE found no significant difference between men and women.

Impaired hypoglycemic awareness was only evaluated in one of our included studies.[84] Although this study found a significant increased risk, it employed a weak study design (cross sectional) and had relatively few subjects (N=401).

Other Literature

We did not identify any other systematic reviews that evaluated risk factors for severe hypoglycemia in people with type 2 diabetes. One literature survey included six prospective and five retrospective studies that enrolled at least 50 participants all on insulin followed for at least 6 months.[151] The risk factors identified included impaired hypoglycemia awareness, advanced age, longer duration of diabetes and of insulin therapy. HbA1c at baseline and dose of insulin were not found to increase risk. However this study included only insulin treated patients, did not limit its review to studies using multivariate analysis, and antedated publication of the three large trials of intensive versus conventional control.

An unpublished abstract examining VA administrative data reported the following risk factors for an inpatient or outpatient diagnosis of hypoglycemia: prior hypoglycemia, history of ketoacidosis or hyperosmolar coma, high HbA1c levels, recent initiation of a new medication, recent hospitalization, use of secretagogues, insulin, fluoroquinolones or tricyclic antidepressants, higher age, low SES (which often correlates with education level) and unmarried status. It is unclear from the abstract how the diagnoses were confirmed and what the severity of the episodes were. In addition, a paper published after our literature search was concluded indicated that dementia and cognitive impairment were independent risk factors for hypoglycemia among older veterans,[139] consistent with our findings.

Limitations of Available Studies

The data are relatively sparse and almost certainly reflect publication bias (negative analyses are less likely to be published). In addition we were unable to pool results across studies due to the heterogeneity of the study designs, analytical methods, and risk factors assessed. Finally, only two studies used negative binomial or zero inflated poisson[16, 84, 93] methodology which may be less likely than standard regression techniques to yield spurious associations in situations in which there are frequent zero counts.[152]

Conclusion for Key Question #2

Independent risk factors for severe hypoglycemia in persons with type 2 diabetes on hypoglycemic medication include: intensive diabetes control, history of hypoglycemia, renal insufficiency, history of microvascular complications, longer diabetes duration, lower education level, African American race and history of dementia. Gender, age and BMI are not consistently associated with risk, although in the two largest studies, higher age and lower BMI were significantly associated with higher risk.

Key Question #3. What is the effect of severe hypoglycemia on other outcomes in adults with type 2 diabetes on one or more hypoglycemic agents (e.g., quality of life, mortality, morbidity, utilization)?

Severe hypoglycemia causes brain fuel deprivation that, if uncorrected, can lead to neurological compromise and death.[143] There is uncertainty about a possible link between hypoglycemia and mortality, cardiovascular events, and other adverse health outcomes.[153-155] Based on studies included in this review, we found no evidence of increased short-term mortality and limited evidence that a history of severe hypoglycemia increases long-term mortality. Few cardiovascular events were reported; coma and seizures were present in 5% to 71% of patients with severe hypoglycemia.

A recent study of over 850,000 patients found greater odds of an acute cardiovascular event during a one year period in type 2 diabetic patients who also experienced a hypoglycemic event (not necessarily severe) during that period (OR 1.79, 95% CI 1.69 to 1.89). The analysis included adjustment for baseline cardiovascular risk factors, comorbidities, and prior cardiovascular events (all of which were significantly more prevalent in the hypoglycemia group).[156] In a study of adverse events reported to the Food and Drug Administration from 1998 through 2005, there were 9597 reports of insulin-associated disability or other serious but non-fatal outcome.[157] However, in a study of patients hospitalized with acute MI, not all of whom had diabetes, spontaneous hypoglycemia in patients not treated with insulin was associated with increased risk for mortality; among patients treated with insulin, hypoglycemia was not associated with increased risk for mortality. This would suggest that hypoglycemia, itself, does not cause adverse events but is, instead, a marker of severe illness.[158] People who are likely to experience hypoglycemia may also be likely to experience other serious health outcomes due to other risk factors.[155]

It is well known that cognitive and psychomotor function decline during a hypoglycemic episode.[159, 160] Therefore, it is theorized that driving performance would be affected. However, whether severe hypoglycemia is associated with an increase in motor vehicle crashes is uncertain. Data from early studies are of questionable value as a result of improvements in methods for self-monitoring of blood glucose and changes in available medications.[161] A more recent study found a nearly four-fold increased risk of a history of severe hypoglycemia in those who experienced a motor vehicle crash.[129]

Much of the information about driving performance is from laboratory studies where hypoglycemia is induced and driving simulators are used. In a recent study of 20 type 2 diabetic individuals with normal hypoglycemic awareness (mean age 52 years, all of whom had a driver's

license for at least 2 years), 11 of the 20 felt hypoglycemic. Of those 11, five (45%) said they would measure their blood glucose and six (55%) said they would not drive. Nine of the 20 "maybe" felt hypoglycemic. Of those nine, three (33%) said they would drive, two (22%) said they would "maybe" drive, two (22%) said they would measure their glucose and two (22%) said they would not drive.[130] It is unknown how results from studies of this type translate to actual driving performance or behavior.

Long-term effects of hypoglycemia, especially repeated episodes of severe hypoglycemia, on cognitive performance are not fully understood.[159, 160] Results, to date, in patients with type 2 diabetes have been mixed.[92, 94] The DCCT/EDIC trial in patients with type 1 diabetes found neither frequency of severe hypoglycemia nor initial treatment group assignment (intensive versus conventional therapy) were associated with cognitive decline over 18 years based on a battery of 17 tests representing eight cognitive domains.[162] The ACCORD-MIND study reported no differences in cognitive outcomes between intensive treatment and standard treatment groups at 40 months. The authors did not relate their findings to the presence or absence of severe hypoglycemic episodes.[163]

Data from the Edinburgh Type 2 Diabetes Study were recently published.[164] Participants, all age 60 to75 years, were asked about severe hypoglycemic events. A history of severe hypoglycemia (one or more episodes) was associated with lower cognitive ability as reflected by the Letter-Number Sequencing test ($p=0.03$), the Trail-Making Test ($p=0.004$), and a composite score based on seven cognitive tests ($p=0.04$). Results were adjusted for prior cognitive ability, demographic characteristics and comorbid conditions. Similar findings were noted for the analysis based on severe hypoglycemia in the year preceding cognitive testing.

Potential reasons for differences across studies have been suggested in the literature. Many studies of cognitive function completed to date may not have sufficient follow-up time to adequately address long-term effects.[159] Differences observed between studies may be due to differential effects of hypoglycemia on the brain in younger versus older people.[160] Increased risk of dementia associated with type 2 diabetes may be due to other factors (e.g., depression, vascular disease, comorbid conditions and associated medications and genetic predisposition).[165] Alternatively, an observed association between hypoglycemia and cognitive decline may be due to the fact that patients with cognitive decline may be less able to manage their diabetes and therefore may experience more hypoglycemic events.[159]

Hypoglycemia, particularly severe hypoglycemia, results in utilization of health care resources. In studies included in this review, we observed that between 0% and 31% of episodes of severe hypoglycemia were seen in an emergency department and between 0% and 33% of episodes resulted in hospital admission. Increased physician visits were also reported. A recent systematic review recommended increased hospitalization and primary care visits for post-hypoglycemic patients.[166] Citing the potential for repeat hypoglycemia, as reported in studies of post-hypoglycemic type 2 diabetes patients taking oral hypoglycemic agents and first treated for a hypoglycemic episode in a prehospital environment, the authors recommended conservative management (i.e., transportation of all patients to a hospital for observation and treatment). They also encouraged the development of evidence-based interventions to increase primary or specialty care visits by post-hypoglycemic patients.

In a study examining nationally representative data, Budnitz et al.[167] estimated that insulin, metformin, glyburide and glipizide were implicated in 13%, 2.3%, 2.2%, and 1.5% of all emergency department visits in the United States in persons age 65 and older. These four were among the top 10 most commonly implicated medications.[167] In a more recent study, this group estimated that insulin and oral hypoglycemic agents accounted for 25% of all adverse drug event-associated emergency hospitalizations in the United States in 2007-2009.[168] These studies did not link the emergency department visits or hospitalizations to episodes of severe hypoglycemia.

Limitations of Available Studies

Few studies that address outcomes of severe hypoglycemic episodes include appropriate control groups. In addition, many outcomes of interest were not widely reported.

Conclusion for Key Question #3

There is good data that severe hypoglycemia is associated with an increased risk of the following outcomes: all-cause mortality (particularly long-term), neurological events (other than non-fatal stroke), hospital and emergency department utilization, and decreased quality of life. There is limited data about many other outcomes of interest including non-fatal MI, non-fatal stroke, cognitive decline, motor vehicle accidents, falls and traumatic injuries, work productivity, and other medical service utilization. In the absence of appropriate control groups it is unclear if many of these outcomes are hypoglycemia-related or simply reflect the age and co-morbidity burden of the population.

RECOMMENDATIONS FOR FUTURE RESEARCH

Key Question #1: Larger population-based prospective studies of people on a variety of hypoglycemic agents that employ accurate methods for ascertaining incidence of severe hypoglycemia should be performed. Studies need to control for or stratify outcomes by important patient, disease and comorbidity factors including: age, gender, race/ethnicity, socio-economic and marital status, disease duration and severity (e.g., HbA1c level, presence or absence of diabetic complications).

Key Question #2: Future research should include studies in VA patients and include the more intriguing possible risk factors including smoking or recent hospital discharge. In addition, future research may lead to the development of a risk factor index if outcomes are significant enough to warrant risk stratification.

Key Question #3: Future studies of outcomes associated with severe hypoglycemia should be prospective, use a uniform and generally accepted definition of severe hypoglycemia, and include, as controls, people with medication-treated diabetes who have not experienced severe hypoglycemia. Also, studies should clearly distinguish between short-term or episode-related versus long-term consequences.

Specific future research needs include:

a. To clarify the association between hypoglycemia and cardiovascular events, research is needed to better understand the effects of hypoglycemia on blood constituents and the

vascular system and larger clinical trials are needed to determine whether hypoglycemia is a cause of cardiovascular events.[153, 154] Better understanding of the role of hypoglycemia in patients already at risk for developing vascular disease is also needed.[153]

b. There is a need for a large-scale, prospective study of accident rates in patients with diabetes compared to appropriate control groups.[161] Better understanding is needed of which driving skills are most likely to be affected by hypoglycemia, at what level of blood glucose driving impairments become observable, and whether results obtained in a laboratory translate to road conditions.[134]

c. Additional research is needed to assess the overall effect of hypoglycemia on patients with type 2 diabetes including quality of life outcomes (both work and recreational). To date, much of the research has focused on type 1 diabetes and the emphasis has been on hypoglycemia as a safety issue.[169]

d. To assess the effect of hypoglycemia on cognitive function, large-scale epidemiological studies with detailed phenotyping of clinical variables and randomized trials of interventions (therapeutic and preventive) that include cognitive testing and brain structure/function assessments are needed.[165, 170]

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REFERENCES

1. Danaei G, Finucane MM, Lu Y, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet.* 2011;378(9785):31-40.

2. Miller DR, Safford MM, Pogach LM. Who has diabetes? Best estimates of diabetes prevalence in the Department of Veterans Affairs based on computerized patient data. *Diabetes Care.* 2004;27 Suppl 2:B10-21.

3. Action to Control Cardiovascular Risk in Diabetes Study G, Gerstein HC, Miller ME, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med.* 2008;358(24):2545-2559.

4. Advance, Patel A, MacMahon S, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2008;358(24):2560-2572.

5. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med.* 2009;360(2):129-139.

6. Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Lancet.* 2010;376(9739):419-430.

7. Action to Control Cardiovascular Risk in Diabetes Study G, Gerstein HC, Miller ME, et al. Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med.* 2011;364(9):818-828.

8. Kelly TN, Bazzano LA, Fonseca VA, Thethi TK, Reynolds K, He J. Systematic review: glucose control and cardiovascular disease in type 2 diabetes. *Ann Intern Med.* 2009;151(6):394-403.

9. Hemmingsen B, Lund SS, Gluud C, et al. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2011(6):CD008143.

10. Ray KK, Seshasai SR, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet.* 2009;373(9677):1765-1772.

11. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, et al. 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.* 2011;343:d4169.

12. Pogach L, Aron D. Balancing hypoglycemia and glycemic control: a public health approach for insulin safety. *JAMA.* 2010;303(20):2076-2077.

13. Higgins JP, Green, S., eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (Updated March 2011). In: Higgins JP, Green, S., ed. Vol 5.1.0: The Cochrane Collaboration; 2011: http://www.cochrane-handbook,org. Accessed August 29, 2011.

14. Schulz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. *Lancet.* 2002;359(9306):614-618.

15. Berntorp K, Haglund M, Larsen S, Petruckevitch A, Landin-Olsson M, Swedish BSG. Initiation of biphasic insulin aspart 30/70 in subjects with type 2 diabetes mellitus in a largely primary care-based setting in Sweden. *Primary care diabetes.* 2011;5(2):89-94.

16. Davis TME, Brown SGA, Jacobs IG, Bulsara M, Bruce DG, Davis WA. Determinants of severe hypoglycemia complicating type 2 diabetes: the Fremantle diabetes study. *J Clin Endocrinol Metab.* 2010;95(5):2240-2247.

17. Holstein A, Plaschke A, Egberts EH. Lower incidence of severe hypoglycaemia in patients with type 2 diabetes treated with glimepiride versus glibenclamide. *Diabetes-Metab Res.* 2001;17(6):467-473.

18. Marre M, Pinget M, Gin H, et al. Insulin detemir improves glycaemic control with less hypoglycaemia and no weight gain: 52-week data from the PREDICTIVE study in a cohort of French patients with type 1 or type 2 diabetes. *Diabetes Metab.* 2009;35(6):469-475.

19. Murata GH, Duckworth WC, Shah JH, Wendel CS, Mohler MJ, Hoffman RM. Hypoglycemia in stable, insulin-treated veterans with type 2 diabetes: a prospective study of 1662 episodes. *J Diabetes Complicat.* 2005;19(1):10-17.

20. Pencek R, Roddy T, Peters Y, et al. Safety of pramlintide added to mealtime insulin in patients with type 1 or type 2 diabetes: a large observational study. *Diabetes Obes Metab.* 2010;12:548-551.

21. UK Prospective Diabetes Study Group U. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet.* 1998;352:837-853.

22. Valensi P, Benroubi M, Borzi V, et al. Initiating insulin therapy with, or switching existing insulin therapy to, biphasic insulin aspart 30/70 (NovoMix 30) in routine care: safety and effectiveness in patients with type 2 diabetes in the IMPROVE observational study. *Int J Clin Pract.* 2009;63(3):522-531.

23. Asche CV, McAdam-Marx C, Shane-McWhorter L, Sheng X, Plauschinat CA. Evaluation of adverse events of oral antihyperglycemic monotherapy experienced by a geriatric population in a real-world setting: a retrospective cohort analysis. *Drugs Aging.* 2008;25(7):611-622.

24. Bodmer M, Meier C, Kr, et al. Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case-control analysis. *Diabetes Care.* 2008;31(11):2086-2091.

25. Leese GP, Wang J, Broomhall J, et al. Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use. *Diabetes Care.* 2003;26(4):1176-1180.

26. Nichols GA, Gandra SR, Chiou C-F, Anthony MS, Alexander-Bridges M, Brown JB. Successes and challenges of insulin therapy for type 2 diabetes in a managed-care setting. *Curr Med Res Opin.* 2010;26(1):9-15.

27. Quilliam BJ, Simeone JC, Ozbay AB. Risk Factors for Hypoglycemia-Related Hospitalization in Patients with Type 2 Diabetes: A Nested Case-Control Study. *Clin Ther.* 2011.

28. Stahl M, Berger W. Higher incidence of severe hypoglycaemia leading to hospital admission in Type 2 diabetic patients treated with long-acting versus short-acting sulphonylureas. *Diabetic Med.* 1999;16(7):586-590.

29. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *The Lancet.* 1998;352(9131):854-865.

30. Abraira C, Colwell JA, Nuttall FQ, et al. Veterans Affairs Cooperative Study on glycemic control and complications in type II diabetes (VA CSDM). Results of the feasibility trial. Veterans Affairs Cooperative Study in Type II Diabetes. *Diabetes Care.* 1995;18(8):1113-1123.

31. Raskin P, Gylvin T, Weng W, Chaykin L. Comparison of insulin detemir and insulin glargine using a basal-bolus regimen in a randomized, controlled clinical study in patients with type 2 diabetes. *Diabetes-Metab Res.* 2009;25(6):542-548.

32. Drouin P, Standl E, Group tDMS. Gliclazide modified release: results of a 2-year study of patients with type 2 diabetes. *Diabetes Obes Metab.* 2004;6:414-421.

33. Haak T, Tiengo A, Draeger E, Suntum M, Waldhausl W. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. *Diabetes Obes Metab.* 2005;7(1):56-64.

34. Ratner RE, Want LL, Fineman MS, et al. Adjunctive therapy with the amylin analogue pramlintide leads to a combined improvement in glycemic and weight control in insulin-treated subjects with type 2 diabetes. *Diabetes Technol The* 2002;4(1):51-61.

35. Rosenstock J, Fonseca V, McGill JB, et al. Similar progression of diabetic retinopathy with insulin glargine and neutral protamine Hagedorn (NPH) insulin in patients with type 2 diabetes: a long-term, randomised, open-label study. *Diabetologia.* 2009;52(9):1778-1788.

36. Buse JB, Wolffenbuttel BHR, Herman WH, et al. The DURAbility of Basal versus Lispro mix 75/25 insulin Efficacy (DURABLE) trial: comparing the durability of lispro mix 75/25 and glargine. *Diabetes Care.* 2011;34(2):249-255.

37. Kennedy L, Herman WH, Strange P, Harris A, Team GA. Impact of active versus usual algorithmic titration of basal insulin and point-of-care versus laboratory measurement of HbA1c on glycemic control in patients with type 2 diabetes: the Glycemic Optimization with Algorithms and Labs at Point of Care (GOAL A1C) trial. *Diabetes Care.* 2006;29(1):1-8.

38. Davies M, Storms F, Shutler S, Bianchi-Biscay M, Gomis R, Group AS. Improvement of glycemic control in subjects with poorly controlled type 2 diabetes: comparison of two treatment algorithms using insulin glargine. *Diabetes Care.* 2005;28(6):1282-1288.

39. Rosenstock J, Schwartz SL, Clark CM, Jr., Park GD, Donley DW, Edwards MB. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. *Diabetes Care.* 2001;24(4):631-636.

40. Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetologia.* 2008;51(3):408-416.

41. Riddle MC, Rosenstock J, Gerich J, Insulin Glargine Study I. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care.* 2003;26(11):3080-3086.

42. Heine RJ, Van Gaal LF, Johns D, et al. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med.* 2005;143(8):559-569.

43. Holman RR, Farmer AJ, Davies MJ, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med.* 2009;361(18):1736-1747.

44. Fritsche A, Schweitzer MA, x00E, ring H-U, Study G. Glimepiride combined with morning insulin glargine, bedtime neutral protamine hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes. A randomized, controlled trial. *Ann Intern Med.* 2003;138(12):952-959.

45. Rayman G, Profozic V, Middle M. Insulin glulisine imparts effective glycaemic control in patients with Type 2 diabetes. *Diabetes Res Clin Pr.* 2006;76:304-312.

46. Dailey GE, 3rd, Noor MA, Park J-S, Bruce S, Fiedorek FT. Glycemic control with glyburide/metformin tablets in combination with rosiglitazone in patients with type 2 diabetes: a randomized, double-blind trial. *Am J Med.* 2004;116(4):223-229.

47. Anderson JH, Jr., Brunelle RL, Keohane P, et al. Mealtime treatment with insulin analog improves postprandial hyperglycemia and hypoglycemia in patients with non-insulin-dependent diabetes mellitus. Multicenter Insulin Lispro Study Group. *Arch Int Med.* 1997;157(11):1249-1255.

48. Liebl A, Prager R, Binz K, et al. Comparison of insulin analogue regimens in people with type 2 diabetes mellitus in the PREFER study: a randomized controlled trial. *Diabetes Obes Metab.* 2009;11:45-52.

49. Matthews DR, Dejager S, Ahren B, et al. Vildagliptin add-on to metformin produces similar efficacy and reduced hypoglycaemic risk compared with glimepiride, with no weight gain: results from a 2-year study. *Diabetes Obes Metab.* 2010;12(9):780-789.

50. Seck T, Nauck M, Sheng D, et al. Safety and efficacy of treatment with sitagliptin or glipizide in patients with type 2 diabetes inadequately controlled on metformin: a 2-year study. *Int J Clin Pract.* 2010;64(5):562-576.

51. Garber A, Henry RR, Ratner R, et al. Liraglutide, a once-daily human glucagon-like peptide 1 analogue, provides sustained improvements in glycaemic control and weight for 2 years as monotherapy compared with glimepiride in patients with type 2 diabetes. *Diabetes Obes Metab.* 2011;13(4):348-356.

52. Arechavaleta R, Seck T, Chen Y, et al. Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: a randomized, double-blind, non-inferiority trial. *Diabetes Obes Metab.* 2011;13(2):160-168.

53. Nauck M, Frid A, Hermansen K, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. *Diabetes Care.* 2009;32(1):84-90.

54. Russell-Jones D, Vaag A, Schmitz O, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. *Diabetologia.* 2009;52(10):2046-2055.

55. Chou HS, Palmer JP, Jones AR, et al. Initial treatment with fixed-dose combination rosiglitazone/glimepiride in patients with previously untreated type 2 diabetes. *Diabetes Obes Metab.* 2008;10(8):626-637.

56. Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care.* 2005;28(5):1083-1091.

57. Schernthaner G, Grimaldi A, Di Mario U, et al. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. *Eur J Clin Invest.* 2004;34(8):535-542.

58. Bari2D, Frye RL, August P, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med.* 2009;360(24):2503-2515.

59. Saloranta C, Hershon K, Ball M, Dickinson S, Holmes D. Efficacy and safety of nateglinide in type 2 diabetic patients with modest fasting hyperglycemia. *J Clin Endocrinol Metab.* 2002;87(9):4171-4176.

60. Aschner P, Katzeff HL, Guo H, et al. Efficacy and safety of monotherapy of sitagliptin compared with metformin in patients with type 2 diabetes. *Diabetes Obes Metab.* 2010;12(3):252-261.

61. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *BMJ.* 2010;340:b4909.

62. Waugh N, Cummins E, Royle P, et al. Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. *Health Technol Assess.* 2010;14(36):1-248.

63. Shyangdan DS, Royle P, Clar C, Sharma P, Waugh N, Snaith A. Glucagon-like peptide analogues for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2011(10):CD006423.

64. Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch CL. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2008(2):CD006739.

65. Swinnen SG, Simon AC, Holleman F, Hoekstra JB, Devries JH. Insulin detemir versus insulin glargine for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2011(7):CD006383.

66. Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2007(2):CD005613.

67. Siebenhofer A, Plank J, Berghold A, et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. *Cochrane Database Syst Rev.* 2006(2):CD003287.

68. Tran K BS, Li H, Cimon K, Daneman D, Simpson SH, Campbell K. *Long-active insulin analogues for diabetes mellitus: meta-analysis of clinical outcomes and assessment of costeffectiveness* [Technoogy Report no 87]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2007.

69. Goudswaard AN, Furlong NJ, Rutten GE, Stolk RP, Valk GD. Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2004(4):CD003418.

70. Clar C, Royle P, Waugh N. Adding pioglitazone to insulin containing regimens in type 2 diabetes: systematic review and meta-analysis. *PLoS One.* 2009;4(7):e6112.

71. Black C, Donnelly P, McIntyre L, Royle PL, Shepherd JP, Thomas S. Meglitinide analogues for type 2 diabetes mellitus. *Cochrane Database Syst Rev.* 2007(2):CD004654.

72. Donnelly LA, Morris AD, Frier BM, et al. Frequency and predictors of hypoglycaemia in Type 1 and insulin-treated Type 2 diabetes: a population-based study. *Diabetic Med.* 2005;22(6):749-755.

73. Chan S-P, Ji L-N, Nitiyanant W, Baik SH, Sheu WHH. Hypoglycemic symptoms in patients with type 2 diabetes in Asia-Pacific-Real-life effectiveness and care patterns of diabetes management: the RECAP-DM study. *Diabetes Res Clin Pr.* 2010;89(2):e30-32.

74. Neil BJ, Baines A, Clothier B, Nelson DB, Bloomfield HE. Self-Monitoring of Blood Glucose in Diabetic Patients Not Taking Insulin: Does It Affect Hypoglycemia? *Federal Practitioner.* 2007 2007:27-33.

75. Moen MF, Zhan M, Hsu VD, et al. Frequency of Hypoglycemia and Its Significance in Chronic Kidney Disease. *Clin J Am Soc Nephrol.* 2009;4:1121-1127.

76. Henderson JN, Allen KV, Deary IJ, Frier BM. Hypoglycaemia in insulin-treated Type 2 diabetes: frequency, symptoms and impaired awareness. *Diabetic Med.* 2003;20(12):1016-1021.

77. Honkasalo M, Elonheimo O, Sane T. Many diabetic patients with recurrent severe hypoglycemias hold a valid driving license. A community-based study in insulin-treated patients with diabetes. *Traffic Injury Prevention.* 2010;11(3):258-262.

78. Sarkar U, Karter AJ, Liu JY, Moffet HH, Adler NE, Schillinger D. Hypoglycemia is more common among type 2 diabetes patients with limited health literacy: the Diabetes Study of Northern California (DISTANCE). *J Gen Inern Med.* 2010;25(9):962-968.

79. Lecomte P, Romon I, Fosse S, Simon D, Fagot-Campagna A. Self-monitoring of blood glucose in people with type 1 and type 2 diabetes living in France: the Entred study 2001. *Diabetes Metab.* 2008;34(3):219-226.

80. Jennings AM, Wilson RM, Ward JD. Symptomatic hypoglycemia in NIDDM patients treated with oral hypoglycemic agents. *Diabetes Care.* 1989;12(3):203-208.

81. Marrett E, Stargardt T, Mavros P, Alexander CM. Patient-reported outcomes in a survey of patients treated with oral antihyperglycaemic medications: associations with hypoglycaemia and weight gain. *Diabetes Obes Metab.* 2009;11(12):1138-1144.

82. Pettersson B, Rosenqvist U, Deleskog A, Journath G, Wandell P. Self-reported experience of hypoglycemia among adults with type 2 diabetes mellitus (Exhype). *Diabetes Res Clin Pr.* 2011;92(1):19-25.

83. Stargardt T, Gonder-Frederick L, Krobot KJ, Alexander CM. Fear of hypoglycaemia: defining a minimum clinically important difference in patients with type 2 diabetes. *Health Qual Life Out.* 2009;7:91.

84. Akram K, Pedersen-Bjergaard U, Carstensen B, Borch-Johnsen K, Thorsteinsson B. Frequency and risk factors of severe hypoglycaemia in insulin-treated Type 2 diabetes: a cross-sectional survey. *Diabetic Med.* 2006;23(7):750-756.

85. Alvarez Guisasola F, et al. Hypoglycaemic symptoms, treatment satisfaction, adherence and their associations with glycaemic goal in patients with type 2 diabetes mellitus: findings from the Real-Life Effectiveness and Care Patterns of Diabetes Management (RECAP-DM) Study. *Diabetes Obes Metab.* 2008;10 Suppl 1:25-32.

86. Williams SA, Pollack MF, Dibonaventura M. Effects of hypoglycemia on health-related quality of life, treatment satisfaction and healthcare resource utilization in patients with type 2 diabetes mellitus. *Diabetes Res Clin Pr.* 2011;91(3):363-370.

87. Marrett E, Radican L, Davies MJ, Zhang Q. Assessment of severity and frequency of self-reported hypoglycemia on quality of life in patients with type 2 diabetes treated with oral antihyperglycemic agents: A survey study. *BMC Research Notes.* 2011;4(251).

88. Lee LJ, Yu AP, Johnson SJ, et al. Direct costs associated with initiating NPH insulin versus glargine in patients with type 2 diabetes: a retrospective database analysis. *Diabetes Res Clin Pr.* 2010;87(1):108-116.

89. Miller ME, Bonds DE, Gerstein HC, et al. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. *BMJ.* 2010;340-4.

90. Zoungas S, Patel A, Chalmers J, et al. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med.* 2010;363(15):1410-1418.

91. Stratton I MS, Holman R, Turner R. Hypertenstion in Diabetes Study IV. Therapeutic requirements to maintain tight blood pressure control. *Diabetologia.* 1996;39:1554-1561.

92. Bruce DG, Davis WA, Casey GP, et al. Severe hypoglycaemia and cognitive impairment in older patients with diabetes: the Fremantle Diabetes Study. *Diabetologia.* 2009;52(9):1808-1815.

93. Davis WA, Brown SGA, Jacobs IG, et al. Angiotensin-converting enzyme insertion/deletion polymorphism and severe hypoglycemia complicating type 2 diabetes: the Fremantle Diabetes Study. *J Clin Endocrinol Metab.* 2011;96(4):E696-700.

94. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP, Jr., Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA.* 2009;301(15):1565-1572.

95. Fadini GP, Rigato M, Tiengo A, Avogaro A. Characteristics and mortality of type 2 diabetic patients hospitalized for severe iatrogenic hypoglycemia. *Diabetes Res Clin Pr.* 2009;84(3):267-272.

96. Sugarman JR. Hypoglycemia associated hospitalizations in a population with a high prevalence of non-insulin-dependent diabetes mellitus. *Diabetes Res Clin Pr.* 1991;14(2):139-147.

97. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Incidence and Risk Factors for Serious Hypoglycemia in Older Persons Using Insulin or Sulfonylureas. *Arch Intern Med.* 1997;157:1681-1686.

98. Stepka M, Rogala H, Czyzyk A. Hypoglycemia: a major problem in the management of diabetes in the elderly. *Aging-Clin Exp Res.* 1993;5(2):117-121.

99. Hepburn DA, MacLeod KM, Pell AC, Scougal IJ, Frier BM. Frequency and symptoms of hypoglycaemia experienced by patients with type 2 diabetes treated with insulin. *Diabetic Med.* 1993;10(3):231-237.

100. Miller CD, Phillips LS, Ziemer DC, Gallina DL, Cook CB, El-Kebbi IM. Hypoglycemia in patients with type 2 diabetes mellitus. *Arch Int Med.* 2001;161(13):1653-1659.

101. Shen JJ, Washington EL. Identification of diabetic complications among minority populations. *Ethnic Dis.* 2008;18(2):136-140.

102. Holstein A, Hahn M, Stumvoll M, Kovacs P. The E23K variant of KCNJ11 and the risk for severe sulfonylurea-induced hypoglycemia in patients with type 2 diabetes. *Hormone Metab Res.* 2009;41(5):387-390.

103. Holstein A, Hahn M, Patzer O, Seeringer A, Kovacs P, Stingl J. Impact of clinical factors and CYP2C9 variants for the risk of severe sulfonylurea-induced hypoglycemia. *Eur J Clin Pharmacol.* 2011;67(5):471-476.

104. Duran-Nah JJ, Rodriguez-Morales A, Smitheram J, Correa-Medina C. Risk factors associated with sympotmatic hyopglycemia in type 2 diabetes mellitus patients. *Revista de Investigacion.* 2008;60(6):451-458.

105. Asplund K, Wiholm BE, Lundman B. Severe hypoglycaemia during treatment with glipizide. *Diabetic Med.* 1991;8(8):726-731.

106. Sato H, Lattermann R, Carvalho G, et al. Perioperative glucose and insulin administration while maintaining normoglycemia (GIN therapy) in patients undergoing major liver resection. *Anes Analg.* 2010;110(6):1711-1718.

107. Holstein A, Plaschke A, Hammer C, Egberts EH. Characteristics and time course of severe glimepiride- versus glibenclamide-induced hypoglycaemia. *Eur J Clin Pharmacol.* 2003;59(2):91-97.

108. Sotiropoulos A, Skliros EA, Tountas C, Apostolou U, Peppas TA, Pappas SI. Risk factors for severe hypoglycaemia in type 2 diabetic patients admitted to hospital in Piraeus, Greece. *Eastern Mediterranean Health Journal.* 2005;11(3):485-489.

109. Holstein A, Plaschke A, Egberts EH. Clinical characterisation of severe hypoglycaemia—a prospective population-based study. *Exp Clin Endocr Diab.* 2003;111(6):364-369.

110. Buse JB, Wolffenbuttel BHR, Herman WH, et al. DURAbility of basal versus lispro mix 75/25 insulin efficacy (DURABLE) trial 24-week results: safety and efficacy of insulin lispro mix 75/25 versus insulin glargine added to oral antihyperglycemic drugs in patients with type 2 diabetes. *Diabetes Care.* 2009;32(6):1007-1013.

111. Holman RR, Thorne KI, Farmer AJ, et al. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med.* 2007;357(17):1716-1730.

112. Raslova K, Bogoev M, Raz I, Leth G, Gall MA, Hancu N. Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes. *Diabetes Res Clin Pr.* 2004;66(2):193-201.

113. Williams-Herman D, Johnson J, Teng R, et al. Efficacy and safety of initial combination therapy with sitagliptin and metformin in patients with type 2 diabetes: a 54-week study. *Curr Med Res Opin.* 2009;25(3):569-583.

114. Lee WC, Balu S, Cobden D, Joshi AV, Pashos CL. Medication adherence and the associated health-economic impact among patients with type 2 diabetes mellitus converting to insulin pen therapy: an analysis of third-party managed care claims data. *Clin Ther* 2006;28(10):1712-1725; discussion 1710-1711.

115. Goh HK, Chew DEK, Miranda IG, Tan L, Lim GH. 24-Hour observational ward management of diabetic patients presenting with hypoglycaemia: a prospective observational study. *Emerg Med J.* 2009;26(10):719-723.

116. Gurlek A, Erbas T, Gedik O. Frequency of severe hypoglycaemia in type 1 and type 2 diabetes during conventional insulin therapy. *Exp Clin Endocr Diab.* 1999;107(3):220-224.

117. Panikar V, Chandalia HB, Joshi SR, Fafadia A, Santvana C. Beneficial effects of triple drug combination of pioglitazone with glibenclamide and metformin in type 2 diabetes mellitus patients on insulin therapy. *J Assoc Physician India.* 2003;51:1061-1064.

118. Rhoads GG, Orsini LS, Crown W, Wang S, Getahun D, Zhang Q. Contribution of hypoglycemia to medical care expenditures and short-term disability in employees with diabetes. *J Occup Environ Med.* 2005;47(5):447-452.

119. Alvarez-Guisasola F, Yin DD, Nocea G, Qiu Y, Mavros P. Association of hypoglycemic symptoms with patients' rating of their health-related quality of life state: a cross sectional study. *Health Qual Life Out.* 2010;8:86.

120. Davis RE, Morrissey M, Peters JR, Wittrup-Jensen K, Kennedy-Martin T, Currie CJ. Impact of hypoglycaemia on quality of life and productivity in type 1 and type 2 diabetes. *Curr Med Res Opin.* 2005;21(9):1477-1483.

121. Harsch IA, Stocker S, Radespiel T, et al. Traffic hypoglycaemias and accidents in patients with diabetes mellitus treated with different antidiabetic regimens. *J Intern Med.* 2002;252(4):352-360.

122. Hermanns N, Kulzer B, Krichbaum M, Kubiak T, Haak T. Affective and anxiety disorders in a German sample of diabetic patients: prevalence, comorbidity and risk factors. *Diabet Med.* 2005;22(3):293-300.

123. Labad J, Price JF, Strachan MWJ, et al. Symptoms of depression but not anxiety are associated with central obesity and cardiovascular disease in people with type 2 diabetes: the Edinburgh Type 2 Diabetes Study. *Diabetologia.* 2010;53(3):467-471.

124. Leiter L YJ-F, Chiason J-L, Harris S, Kleinstiver P, Saauriol L. Assessment of the impact of fear of hypoglycemic episodes on glycemic and hypoglycemia management. *Can J Diabetes.* 2005;29(3):1-7.

125. Lundkvist J, Berne C, Bolinder B, Jonsson L. The economic and quality of life impact of hypoglycemia. *Eur J of Health Econ.* 2005;6(3):197-202.

126. Vexiau P, Mavros P, Krishnarajah G, Lyu R, Yin D. Hypoglycaemia in patients with type 2 diabetes treated with a combination of metformin and sulphonylurea therapy in France. *Diabetes Obes Metab.* 2008;10 Suppl 1:16-24.

127. Ben-Ami H, Nagachandran P, Mendelson A, Edoute Y. Drug-induced hypoglycemic coma in 102 diabetic patients. *Arch Intern Med.* 1999;159(3):281-284.

128. Greco D, Pisciotta M, Gambina F, Maggio F. Severe hypoglycaemia leading to hospital admission in type 2 diabetic patients aged 80 years or older. *Exp Clin Endocr Diab.* 2010;118(4):215-219.

129. Redelmeier DA, Kenshole AB, Ray JG. Motor vehicle crashes in diabetic patients with tight glycemic control: a population-based case control analysis. *PLoS Med* 2009;6(12):e1000192.

130. Stork ADM, van Haeften TW, Veneman TF. The decision not to drive during hypoglycemia in patients with type 1 and type 2 diabetes according to hypoglycemia awareness. *Diabetes Care.* 2007;30(11):2822-2826.

131. Zargar AH, Wani AI, Masoodi SR, et al. Causes of mortality in diabetes mellitus: data from a tertiary teaching hospital in India. *Postgrad Med.* 2009;85(1003):227-232.

132. Dailey G, Strange P, Riddle M. Reconsideration of severe hypoglycemic events in the treat-to-target trial. *Diabetes Tech Ther.* 2009;11(8):477-479.

133. Cobden D, Lee WC, Balu S, Joshi AV, Pashos CL. Health outcomes and economic impact of therapy conversion to a biphasic insulin analog pen among privately insured patients with type 2 diabetes mellitus. *Pharmacotherapy.* 2007;27(7):948-962.

134. Daly P KL, Lorber D. *FMCSA Expert Panel Commentary and Recommendations: Diabetes and CMV Drive Safety* 2006.

135. Hemmelgarn B, Levesque LE, Suissa S. Anti-Diabetic Drug Use and the Risk of Motor Vehicle Crash in the Elderly. *Can J Clin Pharmacol.* 2006;13(1):e112-e120.

136. Aschner P, Kipnes MS, Lunceford JK, et al. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care.* 2006;29(12):2632-2637.

137. Bennett WL, Maruthur NM, Singh S, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. *Ann Intern Med.* 3 2011;154(9):602-613.

138. Qayyum R, Bolen S, Maruthur N, et al. Systematic review: comparative effectiveness and safety of premixed insulin analogues in type 2 diabetes. *Ann Intern Med.* 2008;149(8):549-559.

139. Feil DG, Rajan M, Soroka O, Tseng CL, Miller DR, Pogach LM. Risk of hypoglycemia in older veterans with dementia and cognitive impairment: implications for practice and policy. *J Am Geriatr Soc.* 2011;59(12):2263-2272.

140. Unger J, Parkin C. Hypoglycemia in insulin-treated diabetes: a case for increased vigilance. *Postgrad Med.* 2011;123(4):81-91.

141. Amiel SA, Dixon T, Mann R, Jameson K. Hypoglycaemia in Type 2 diabetes. *Diabet Med.* 2008;25(3):245-254.

142. Graveling AJ, Frier BM. Hypoglycaemia: an overview. *Prim Care Diabetes.* 2009;3(3):131-139.

143. Cryer PE. Diverse causes of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med.* 2004;350(22):2272-2279.

144. Banarer S, Cryer PE. Hypoglycemia in type 2 diabetes. *Med Clin North Am.* 2004;88(4):1107-1116.

145. Biesenbach G, Raml A, Schmekal B, Eichbauer-Sturm G. Decreased insulin requirement in relation to GFR in nephropathic Type 1 and insulin-treated Type 2 diabetic patients. *Diabet Med.* 2003;20(8):642-645.

146. Snyder RW, Berns JS. Use of insulin and oral hypoglycemic medications in patients with diabetes mellitus and advanced kidney disease. *Semin Dial.* 2004;17(5):365-370.

147. Weir MA, Gomes T, Mamdani M, et al. Impaired renal function modifies the risk of severe hypoglycaemia among users of insulin but not glyburide: a population-based nested case-control study. *Nephol Dial Transpl.* 2011;26(6):1888-1894.

148. Punthakee Z, Miller ME, Launer LJ, et al. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: Post hoc epidemiologic analysis of the ACCORD trial. *Diabetes Care.* 2012;35(4):787-793.

149. Holt P. Taking hypoglycaemia seriously: diabetes, dementia and heart disease. *Br J Community Nurs.* 2011;16(5):246-249.

150. Croxson. Hypoglycaemia, cognition and the older person with diabetes. *Prat Diab Int.* 2010;27(6):219-220.

151. Akram K, Pedersen-Bjergaard U, Borch-Johnsen K, Thorsteinsson B. Frequency and risk factors of severe hypoglycemia in insulin-treated type 2 diabetes: a literature survey. *J Diabetes Complicat.* 2006;20(6):402-408.

152. Bulsara MK, Holman CD, Davis EA, Jones TW. Evaluating risk factors associated with severe hypoglycaemia in epidemiology studies-what method should we use? *Diabet Med.* 2004;21(8):914-919.

153. Wright RJ, Frier BM. Vascular disease and diabetes: is hypoglycaemia an aggravating factor? *Diabetes Metab Res Rev.* 2008;24(5):353-363.

154. Desouza CV, Bolli GB, Fonseca V. Hypoglycemia, diabetes, and cardiovascular events. *Diabetes Care.* 2010;33(6):1389-1394.

155. Yakubovich N, Gerstein HC. Serious cardiovascular outcomes in diabetes: the role of hypoglycemia. *Circulation.* 2011;123(3):342-348.

156. Johnston SS, Conner C, Aagren M, Smith DM, Bouchard J, Brett J. Evidence linking hypoglycemic events to an increased risk of acute cardiovascular events in patients with type 2 diabetes. *Diabetes Care.* 2011;34(5):1164-1170.

157. Moore TJ, Cohen MR, Furberg CD. Serious adverse drug events reported to the Food and Drug Administration, 1998-2005. *Arch Intern Med.* 2007;167(16):1752-1759.

158. Kosiborod M, Inzucchi SE, Goyal A, et al. Relationship between spontaneous and iatrogenic hypoglycemia and mortality in patients hospitalized with acute myocardial infarction. *JAMA.* 2009;301(15):1556-1564.

159. Warren RE, Frier BM. Hypoglycaemia and cognitive function. *Diabetes Obes Metab.* 2005;7(5):493-503.

160. Reijmer YD, van den Berg E, Ruis C, Kappelle LJ, Biessels GJ. Cognitive dysfunction in patients with type 2 diabetes. *Diabetes Metab Res Rev.* 2010;26(7):507-519.

161. MacLeod KM. Diabetes and driving: towards equitable, evidence-based decision-making. *Diabet Med.* 1999;16(4):282-290.

162. Jacobson AM, Musen G, Ryan CM, et al. Long-term effect of diabetes and its treatment on cognitive function. *N Engl J Med.* 2007;356(18):1842-1852.

163. Launer LJ, Miller ME, Williamson JD, et al. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. *Lancet Neurol.* 2011;10(11):969-977.

164. Aung PP, Strachan MW, Frier BM, Butcher I, Deary IJ, Price JF. Severe hypoglycaemia and late-life cognitive ability in older people with Type 2 diabetes: the Edinburgh Type 2 Diabetes Study. *Diabet Med.* 2012;29(3):328-336.

165. Strachan MW, Reynolds RM, Frier BM, Mitchell RJ, Price JF. The relationship between type 2 diabetes and dementia. *Br Med Bull.* 2008;88(1):131-146.

166. Fitzpatrick D, Duncan EA. Improving post-hypoglycaemic patient safety in the prehospital environment: a systematic review. *Emerg Med J.* 2009;26(7):472-478.

167. Budnitz DS, Shehad N, Kegler SR, Richards CL. Medication use leading to emergency department visits for adverse drug events in older adults. *Ann Intern Med.* 2007;147(11):755-765.

168. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med.* 2011;365(21):2002-2012.

169. Barendse S, Singh H, Frier BM, Speight J. The impact of hypoglycaemia on quality of life and related patient-reported outcomes in Type 2 diabetes: a narrative review. *Diabet Med.* 2012;29(3):293-302.

170. Biessels GJ. Intensive glucose lowering and cognition in type 2 diabetes. *Lancet Neurol.* 2011;10(11):949-950.

171. Barnett AH, Krentz AJ, Strojek K, et al. The efficacy of self-monitoring of blood glucose in the management of patients with type 2 diabetes treated with a gliclazide modified release-based regimen. A multicentre, randomized, parallel-group, 6-month evaluation (DINAMIC 1 study). *Diabetes Obes Metab.* 2008;10(12):1239-1247.

172. Bolli G, Dotta F, Rochotte E, Cohen SE. Efficacy and tolerability of vildagliptin vs. pioglitazone when added to metformin: a 24-week, randomized, double-blind study. *Diabetes Obes Metab.* 2008;10(1):82-90.

173. Bolli G, Dotta F, Colin L, Minic B, Goodman M. Comparison of vildagliptin and pioglitazone in patients with type 2 diabetes inadequately controlled with metformin. *Diabetes Obes Metab.* 2009;11(6):589-595.

174. Dormandy JA, Charbonnel B, Eckland DJA, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet.* 2005;366(9493):1279-1289.

175. Marre M, Shaw J, Br, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). *Diabetic Med.* 2009;26(3):268-278.

176. Meneghini LF, Rosenberg KH, Koenen C, Merilainen MJ. Insulin detemir improves glycaemic control with less hypoglycaemia and no weight gain in patients with type 2 diabetes who were insulin naive or treated with NPH or insulin glargine: clinical practice experience from a German subgroup of the PREDICTIVE study. *Diabetes Obes Metab.* 2007;9(3):418-427.

177. Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP, Sitagliptin Study G. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. *Diabetes Obes Metab.* 2007;9(2):194-205.

178. Olansky L, Reasner C, Seck TL, et al. A treatment strategy implementing combination therapy with sitagliptin and metformin results in superior glycaemic control versus metformin monotherapy due to a low rate of addition of antihyperglycaemic agents. *Diabetes Obes Metab.* 2011;13(9):841-849.

179. Pratley RE, Nauck M, Bailey T, et al. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. *Lancet.* 2010;375(9724):1447-1456.

180. Standl E, Maxeiner S, Raptis S, Group HOES. Once-daily insulin glargine administration in the morning compared to bedtime in combination with morning glimepiride in patients with type 2 diabetes: an assessment of treatment flexibility. *Hormone Metab Res.* 2006;38(3):172-177.

181. Goldstein BJ, Feinglos MN, Lunceford JK, Johnson J, Williams-Herman DE, Sitagliptin 036 Study G. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. *Diabetes Care.* 2007;30(8):1979-1987.

182. Zinman B, Gerich J, Buse JB, et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). *Diabetes Care.* 2009;32(7):1224-1230.

183. Quilliam BJ, Simeone JC, Ozbay AB, Kogut SJ. The incidence and costs of hypoglycemia in type 2 diabetes. *Am J Manag Care.* 2011;17(10):673-680.

184. Charbonnel B, DeFronzo R, Davidson J, et al. Pioglitazone use in combination with insulin in the prospective pioglitazone clinical trial in macrovascular events study (PROactive19). *J Clin Endocrinol Metab.* 2010;95(5):2163-2171.

185. Drouin P. Diamicron MR once daily is effective and well tolerated in type 2 diabetes: a double-blind, randomized, multinational study. *J Diabetes Complicat.* 2000;14(4):185-191.

186. Abraira C, Duckworth W, McCarren M, et al. Design of the cooperative study on glycemic control and complication in diabetes mellitus type 2 Veterans Affairs Diabetes Trial. *J Diabetes Complicat.* 2003;17:314-322.

187. Garber A, Henry R, Ratner R, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet.* 2009;373(9662):473-481.

188. Hypertension in Diabetes Study IV. Therapeutic requirements to maintain tight blood pressure control. *Diabetologia.* 1996;39(12):1554-1561.

189. Rosenstock J, Ahmann AJ, Colon G, Scism-Bacon J, Jiang H, Martin S. Advancing insulin therapy in type 2 diabetes previously treated with glargine plus oral agents: prandial premixed (insulin lispro protamine suspension/lispro) versus basal/bolus (glargine/lispro) therapy. *Diabetes Care.* 2008;31(1):20-25.

190. U.K.Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia.* 2007;50:1140-1147.

191. UKPDS 28: a randomized trial of efficacy of early addition of metformin in sulfonylurea-treated type 2 diabetes. U.K. Prospective Diabetes Study Group. *Diabetes Care.* 1998;21(1):87-92.

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