APPENDIX A. SEARCH STRATEGY

Database: Ovid MEDLINE(R)
Search Strategy:

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1 exp Hypoglycemia/ or hypoglycemia.mp.
2 exp Diabetes Mellitus, Type 2/ or type 2 diabetes.mp.
3 1 and 2
4 limit 3 to (english language and humans)
5 limit 4 to (addresses or bibliography or biography or dictionary or directory or duplicate publication or editorial or interview or introductory journal article or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or portraits or comment or historical article or interview or case reports)
6 4 not 5
7 limit 6 to "all child (0 to 18 years)"
8 limit 6 to "all adult (19 plus years)"
9 7 not 8
10 6 not 9

NOTE: an additional search was performed using the British spelling (hypoglycaemia) as a title/abstract word

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APPENDIX B. CRITERIA USED IN QUALITY ASSESSMENT OF NON-RANDOMIZED STUDIES

We evaluated each non-randomized trial based on the five elements below. To be considered low risk of bias for any element, a "yes" response was required for each of the questions (a, b, c) pertaining to the element, if applicable. Plots were developed to show the percent of the non-randomized trials in each area (human resources practices, organizational culture, and physical environment) that were assigned a yes (met criteria) or no (failed to meet criteria) for each element.

1) **Population**
   a. Is the sample representative of the population of interest?
   b. Did researchers apply inclusion/exclusion criteria uniformly to all comparison groups and is the selection of the comparison group appropriate?
   c. Is the sampling method appropriate (i.e., appropriate database or sample for research question, adequate response rate for survey studies, etc.)?

2) **Outcomes**
   a. Are important outcomes assessed and *reported* (i.e., not just intermediate or surrogate outcomes)?
   b. Was the length of follow-up appropriate for the research questions (consider benefits and harms)?
   c. Is the impact of loss to follow-up (or differential loss to follow-up) considered in the analysis?

3) **Measurement**
   a. Are outcome, predictor and covariates assessed in the same way for everyone?
   b. Is this blinded such that, for example, a person's exposure status would not be known at the time outcome status was assessed? This is where recall bias and other types of differential assessment come into play.
   c. Are the tools used to assess exposures and outcomes accurate and reliable (i.e., are standard measures used)?

4) **Confounding**
   a. Are the statistical methods and study design adequate for minimizing confounding?
   b. Aside from the exposure of interest, are groups balanced in terms of factors that might bias the exposure and outcome association?
   c. Are the appropriate confounding factors included in the analysis?

5) **Intervention (if applicable)**
   a. Is the intervention clearly described and transferrable (i.e., could someone else repeat this study with different staff and patients and get similar results)?

APPENDIX C. PEER REVIEW COMMENTS/AUTHOR RESPONSES

REVIEWER COMMENT	RESPONSE
1. Are the objectives, scope, and methods for this review clearly described?	
Yes	
Yes	
Yes For the most part the scope/methods are clearly articulated and relatively easy to follow. A couple minor points that may warrant clarification in the methods: 1) Though the results clearly delineate how each study defined severe hypoglycemia, I did not see the review methods specify how you were defining "severe hypoglycemia" for the purposes of study selection – I got the sense from results that you were very inclusive and left the definitions up to each study, but this would be worth stating explicitly in the methods. I also inferred from results that study had to essentially report incidence of symptomatic hypoglycemia – again, worth stating in methods. Also, what if the study did not explicitly define "severe hypoglycemia" but rather just presented incidences of glucose < 40 or < 60 or < 70? I assume these studies would be excluded because there was no mention of symptoms/need for assistance? 2) What is the rationale for excluding studies of duration < 6 mos? Severe hypoglycemia is not really a time-dependent phenomenon (though the consequences of it may be). In any case, this is probably a moot point given the supplemental search, but may be worth more clearly defining rationale here. Also, the KQ1 "extension" is not mentioned in the methods, but then is presented in flow diagram – this may be confusing for readers and may want to include "extension" rationale and methods in the Methods section. Introduction – small point – the exec summ background paragraph states intensive control only associated with reduction in microalbuminuria while the introduction in body of paper more properly states the broader impact of intensive control (esp since these include UKPDS) on other microvascular outcomes. Analytic framework – the one thing that seems to be missing from this is patient behaviors – certainly things like exercise, inconsistent meals, medication mishandling etc would contribute to risk. I doubt these things are identified in any of the included studies, but the lack of such evidence may still be important to know about.	We moved the definition of severe hypoglycemia to the Methods section. We chose to exclude studies with fewer than 500 subjects and less than 26 weeks' duration for feasibility; as it is we abstracted 60 studies for KQ1. As suggested, we included the rationale and methods for KQ1-extension in the Methods Section. We revised the executive summary background and the analytic framework as recommended.
No Although this dichotomous question requires a yes/no answer, neither is really correct. The review fails to put the issue of hypoglycemia in proper context. There is considerable variation in the definitions applied in studies of hypoglycemia. This variation and controversy surrounding it is important background. In addition, although a very explicit definition of severe hypoglycemia was chosen, there is a serious limitation as far as answering the Key Question #1: What is the incidence of clinically significant hypoglycemia? Their definition of severe hypoglycemia chosen was: "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." There is clinically significant hypoglycemia that does not meet this definition. In addition, it does not address the issue of hypoglycemia unawareness which can result in unrecognized and untreated hypoglycemia with levels of glucose <40 mg/dl. (Compare reported rates to those reported on CGMS)	We agree that there is clinically significant hypoglycemia that does not meet our definition and that asymptomatic low blood sugar (e.g., hypoglycemia unawareness) is not accounted for in this definition; however this is the definition that we chose based on its common use in the literature and that was approved by our TEP. We have acknowledged this point in our discussion.
Yes	
2. Is there any indication of bias in our synthesis of the evidence?	
Yes While there is no bias in selection of studies, from my perspective the report does not sufficiently emphasize the rates of serious hypoglycemia and possible morbidity/mortality for patients who are treated in the control arms of clinical studies or from observational data. For example, rates of potentially serious hypoglycemia in insulin treated patients was 59% in a study from a large HMO (Sarkar, 2010, Question 1). The association of serious hypoglycemia and morbidity/mortality from the standard arms of ACCORD/VADT/ADVANCE. Although observation data is not of as high quality, there are strong signals of high rates and potential harms in the selected VA populations which are not incompatible with patient self reported data. These issues are commented upon in section 4.	Although it was included in KQ3, we realized that Sarkar et al. 2010 should have been included in KQ1 ext and added it. Thank you.

REVIEWER COMMENT	RESPONSE
Yes I understand that large trials are needed to detect outcomes (i.e. severe hypoglycemia) that occur relatively infrequently. However, there were many trials with 400-499 patients with T2DM that reported the incidence of severe hypoglycemia. Some of these trials were part of the drug development program for the agent. What was the reasoning behind selecting the 500 patient cut-off? I am concerned that omitting these trials could introduce bias?	See previous page, first response.
No	
Yes Although this dichotomous question requires a yes/no answer, neither is really correct. My concern the way the results are presented and the use of the word "low" as in the following: "Overall incidence of severe hypoglycemia was low in the vast majority of the 60 reviewed studies, particularly those of metformin (0-1.5%), glucagon-like peptide-1 GLP-1 analogs (< 1%), dipeptidyl-peptidase-4 (DPP-4) inhibitors (<1%), insulin detemir (<1%), insulin aspartame (<1%), glinides (0%) and thiazolidinediones (TZDs) (<1%). Annual rates of severe hypoglycemia were greater than 1% for sulfonylureas and the following insulin preparations: neutral protamine Hagedorn (NPH), glargine, lispro and glulisine." "Low" is in the eye of the beholder. When up to 18% of patients on insulin report an episode of hypoglycemia requiring assistance in the previous year, that doesn't sound low. I do, however, appreciate consideration of additional studies "to gain a broader population-based perspective on incidence of symptomatic hypoglycemia."	We agree that use of the term "low" to describe the frequency of severe hypoglycemia is a value judgment and we have either removed or modified that term in the final report.
No	
3. Are there any <u>published</u> or <u>unpublished</u> studies that we may have overlooked?	
Yes 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 Dec; 59(12):2263-72. Epub 2011 Dec 8. (rates of coded hypoglycemia in Veterans with cognitive impairment or dementia Seaquist ER, Miller ME, Bonds DE, Feinglos M, Goff DC Jr, Peterson K, Senior P; for the ACCORD Investigators. The Impact of Frequent and Unrecognized Hypoglycemia on Mortality in the ACCORD Study. Diabetes Care. 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 May; 47(5):447-52. Diabetes Care. 2012 Feb; 35(2):409-414. Epub 2011 Dec 16.	We thank the reviewers for bringing these articles to our attention. Of these, 3 were published after November 2011 which is when our last literature search was performed (Bonds, Feil, Seaquist); 2 had been excluded due to the fact that severe hypoglycemia was not defined (Raz, Swinnen); one we had already included (Rhoads), one was a duplicate publication of a study already included (Miser); one was a study of a newer agent approved by the FDA after our study was initiated (Owens); two meet our criteria, were not previously reviewed and have been added to our final report in KQ1 (Nauck, Russell Jones).

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REVIEWER COMMENT	RESPONSE
I randomly selected a few of the drugs (lispro, detemir, linagliptin, and liraglutide) and searched PubMed to see if there were other relevant articles. I came across the following articles that were >500 patients, ≥ 6 months, and presented data on severe hypoglycemia. It is not clear to me why these studies were excluded. Raz I, et al. Effects of prandial versus fasting glycemia on cardiovascular outcomes in type 2 diabetes: the HEART2D trial. Diabetes Care. 2009 Mar;32(3):381-6. Miser WF, et al, Randomized, open-label, parallel-group evaluations of basal-bolus therapy versus insulin lispro premixed therapy in patients with type 2 diabetes mellitus failing to achieve control with starter insulin treatment and continuing oral antihyperglycemic drugs: a noninferiority intensification substudy of the DURABLE trial. Clin Ther. 2010 May;32(5):896-908. Swinnen SG, et al. A 24-week, randomized, treat-to-target trial comparing initiation of insulin glargine once-daily with insulin detemir twice-daily in patients with type 2 diabetes inadequately controlled on oral glucose-lowering drugs. Diabetes Care. 2010 Jun;33(6):1176-8. Owens DR, et al. Efficacy and safety of linagliptin in persons with type 2 diabetes inadequately controlled by a combination of metformin and sulphonylurea: a 24-week randomized study. Diabet Med. 2011 Nov;28(11):1352-61. Russell-Jones D, et al. Liraglutide Effect and Action in Diabetes 5 (LEAD-5) met+SUStudy Group. 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 Oct;52(10):2046-55. Nauck M, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin in type 2 diabetes. Diabetes Care 2009; 32: 84-90.	See comment above.
No It is not specified in methods whether or not long-term consequences of inpatient hypoglycemia are considered an included study or not, but there is a study looking at long-term outcomes in patients who had had inpatient hypoglycemia: Svensson AM, McGuire DK, Abrahamsson P, Dellborg M. Association between hyper- and hypoglycaemia and 2 year all-cause mortality risk in diabetic patients with acute coronary events. Eur Heart J. 2005;26:1255-61.	This article was not included because it focused on inpatients.
No	
1) More recent reports from ACCORD should be included, notably the ACCORD-EYE study and the ACCORD-MIND study, which showed reduction of retinopathy and reduction of brain shrinkage with intensive control of type 2 diabetes. 2) Include the 3 year results of the 4T study: Holman RR et al. NEJM 2009;361:1736-47 3) In addition to the report by Zoungas on associations of hypoglycemia with mortality risk, consider: Kosiborod M et al. JAMA 209;301:1556-64 and Boucai L et al. Am J Med 2011;124: 1028-35	We have reviewed all the articles mentioned, none of which met our criteria for inclusion (Kosiborod, ACCORD-EYE and ACCORD-MIND) or had already been included (4T Holman). Some of these, however, have been included in the discussion.

REVIEWER COMMENT	RESPONSE
4. Additional suggestions or comments	
From my perspective, the literature supports the following logic sequence that is relevant to VHA patient safety issues which I do not believe come thru in recommendations of the report. 1. Based upon randomized trials of medications, most of which are industry funded and of shorter duration, serious hypoglycemia is uncommon, even in insulin treated patients. 2. The recent ACCORD, VADT, ADVANCE studies were consistent in that while serious hypoglycemia was more common in the intensive arm, the health impact was greater in the standard arm for cardiovascular morbidity, and mortality (Zoungas NEJM 2010, Bonds DE BMJ 2010, Davis SJ (abstract, 2009), as well as with increased medical assistance (Miller et al BMJ 2010). The adjusted strength of association in the standard group in Accord was 2.87 (1.73 to 4.76); ADVANCE death from a cardiovascular cause (hazard ratio, 2.68; 95% CI, 1.72 to 4.19), VADT is not published, but the OR for recurrent severe hypoglycemia and mortality was 3.7. Although the recent article by Bonds et al (2012) found that prior episodes of serious hypoglycemia attenuated the association between hypoglycemia and mortality, it did not do so in the control arm. While it is not likely that this issue will even be conclusively resolved, the reviewer concludes that hypoglycemia is a strong risk factor for cardiovascular death in patients who are not "intensively treated" 3. The risk factors for serious hypoglycemia are varied and differ across the studies, but include other medical conditions, minority status, neuropathy, cognitive impairment, limited health literacy. Although causality of hypoglycemia upon adverse outcomes cannot be proven, the results from the 3 major trials would clearly indicate that Veterans at high risk for serious hypoglycemia can be identified. 4. The studies underestimate the risk of severe hypoglycemia in general practice, particularly for insulin treatment. A surveillance studies in an HMO (Sarkar 2010) noted that 59% of patients on insulin reported a significant hypoglycemia within a year. The Budnitz 2010 study, which will be included after review, will underscore that insulin and sulfonylurea remain high risk medications in the elderly. As noted, the Veteran literature is limited, but renal disease and cognitive impairment are two highly prevalent conditions associated with coded hypoglycemia; other factors, such as decreased health literacy, are also likely to be common in the Veteran population. The ESP did identify Moen et al. as an article documenting an association with biochemical hypoglycemia and death in Veterans with CKD. Additionally, other studies (see section 2) indicate high rates of coded hypoglycemia in Veterans with coded hypoglycemia on insulin, and in an insured population on insulin. The rates of up to 17% cited in the conclusion of Key Question 1 may thus underestimate the rates in high risk populations on insulin therapy in both insured and Veteran populations.	Most of these excellent points have been included in our revised discussion.
In several places, insulin aspart is written as insulin aspartame. Insulin aspartame is incorrect and should be corrected so that it reads insulin aspart. For the DPP-4 inhibitors, studies using vildagliptin were included (p. 95, 130-131); however, this product is not FDA approved. In the Insulin glargine (primary therapy) studies, 4/5 allowed the patient's prior oral diabetes medications to be continued (only Rosenstock 2001 did not allow concomitant oral agents). Therefore, these 4 trials were not truly primary therapy studies. On p.126 Table 3b, Buse 2011 is listed under A. Regular Insulin and Lispro Studies; Fast-short Acting. The lispro used in this study was the 75/25 mix, which is an intermediate and fasting acting mixture so it should be listed under C. Biphasic Insulin: Intermediate and fast-acting mixture.	As suggested, we changed "aspartame" to "aspart". Although vildagliptin is not FDA approved, it does appear in some of our tables because it was included in some of the studies that also used FDA approved agents. The Buse study is now listed under "C" on Table 3B, as suggested.

REVIEWER COMMENT	RESPONSE
Nicely done, thorough report. My main suggestion has to do with the statement "Overall incidence of severe hypoglycemia was low in the vast majority of the 60 reviewed studies…". Though this is true, it is somewhat misleading because the subsequent summary statements do not delve into the issue of glucose targets enough. If the achieved HbA1c in 58/60 studies were 7.5% or 8% in the intervention group, the low incidence of hypoglycemia in the vast majority of studies doesn't really mean too much and it may suggest to readers that the bulk of evidence suggests that severe hypoglycemia is infrequent. I think the intensity of control really matters here and should be more clearly emphasized. It is hard to figure out from results and tables how the glucose target and/or glucose achieved relates to hypoglycemia incidence. Consider also saying more about the intensive vs less intensive evidence base in the summary statements/exec summary. Also, it might be useful to include the glucose targets for each of the studies in Table 3. P18 – the NPH v glargine meta-analysis results are interesting. Many clinicians consider using glargine to help minimize hypoglycemia risk from NPH. I know this is not the focus of this paper, but the finding that the two drugs had equivalent risk of hypoglycemia has potential clinical importance and you could consider highlighting this more. Also, this is a pretty broad CI – I'm not sure I would say "risk is slightly higher" but not statistically significant – would probably just say no significant difference.	As suggested, we included an additional column in Table 1 (formerly Table 3) specifying the A1C targets and commented more extensively on the issue of intensive control in the executive summary, the summary statement, and the discussion. We amended the statement regarding NPH vs glargine to indicate that the risk was not different, as recommended.
This is a well done review of hypoglycemia from the Evidence Based Synthesis Program ESP of the V.A. The goal of ESP Centers is to generate evidence synthesis on clinical practice topics and develop clinical policies informed by evidence guide the implementation of effective services to improve patient outcomes and set the direction for future research. The current report examines in great detail the data available on hypoglycemia in adults with type 2 diabetes. The study is well done and provides a complete, well documented compilation of current information on severe hypoglycemia and will be a major resource for investigators in the area. It will also be of use in clinical care of patients in the V.A. The methods used in the study are appropriate and comprehensive. The study will be a very useful compilation of data on hypoglycemia for future clinical studies and will be of use in defining future directions. It has some limitations in its use by non-investigators in that the limitations of the various studies are not as well delineated in an easily accessible manner for the non-expert. Many of these limitations are mentioned throughout the document, but it would be much more useful to the routine reader to have these limitations defined and a summary to help to better evaluate the data. As a simple example, many of the studies examining hypoglycemia in randomized control trials (RCTs) are obtained from pharmaceutical studies whose purpose is to establish non-inferiority of their agent against other agents in a very highly selected population. This is mentioned in the document, but again that could be lost for someone who does not read every word in the document. Another example is the use of superficially similar excellent studies, but directed at different populations and for different reasons to come to a single conclusion. One of the best examples of this are the ACCORD and ADVANCE trials, two of the best studies done on treatment of patients with type 2 diabetes but directed at different populations for different purposes. The ADVANCE study consisted of relatively mild diabetes with very few of the patients on insulin and low A1cs and ACCORD with a much more difficult population with almost half of the patients on insulin and much higher A1cs at the initiation of the study. The ACCORD trial had higher hypoglycemic numbers and consequences of treatment that may have been related to hypoglycemia which were quite detrimental. *(continued)*	Thank you. We have summarized the limitations of the data in the executive summary and the discussion.

REVIEWER COMMENT	RESPONSE
(continued) Some of these issues of concern for the reader could be addressed in an additional summary of the limitations as mentioned above of individual studies. Another limitation of the current presentation is the difficulty in extracting clinical guidelines for care. While mentioned in the study, the clinical results in terms of outcomes of studies with high hypoglycemic rates may not justify the risk of very intensive control and perhaps standards of care could be qualified to include the risk of complications of treatment more clearly in the guideline. A few specific comments: Some agents used for treatment of patients with type 2 diabetes, rarely if ever cause hypoglycemia when used as individual agents in patients without severe complications. The report clearly defines most of these including metformin, DPP-4 inhibitors, glinides, etc. Some of the insulins have not been extensively tested in routine use for example detemir data are mostly derived from pharmaceutical studies carefully designed to limit the risk of hypoglycemia. Other agents such NPH or glargine have much real world data and appear to be much riskier. For true risk of hypoglycemia with agents that do not typically cause hypoglycemia, it could be useful to include studies that use these agents in combination with the hypoglycemic agents such as insulin. This might give a better view of the risk in the usual use of these agents. Minor Comments A few typographical errors are present in the manuscript, the most glaring of which is on page 4 under Conclusions-an incomplete sentence is somewhat confusing. Overall this is an extremely useful, carefully done, and valuable document for dissemination to professionals in practice and to researchers who will be planning future studies. I highly endorse this document and believe that it will be of great use in the V.A. and outside the V.A. for other practitioners and scientists.	

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REVIEWER COMMENT	RESPONSE
1) Page 1 para 2: Microvascular complications other than albuminuria have indeed been shown: see the ACCORD-EYE study report in NEJM 2) In Key Question #2 and elsewhere: glycated Hb is usually abbreviated as HbA1c, not HgbA1c. 3) Page 3 para 1: Here and elsewhere insulin aspart is incorrectly referred to as 'aspartame.' Aspartame is an artificial sweetner; aspart is an insulin analogue. If the computer search was done with 'aspartame' it is no wonder no significant hypoglycemia was found. It cannot be concluded that aspart does not cause severe hypoglycemia or that it differs from other rapid acting insulin analogues in this way. An excellent report including data on hypoglycemic risk with aspart is: Holman RR et al. NEJM 2009;361:1736-47. Furthermore, the main prandial insulin used in the ACCORD trial was aspart, and in the intensive arm of this trial the incidence of events requiring medical assistance was greater than 3% yearly. 4) Page 4, para 2: Here and elsewhere, 'data' is a plural noun. 5) Page 9 bullet point 6: Why was gliclazide excluded from analyses? The ADVANCE trial is one of the best sources of information on long-term hypoglycemic risks, and it used gliclazlide. This drug is widely used throughout the world. 6) Page 9 bullet point 3: A crucial point is glossed over here. Studies were included if they reported severe hypoglycemia, but there are wide variations between studies in both definitions of severe events and (just as important) ascertainment of such events. This is the main limitation of this analysis. 7) Page 20 para 1: Ramadan is incorrectly spelled 'Ramadam.' 8) Page 21 last section: This summary statement reports annual incidence of severe events greater than 1% for NPH, glargine, lispro, glulisine, and sulfonylureas. Notably missing are aspart (a leading cause of severe events in ACCORD), premixed insulin (a leading cause of events in 4T and possibly the main cause of severe events in clinical practice), and regular insulin (certainly a leading cause of events when used in sliding scales in hospital, but not tested in big clinical trials and therefore missing from this analysis). Somewhere the probably causes of these omissions should be discussed. 9) Page 41 next to last para, which reads: "It is also possible that the robust recent findings that intense glycemic control results in a more than two-fold increase in risk of severe hypoglycemia without any clear outcomes benefits, may lead to an appropriate relaxation in HgbA1c goal levels by both clinicians and guideline developers." This statement should be amended in several ways. First, some guidelines are currently available which make the point that altering the A1c goals is appropriate for some patients, but not others. These actual guidelines should be cited for balance to this speculation. Also, the statement that there are no "clear outcomes" is incorrect. In ADVANCE and VADT, microalbuminuria was reduced. In ACCORD, microalbuminuria, retinopathy, and brain shrinkage were all reduced. In the long-term followup of UKPDS, all-cause mortality was reduced 27% in addition to microvascular events.	1) We have re-worded the executive summary to reflect the benefits of tight control on a variety of microvascular complications 2) All HgbA1C have been changed to HbA1C 4) The verbs accompanying the noun "data" are now in the plural form 5) As per our pre-determined methodology, gliclazide was not included since it is not an FDA approved medication 6) Our discussion points out that definitions and ascertainment of hypoglycemic events varied between studies and ascertainment may have been incomplete 7) We have corrected the spelling for Ramadan
5. Are there any clinical performance measures, programs, quality improvement measures, patient care services, or conferences that will be directly affected by this report? If so, please provide detail.	
Insulin was identified as a high risk medication within VHA in the high alert medication group, with a final report issued in 2009. More recently, there has been renewed discussion in OSC, PBM, and some VISNs about the need to identify Veterans who at higher risk for hypoglycemia in order to decrease potential over treatment and to improve care coordination (e.g. telehealth, post hospital discharge) for those with identified events.	
Pharmacy Benefits Management Services (PBM) along with the Medical Advisory Panel and VISN Pharmacist Executives are responsible for determining formulary status and guidance for use for pharmaceutical agents in the VA. The PBM would need to be made aware of any policies that would result from this report.	
This summary could well affect the nature of diabetes performance measurement.	
An important result of this report might be the design of prospective and structured collection of data to address the questions incompletely answered by this review of heterogenous data.	We have included this point in our discussion.

REVIEWER COMMENT	RESPONSE
6. Please provide any recommendations on how this report can be revised to more directly address or assist implementation needs.	
As noted in comment 4, the reviewer recommends that the report give greater prominence to concerns that serious hypoglycemia is an identified risk factor for morbidity in and morality in “non-intensively treated subjects” from ACCORD, ADVANCE and VADT with mean achieved A1cs of 7.5%-8.4%; rates based upon survey and administrative data indicate incidence of potential serious hypoglycemia up to 59%; and that risk factors for hypoglycemia are not uncommon among the Veteran population.	
See above responses to 1 and 2.	
1) This analysis and report are carefully done and generally confirm the findings of earlier efforts, including some important recently published data. However, the important limitations of the methods necessarily used should be included in the report. 2) One such limitation is that the endpoint in question (hypoglycemia) is rarely the primary endpoint of clinical studies, and in many cases it is not a secondary endpoint either, just an occasionally reported safety observation. Application of rigorous meta-analytic methods cannot overcome this limitation of the data provided. 3) Another limitation is that only some of the therapeutic agents commonly used have been included in the large, structured trials selected for this analysis. Hence, data are not available for drugs of interest. Regular insulin, for example, is a leading cause of hypoglycemia but its relative importance cannot be assessed using the present methods. 4) Two other agents which pose significant risk of severe hypoglycemia also cannot be addressed by the present methods for similar reasons: the sulfonylurea glyburide, and all forms of premixed insulin. Hypoglycemia. 5) Because of the limitations of the evidence available, few firm conclusions are possible. Rather, most of the observations are hypothesis-generating. Hence, a leading conclusion from this report should be that collection of better data, using the excellent VA data-handling system, would be very helpful.	We have included most of these points and limitations in our discussion.

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APPENDIX D. STUDY QUALITY TABLES

Table 1. Individual Study Quality for KQ1, Randomized Studies

Study	Allocation concealment	Blinding	Intention-to treat analyses	Withdrawals adequately described	Quality
Abraira (VA-CSDM) 1995[30]	Unclear	Outcomes/ endpoints	No	Yes	Fair
ACCORD 2008, 2011[3, 7]	Adequate	Outcomes/ endpoints	Yes	Yes	Good
ADVANCE 2008[4]	Adequate	Outcomes/ endpoints	Yes	Yes	Good
Anderson 1997[47]	Unclear	No	Yes	No	Fair
Arechaveleta 2011[52]	Unclear	Yes (double)	Yes	Yes	Fair
Aschner 2006[136]	Unclear	Yes (double)	Yes	Yes	Fair
Aschner 2010[60]	Unclear	Yes (double)*	No	Yes	Fair
BARI 2D[58]	Unclear	Outcomes/ endpoints	Yes	Yes	Fair
Barnett 2008[171]	Adequate	No	Yes	Yes	Fair
Bolli 2008 and 2009[172, 173]	Unclear	Yes (double)	Yes	Yes	Fair
Buse 2009, 2011[36, 110]	Adequate	Outcomes/ endpoints	Yes	Yes	Good
Chou 2008[55]	Unclear	Yes (double)	No	Yes	Fair
Dailey 2004[46]	Unclear	No	Yes	Yes	Fair
Davies 2005[38]	Unclear	No	No	Yes	Fair
Dormandy (PROactive) 2005[174]	Adequate	Yes (double)*	Yes	Yes	Good
Drouin 2004[32]	Unclear	Yes (double)	No	Yes	Fair
Duckworth (VA-DT) 2009[5]	Adequate	Outcomes/ endpoints*	Yes	Yes	Good
Fritsche 2003[44]	Adequate	No	No (2 excluded)	Yes	Fair
Garber 2011[51]	Adequate	Yes (double)	No (1 excluded)	Yes	Good
Haak 2005[33]	Adequate	No	Yes	Yes	Fair
Heine 2005[42]	Adequate	No	No	Yes	Fair
Holman 2009, 2007[43, 111]	Adequate	Outcomes/ endpoints	No (1 excluded)	Yes	Good
Kendall 2005[56]	Unclear	Yes (double)	No (1 excluded)	Yes	Fair
Kennedy 2006[37]	Adequate	No	No	Yes	Fair
Liebl 2009 PREFER[48]	Unclear	No	No	Yes	Fair
Marre 2009[175]	Unclear	Yes (double)	No (1 excluded)	Yes	Fair
Matthews 2010[49]	Unclear	Yes (double)	No	Yes	Fair
Meneghini PREDICTIVE 2007[176]	Unclear	No	No	Yes	Fair
Nauck 2009[177]	Adequate	Yes (double)	No (2 excluded)	Yes	Good
Olansky 2011[178]	Unclear	Yes (double)	No	Yes	Fair
Pratley 2010[179]	Adequate	Outcomes/ endpoints	No (7 excluded)	Yes	Good
Raskin 2009[31]	Unclear	No	Yes	Yes	Fair
Ratner 2002[34]	Unclear	Yes (double)	No	Yes	Fair
Rayman 2007[45]	Unclear	No	No	Yes	Fair

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Study	Allocation concealment	Blinding	Intention-to treat analyses	Withdrawals adequately described	Quality
Riddle 2003, Dailey 2009[41, 132]	Adequate	Outcomes/ endpoints	No	Yes	Fair
Rosenstock 2001[39]	Unclear	No	Yes	Yes	Fair
Rosenstock 2008[40]	Adequate	No, open-label	No	Yes	Fair
Rosenstock 2009[35]	Unclear	No	No	Yes	Fair
Russell-Jones 2009[54]	Adequate	Double*(insulin arm open-label)	No	Yes	Good
Saloranta 2002[59]	Unclear	Yes (double)	Unclear	No	Fair
Schernthaner 2004[57]	Unclear	Yes (double)	No	Yes	Fair
Seck, 2010, Nauck 2007[50, 177]	Unclear	Yes (double)	No	Yes	Fair
Standl 2006[180]	Unclear	No	No	Yes	Fair
UKPDS 33[21]	Adequate	Unclear	Yes	No	Good
Williams-Herman 2009, Goldstein 2007[113, 181]	Unclear	Yes (double)*	No	Partially	Fair
Zinman 2009[182]	Adequate	Yes (double)	No (3 excluded)	Yes	Good

*plus end points adjudicated by blinded committee

Table 2. Individual Study Quality for KQ1, Non-Randomized Studies

Study	Design	Population of interest	Outcomes assessed and reported	Measurement same for all subjects	Confounding controlled
Asche 2008[23]	Retrospective cohort	Yes	Yes	Yes	Yes
Berntorp 2011[15]	Prospective cohort	Yes	Yes	Yes	No
Bodmer 2008[24]	Retrospective cohort with nested case/ control	Yes	Yes	Yes	Yes
Davis 2010[16]	Prospective cohort	Partially*	No	Yes	Yes
Holstein 2001[17]	Prospective cohort	Yes	Yes	Yes	Yes
Leese 2003[25]	Retrospective cohort	Yes	Yes	Yes	No
Marre 2009 (PREDICTIVE)[18]	Prospective cohort	Partially*	Yes	Yes	No
Murata 2005[19]	Prospective cohort	Yes	Yes	Yes	No
Nichols 2010[26]	Retrospective cohort	Yes	Yes	Yes	No
Pencek 2009[20]	Prospective cohort	Yes	Yes	Yes	No
Quilliam 2011[183]	Retrospective cohort	Yes	Yes	Yes	Yes
Stahl 1999[28]	Retrospective case series	No	Yes	Yes	Yes
UK Hypoglycaemia Study Group[21]	Prospective cohort	Yes	Yes	No	No
Valensi 2009 IMPROVE[22]	Prospective cohort	Yes	Yes	Yes	Yes

*Included diabetes type 1

Table 3. Individual Study Quality for KQ2, Randomized and Non-Randomized Studies

RANDOMIZED CONTROLLED TRIALS					
Study	**Allocation concealment**	**Blinding**	**Intention-to treat analyses**	**Withdrawals adequately described**	**Quality**
ACCORD Miller 2010[89]	Adequate	Outcomes/ endpoints	Yes	Yes	Good
ADVANCE Zoungas 2010[90]	Adequate	Outcomes/ endpoints	Yes	Yes	Good
NON-RANDOMIZED TRIALS					
Study	**Design**	**Population of interest**	**Outcomes assessed and reported**	**Measurement same for all subjects**	**Confounding controlled**
Akram 2006[84]	Cross-sectional survey	No	Yes	No	Yes
Bruce 2009[92]	Prospective cohort	No	No	No	No
Davis 2010[16]	Prospective cohort	Partially*	No	Yes	Yes
Davis 2011[93]	Prospective cohort	Partially*	Yes	No	Yes
Duran-Nah 2008[104]	Case-control	No	Yes	Yes	Yes
Holstein 2009[102]	Case-control	No	Yes	Yes	Yes
Holstein 2011[103]	Case-control	No	Yes	Yes	Yes
Miller 2001[100]	Cross-sectional	Yes	Yes	Yes	Yes
Quilliam 2011[27]	Nested Case-control	Yes	No	Yes	Yes
Sarkar 2010[78]	Cross-sectional	Yes	Yes	No	Yes
Shen 2008[101]	Cross-sectional	Yes	Yes	Yes	Yes
Shorr 1997[97]	Retrospective cohort	Yes	Yes	Yes	Yes

*Included diabetes type 1

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APPENDIX E. EVIDENCE TABLES

Table 1. Characteristics of Included Studies

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Abraira 1995[30] United States (VA Cooperative Study) Government	RCT 27 months	Inclusion criteria: Men ages 40-69, with non-insulin dependent diabetes who were being treated with insulin or judged clinically to require insulin because of failure of other therapy Exclusion criteria: Serious illness or predicted poor compliance, diagnosed >15 years prior	N=153 Age: 60.2 years % male: 100 Race/ethnicity: White=49.5 Black=24 Other=3 BMI: 31.0 Duration of diabetes: 7.8 years History of MI: 13.7% History of CHF: 2.0% History of CVA: 6.5% Current smoker: 15%	Intensive group: stepped regimen of insulin goal of HbA1c =5.1+/-1% Standard group: one or two injections of insulin/ day Goal was to avoid diabetic symptoms, excessive glycosuria, or overt hypoglycemia	Impaired consciousness requiring the help of another person, or coma, or seizure; confirmed low blood glucose concentration or rapid response to treatments expected to raise the level of blood glucose also required	Allocation Concealment: Yes Blinding: Yes Intention-to-Treat Analysis (ITT): No Withdrawals/dropouts adequately described: Yes
ACCORD 2008;[3] **Miller 2010;**[89] **ACCORD 2011**[7]**; Bonds 2009**[61] 2 countries, 77 centers Government/ industry	RCT Mean: 42 months	Inclusion criteria: type 2 diabetes and HbA1c ≥7.5%; either 40-79 years old with CV disease or 55-79 years old with significant atherosclerosis, albuminuria, LVH, or at least 2 additional risk factors for CV disease Exclusion criteria: Frequent or recent serious hypoglycemic events, unwillingness to do home glucose monitoring or inject insulin, BMI > 45, Cr > 1.5 mg/dL or other serious illness	N=10,251 Age: 62.2 years % male: 61.5 Race/Ethnicity (%): White=64.5 Black=19.0 Hispanic=7.2 BMI: 32.2 Duration of Diabetes: 10 years HbA1c: 8.3% (median)	Intensive group: Targeted an HbA1c below 6.0% Standard group: Targeted an HbA1c from 7.0% to 7.9%	Requiring medical assistance Requiring any assistance	Allocation Concealment: Yes Blinding: Outcomes assessment (endpoints) Intention-to-Treat Analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes
ADVANCE 2008[4]**ADVANCE 2009 deGalan ADVANCE 2010**[90] 20 Countries; 215 centers Government/ Industry	RCT Median: 60 months	Inclusion criteria: Diagnosis of type 2 diabetes at 30 years or older, an age of at least 55 years at the time of study entry, and a history of major macrovascular or microvascular disease or at least one other risk factor for vascular disease Exclusion criteria: Definite indication for, or contraindication to, any of the study treatments or a definite indication for long-term insulin therapy at the time of study entry	N=11,140 Age: 66 years % male: 57.5 Weight (lbs): 171.6 BMI: 28 Type 2 (%): 100 Duration of diabetes: 8.0 years HbA1c: 7.5% Aspirin: 44%	Intensive glucose control:defined as the use of gliclazide (modified release) plus other drugs as required to achieve a glycosylated Hgb value of 6.5% or less. Standard glucose control:(with target glycosylated Hgb level defined on the basis of local guidelines	Blood glucose < 2.8 mmol/L or the presence of typical symptoms and signs of hypoglycemia without other apparent cause. Severe: transient dysfunction of the CNS unable to treat themselves (i.e. requiring assistance from another person)	Allocation Concealment: Yes Blinding: Outcomes assessment (endpoints) Intention to Treat Analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes

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Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Akram 2006[84] Denmark Government	Cross-sectional survey (response rate: 62%) Questionnaire administered at the Steno Diabetes Center between February and May 2003	Inclusion criteria: Type 2 diabetes treated for at least one year with diet or oral glucose-lowering agents before commencement of insulin therapy. Exclusion criteria: Patients treated with sulfonylureas, ESRD, malignant disease, pregnancy, inability to complete questionnaire	N=401 Age: 66 years % male: 58 BMI: 29 Duration of diabetes: 15 years Insulin duration: 7 years HbA1c: 8.3% Impaired hypoglycemic awareness: 46%	N/A	Need for 3rd party assistance	Population: No Outcomes: Yes Measurement: No Confounding: Yes Intervention: N/A
Alvarez-Guisasola 2008[85] Europe Multicenter Industry	Cross-sectional Patient medical records and The Treatment Satisfaction Questionnaire for Medication June 2006 to February 2007	Inclusion criteria: Type 2 diabetes, age > 30 whose physicians added a SU or a TZD to metformin monotherapy between Jan 2001 and Jan 2006 and who had at least one HbA1c measure in the 12-month period before the visit date Exclusion criteria: Type 1 diabetes; pregnant women, including those with gestational diabetes; patients with diabetes secondary to other factors and patients who could not complete the questionnaire or were participating in another clinical study	N=1709 Age: 62.9 years % male: 54.9 BMI: 31.7 Duration of diabetes: 7.8 years HbA1c: 7.1% Microvascular complications: 2.2 Macrovascular complications: 26.4	N/A Target HbA1c ≤ 6.5%	Needing the assistance of others to manage symptoms or needing medical attention	Population: No Outcomes: No Measurement: Yes Confounding: No Intervention: N/A
Alvarez-Guisasola 2010[119] Seven European Countries Industry	Cross-sectional Patient medical records and The Treatment Satisfaction Questionnaire for Medication 5 years	Inclusion criteria: Type 2 diabetes, age > 30; physician added a SU or a TZD to metformin monotherapy Jan 2001 to Jan 2006 and who had at least one HbA1c measure in the 12-month period before the visit date Exclusion criteria: Type 1 diabetes; pregnant women, including those with gestational diabetes; patients with diabetes secondary to other factors and patients who could not complete the questionnaire or were participating in another clinical study	N=1709 Age: 63 years % male: 55 BMI: 31.7 Duration of diabetes: 7.84 Microvascular events: 2.2% Cardiovascular events: 26.4% HbA1c: 7.1%	N/A Target HbA1c ≤ 6.5%	Needing the assistance of others to manage symptoms or needing medical attention	Population: No Outcomes: No Measurement: Yes Confounding: No Intervention: N/A

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Anderson 1997[47] 16 countries Industry	RCT - crossover 26 weeks	Inclusion criteria: Type 2 diabetes, ages 35-85, on insulin for at least 2 months Exclusion criteria: Other severe disease, use of beta blockers or glucocorticoids, use of insulin infusion device, severe hypoglycemia unawareness, insulin dose > 2.0U/kg or BMI > 35	N=722 Age: 59 years % male: 54 BMI: 28 Duration of Diabetes: 12.4 years Duration of insulin: 6.0 years HbA1c: 8.9%	Intervention: Insulin lispro Control: regular insulin	Episode requiring glucagon or IV glucose	Allocation Concealment: Unclear Blinding: No Intention-to-Treat Analysis (ITT): Yes Withdrawals/dropouts adequately described: No
Arechavaleta 2011[52] Multinational Industry	RCT 30 weeks	Inclusion criteria: Patients ≥18 years of age, with type 2 diabetes and with inadequate glycemic control (defined as HbA1c ≥ 6.5% and ≤9.0%) while on metformin as well as diet and exercise for at least 12 weeks prior to the screening visit Exclusion criteria: History of type 1 diabetes, used any OHA besides metformin within 12 weeks of the screening visit, had renal function impairment prohibiting the use of metformin or had a fasting finger stick glucose of <6.1 or >13.3 mmol/l at randomization	N=1035 Age: 54.9 years % male: 54.4 Race/Ethnicity (%): White=57.5 Asian=21.3 Multiracial=14.9 Other=5.2 Black or AA=1.2 Weight (lbs): 178.9 BMI: 30 Duration of diabetes: 6.8 HbA1c: 7.5%	Sitagliptin + metformin (n=516) Glimepiride + metformin (n=519)	Requiring non-medical assistance of others, and those requiring medical intervention or exhibiting markedly depressed level of consciousness or seizure	Allocation concealment: Unclear Blinding: Yes Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes
Asche 2008[23] United States Industry	Retrospective cohort 30 weeks	Inclusion criteria: Patients with type 2 diabetes age ≥65 treated with metformin, SUs or TZDs (never having been on any of these meds before)	N=5438	SU: 58/2223 (2.6%) SU without insulin: 55/2117 (2.6%) SU with insulin: 3/106 (2.8%) metformin: 0 TZD: 20/889 (2.2%): TZD w/o insulin: 12/702 (1.7%) TZD w/ insulin: 8/187 (4.3%)	Drug-related AE defined as being coded in the database (i.e., a visit to a provider) for hypoglycemia in people who had NOT had a similar drug-related AE PRIOR to the initiation of the metformin, SU or TZD	Population: Yes Outcomes: Yes Measurement: Yes Confounding: Yes Intervention: N/A

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Aschner 2006[136] Multinational Industry	RCT 24 weeks	Inclusion criteria: 18-75 years old; compliant during run-in Exclusion criteria: Unstable cardiac disease, significant renal impairment, elevated AST, ALT, or CK	N=741 Duration of diabetes: 4.4 years HbA1c: 8%	Sitagliptin monotherapy:100 mg qd Sitagliptin monotherapy: 200 mg qd Placebo: qd	Loss of consciousness or requirement for medical assistance	Allocation concealment: unclear Blinding: Yes Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes
Aschner 2010[60] Multinational 23 countries 113 sites Industry	RCT 24 weeks	Inclusion criteria: Type 2 diabetes, 18-78 years old had not been on any anti-hyperglycemic medications for at least 16 weeks with HbA1c between 6.5% and 9.0%	N=894 Age: 56 years % males: 46 BMI: 30.8 Duration of Diabetes: 2.4 years HbA1c: 7.2%	Sitagliptin 100mg qd (528) Metformin 1000 mg bid (522)	Required medical assistance	Allocation concealment: Unclear Blinding: Yes Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Yes
Asplund 1991[105] Sweden NR	Case-control Swedish Adverse Drug Reactions Advisory Committee N/A	Inclusion criteria: Cases 19 patients with hypoglycemia (fatal or otherwise serious, unexpected, or remarkable) in patients treated with glipizide 1980-87 Controls patients on glipizide from local health care centers, matched on gender and birth date	N=19 cases Age: 75 years % male: 42 Duration of diabetes (before event): 3 years (median)	N/A	Fatal or otherwise serious, unexpected, or remarkable	Population: No Outcomes: No Measurement: No Confounding: No Intervention: N/A
BARI 2D 2009[58] Multinational 6 countries 49 sites Government/ Industry	RCT 5.3 years	Inclusion criteria: Type 2 diabetes and CAD, candidates for elective PCI or CABG. Exclusion criteria: Required immediate re-vascularization, had left main disease, Cr > 2, HbA1c > 13%, class 3 or 4 CHF, hepatic dysfunction, PCI or CABG within 12 months	N=2368 Age: 62.4 years % male: 70 BMI: 32 Type 2 (%): 100 Diabetes duration: 10.4 years Currently on insulin: 28% Baseline HbA1c: 7.7% Smoking in previous year: 22% ACE inhibitor: 77% Antithrombotic agent: 88% Beta blocker: 73%	Revascularization vs. medical therapy for CAD and insulin sensitive therapy vs. insulin therapy Target HbA1c < 7.0%	Requiring assistance with treatment and either a blood glucose level of <50 mg per deciliter or confusion, irrational or uncontrollable behavior, convulsions, or coma reversed by treatment that raises blood glucose levels	Allocation concealment: Unclear Blinding: Outcomes assessment (endpoints) Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Barnett 2008[171] Multinational 7 countries Industry	RCT 27 weeks	Inclusion criteria: Patients with type 2 diabetes, age 40-80 years old, on OHAs with HbA1c between 7% and 10%	N=610 Age: 56 years % male: 50 Weight: 251.7 lbs BMI: 30.4 Duration of diabetes: 2.8 years	Self-monitored blood glucose(SMBG) No SMBG	Required 3d party assistance (grade 3) or required medical assistance (grade 4)	Allocation concealment: Adequate Blinding: No Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes
Ben-Ami 1999[127] Israel NR	Case series Medical records – drug-induced hypoglycemic coma (admitted with or developed in hospital)	Inclusion criteria: Adult; nonalcoholic; nonepileptic; age 17 and older, type 2 or type 1 diabetes	N=102 Age (median): 72 years % male: 40 Type 2: 92% Duration of diabetes (median): 10 years	N/A	All patients had drug-induced hypoglycemic coma	Population: No Outcomes: Yes Measurement: No Confounding: N/A Intervention: N/A
Berntorp 2011[15] Sweden 200 sites Industry	Prospective observational 6 months	Inclusion criteria: Patients with at least one prescription for a SU, biguanide, TZD, acarbose, or prandial glucose regulator; with or without insulin use; ages 30-79	N=1154 Age: 65 years % male: 60 BMI: 29.4 Duration of Diabetes: 8.1 years HbA1c: 8.8%	N/A	Event w/ severe CNS symptoms consistent with hypoglycemia in which subject was unable to treat himself/ herself and either plasma glucose <3.1 mmol/L or reversal of symptoms upon glucagon/glucose administration	Population: Yes Outcomes: No Measurement: No Confounding: No Intervention: N/A
Bodmer 2008[24] United Kingdom Industry	Retrospective cohort with nested case control Large administrative database N/A	Inclusion criteria: At least one prescription for a SU, biguanide, TZD, acarbose, or prandial glucose regulator; with or without insulin use; ages 30-79 Exclusion criteria: Type 1 diabetes, pts with <3years data in the database before prescreen of first diabetes drug, pts with h/o ETOH, cancer, and gestational diabetes	N=50,048 Age: 60.7 years % male: 45 Case subjects: 2025 w/ recorded hypoglycemia; 73 "severe"	N/A	Mild/moderate: treated by the GP Severe: hospitalized or died	Population: Yes Outcomes: Yes Measurement: No Confounding: Yes Intervention: N/A

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Bolli 2008;[172] **Bolli 2009**[173] 9 countries 118 centers Industry	RCT 24 week reporting (2008) 52 week reporting (2009)	Inclusion criteria: Type 2 diabetes with HbA1c of 7.5% to 11.0% on a stable dose of metformin ≥1500 mg/day. Age 18-77, BMI 22-45, FPG < 15mmol Exclusion criteria: History of type 1 or secondary forms of diabetes; acute metabolic diabetic complications; myocardial infarction, unstable angina or coronary artery bypass surgery within the previous 6 months; CHF or liver disease	N=576 Age: 57 years % male: 63 Race/ Ethnicity (%): White=82 Hispanic=9 Asian=4 Black=3 Other=2 Weight (lbs): 200.2 BMI: 32 Type 2 (%): 100 Duration of diabetes: 6.4 years Baseline HbA1c: 8.4%	Vildagliptin 50 mg bid Pioglitazone 30 mg qd In patients on a stable metformin dose	Any episode requiring the assistance of another party	Allocation concealment: Unclear Blinding: Yes Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Yes
Bruce 2009[92] Australia Multiple sources including industry	Prospective Cohort 1.6 years (median)	Inclusion criteria: 302 of the 587 survivors age ≥ 70 agreed to cognitive assessment in 2001; of the 246/302 who were NOT demented in 2001, 205 agreed to second assessment 18 months later	N=205 Age: 76 years Type 2 (%): 99 On insulin: 28% On SU: 45% Severe hypoglycemia: 7.2% HbA1c≤7: 46%	N/A	Episodes requiring second party assistance	Population: No Outcomes: No Measurement: No Confounding: No Intervention: N/A
Buse 2009;[110] **Buse 2011**[36] 11 countries 242 sites Industry	RCT 24 weeks	Inclusion criteria: Insulin naïve, 30-80 years old, HbA1c>7% on at least 2 OHAs for 90 days Exclusion criteria: History of scheduled long term insulin use; recent use of other OHAs, BMI>45, recent history of severe hypoglycemia; significant hematology, oncology, renal, cardiac, hepatic, or GI disease; steroid use, pregnant or nursing	N=2091 Age: 57 years % male: 53 Race/Ethnicity (%) White=63 Asian=15 Hispanic=12 Black=6 Other=3 Weight (lbs): 195.8 BMI: 32 Type 2 (%):100 Duration of diabetes: 9.5 years HbA1c: 9.1%	Lispro mix (75/25) Glargine Added to patient's current OHA therapy which had to be maintained at current doses Target HbA1c<6.5%	Requiring assistance from another person for treatment with oral carbohydrate, intravenous glucose, or glucagon	Allocation concealment: Yes Blinding: NoIntention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes Withdrawals (by group): Yes

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Chou 2008[55] 19 countries 155 centers Industry	RCT 28 weeks	Inclusion criteria: Men and women, ages 18 to 75, type 2 diabetes, HbA1c of 7.5-12.0%, fasting C-peptide ≥ 0.8 ng/ml, FPG ≥126 mg/dl, treated with diet and/or exercise alone or who had not taken oral anti-diabetic medication or insulin for >15 days in preceding 4 months Exclusion criteria: History of severe hypoglycemia, severe edema or prior history of severe edema, prior history of hepatocellular reaction, clinically significant hepatic or renal disease, unstable or severe angina or CHF requiring pharmacological treatment, anemia, uncontrolled HTN (systolic >170 mmHg or diastolic >100 mmHg on therapy)	N=901 Age: 54.0 years % male: 58.8 Race/Ethnicity (%): White=77.3 Hispanic/Latino=9.4 Asian=7.8 Black=4.8 Other=0.7 Weight (lbs): 199.1 BMI: 31.6 Type 2 (%): 100 Duration of diabetes (median): 1.5 years Baseline HbA1c: 9.1%	1) Glimepiride (GLIM) monotherapy (1 mg OD titrated to max of 4 mg OD); n=225 2) Rosiglitazone (RSG) monotherapy (4 mg OD titrated to max of 8 mg OD); n=232 3) RSG/GLIM regimen A (4 mg/1 mg titrated to max of 4 mg/4 mg OD); n=225 4) RSG/GLIM regimen B (4 mg/1 mg titrated to max of 8 mg/4 mg); n=219 Target HbA1c: documented ≤6.5% and <7.0%	Not defined; reported results for patients with hypoglycemia receiving external assistance	Allocation concealment: Unclear Blinding: Yes Intention to treat analysis (ITT): No (1 dose required) Withdrawals/dropouts adequately described: Yes
Cobden 2007[133] United States Industry	Retrospective pre-post cohort 6 months before and 2+ years after conversion to pen device Medical and pharmaceutical claims - PharMetrics Database January 1, 2001 to April 30th 2005	Inclusion criteria: Age 18 or older, multiple diagnostic claims for type 2 diabetes, converted to BIAsp 70/30 pen for the first time; previously treated with insulin administered by syringe; data for 6 months before conversion and at least 2 years after	N=496 Age: 45.1 years % male: 56.4	N/A	Requiring emergency department visits or hospitalizations	Population: Yes Outcomes: Yes Measurement: Yes Confounding: Yes Intervention: Yes

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Dailey 2004[46] Multinational multicenter NR	Randomized, open labeled, parallel group study 26 weeks	Inclusion criteria: Established type 2 diabetes, age ≥ 18 years who had been on insulin therapy for ≥ 6 months before study with HbA1c 6-11%. Exclusion criteria: Clinically significant hepatic disease, renal impairment, a history of lactic acidosis, unstable or severe angina, known congestive heart failure (CHF, New York Heart Association class I, II, III, or IV), or uncontrolled hypertension	Age: 58.3 years % male: 52.9 Race/Ethnicity (%): Caucasian=85.4 Black=11.3 Asian=1.9 Multiracial=1.4 Hispanic Origin=6.8% BMI: 34.6 Type 2 (%):100 Duration of diabetes: 14.0 years HbA1c: 7.6%	Intervention: Glulisine subcutaneous injections 0-15 before breakfast and dinner (n=435) Comparator: RHI/NPH subcutaneous injections 30-45 before breakfast and dinner (n=441)	Severe hypoglycemia: symptomatic requiring assistance from another person and BG < 36 mg/dl or associated with prompt recovery following oral carbohydrate, IV glucose or glucagon	Allocation Concealment: Unclear Blinding: No (open-label) Intention to Treat Analysis (ITT): Yes Withdrawals/Dropouts adequately described: Yes
Davies 2005[38] Multinational Industry	RCT 24 weeks	Inclusion criteria: Type 2 diabetes sub-optimally controlled; age ≥ 18; on any OHA or insulin for > 6 months, requiring in the opinion of local MD basal long acting insulin, HbA1c > 7% and < 12%; BMI < 40 Exclusion criteria: Impaired renal function, acute or chronic metabolic acidosis; active liver disease or elevated ALT or AST; h/o hypoglycemic unawareness; diabetic retinopathy w/ recent surgery or planned surgery within 3 months; pregnancy	N=4961 Age: 58 % male: 49 BMI: 29 Type 2 (%): 100 Duration of diabetes: 12.3 years Duration of insulin use: 5.1 years	Algorithm 1: titration at every visit; managed by MD. Glargine 10 IU qhs (N=2529) Algorithm 2: titration every 3 days managed by patient (N=2504) in insulin naïve pts Glargine at a dose = to highest value of FBG in MMol over previous 7 days	Requiring assistance from another person and BG < 50 mg/dl	Allocation concealment: UnclearBlinding: No Intention to treat analysis (ITT): Partially Withdrawals/dropouts adequately described: Yes
Davis 2005[120] Wales and United Kingdom Industry	Cross-sectional survey N/A	Inclusion criteria: Patients with known type 1 or type 2 diabetes N=3200	Response rate: 861/3200 (27%) % male: 55 Type 2 (%): 69	N/A	Help from other person required	Population: No Outcomes: No Measurement: No Confounding: Yes Intervention: N/A

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Davis 2010[16] Australia Industry	Prospective Cohort Western Australia Ambulance Database and Western Australia Data Linkage System 5 years after last patient enrollment	Inclusion criteria: All patients with type 2 diabetes	N=616 Age: 67 years % male: 52.3 BMI: 28 Type 2 (%): 100 Duration of Diabetes: 7.7 years (median) HbA1c (%): Median=7.2%	Target HbA1c: N/A	Requiring ambulance attendance, emergency department services, and/or hospitalization	Population: No Outcomes: No Measurement: Yes Confounding: No Intervention: N/A
Davis 2011[93] Australia Industry	Prospective Cohort Fremantle Hospital primary catchment area with morbidity/ mortality data obtained through WA Data Linkage System 8 years	Inclusion criteria: All patients with type 2 diabetes in the Fremantle Hospital primary catchment	N=602 Age: 67.1 years % male: 52 Duration of diabetes: 7.7 years (median) HbA1c: 7.2%	N/A	Patient with a subnormal blood/ plasma/serum glucose required documented health service use (ambulance, emergency department, or hospitalization)	Population: No Outcomes: Yes Measurement: No Confounding: Yes Intervention: N/A

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Dormandy 2005[174] Charbonnel 2010 PROactive[184] 19 countries Industry	RCT Mean: 34.5 months	Inclusion criteria: Adults (aged 35–75 yr, inclusive); type 2 diabetes; history of macrovascular disease; current use of pioglitazone or other thiazolidinediones and insulin Exclusion criteria: Monotherapy for 2 wk or longer at any time in the previous 3 months	N=5238 Age: 61.7 years % male: 66.1 Race/Ethnicity (%): White=98.6 BMI: 30.9 Type 2 (%): 100 Duration of diabetes: 9.5 years Baseline HbA1c: 8.1% Smoking: Current: 13.8% Past: 45%	Pioglitazone titrated from 15-45 Placebo Charbonel SGA an analysis of those in each randomized group who were receiving insulin at baseline *with insulin at baseline Pioglitazone (n=864) 45 U/day Placebo (n=896) *w/o insulin at baseline Pioglitazone 45 U/day Placebo	Resulting in hospital admission	Allocation concealment: Yes Blinding: Yes Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes
Drouin 2000[185] and 2004[32] Multinational NR	RCT 10 months then 2 months during which all diamicron pts switched to diamicron MR, then 12 month open-label on diamicron MR	Inclusion criteria: Type 2 diabetes for at least 6 months, > 35 years old, BMI 22-35 treated for at least 3 months with diet with or without an OHA agent; HbA1c of 7.8% to 13.9% after washout from any previous OHA	N=507 Age: 61.5 years % male: 54 BMI: 28.5 Duration of diabetes: 6.5 years HbA1c: 8.14%	Diamicron (gliclazide) n=399 Diamicron MR (gliclazide modified release) n=401	Grade 3: required external assistance Grade 4: required medical assistance	Allocation concealment: Unclear Blinding: Yes Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Yes

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Duckworth 2009 VA-DT[5] Abraira 2003[186] United States 20 sites Government/ Industry	RCT Median: 5.6 years	Inclusion criteria: Male and female veterans; ≥ 41 years old; nonresponsive to a maximum dose of at least one oral agent and/or daily insulin injections (centrally measured HbA1c level > 4 SD above normal mean (i.e., ≥ 7.5%) or else local HbA1c ≥ 8.3%)	N=1791 Age: 60.4 years % male: 97 Race/Ethnicity (%): White=62 Hispanic white=16.2 Black=16.7 Other=5 Weight (lbs): 214 BMI: 31.3 Type 2 (%): 100 Duration of diabetes: 11.5 years HbA1c: 9.4% Insulin: 52% Current smoker: 16%	Intensive Goal of absolute reduction of 1.5% in the HbA1c compared to standard Rx (N=892) Standard regimen One-half the max dose of intensive regimen (N=899)	Life threatening, death, hospitalization, disability or incapacity or other event requiring medical intervention/treatment	Allocation Concealment: Yes Blinding: No Intention-to-Treat Analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes
Duran-Nah 2008[104] Mexico NR	Case control N/A	Inclusion criteria: Cases: consecutive patients with type 2 diabetes ≥ 30 years old, presenting to ER and hospitalized for symptomatic hypoglycemia, had to be on a diabetes medication. Controls: type 2 diabetes patients admitted for other problems	N=282 % male: 38 Age: 59 years Duration of diabetes: 13.7 years	N/A	≤ 72 mg/dL glucose concentration, with a neurological clinical picture consistent with a severely confused mental state or worse, non-arousable	Population: No Outcomes: Yes Measurement: Yes Confounding: Yes Intervention: N/A
Fadini 2009[95] Italy NR	Retrospective Cohort Chart analysis of ER visits for hypoglycemia over 6 years	Inclusion criteria: Patients type 2 diabetes presenting to ER with one of the relevant ICD9 codes Exclusion criteria: Patients with type 1 diabetes, secondary diabetes, other potential cause of coma	N=192 (126 cases included) Age: 77 years % male: 44	N/A	Led to hospitalization	Population: No Outcomes: Yes Measurement: Yes Confounding: No Intervention: N/A

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Fritsche 2003[44] 13 European countries 111 sites Industry	RCT 24 weeks	Inclusion criteria: Type 2 diabetes, <75 years old, BMI <35, previous oral therapy with any sulfonylurea or combination, FBG≥120 mg/dl, HbA1c 7.5-10.5% Exclusion criteria: Pregnancy, breast feeding, insulin or other investigational drugs in previous 3 months, clinically relevant somatic or mental diseases	N=468 Age: 61 years % male: 53.7 Duration of diabetes: 8.8 years Weight (lbs): 178.9 BMI: 28.7 HbA1c: 9.1%	Bedtime NPH, Bedtime glargine, Morning glargine All groups on 3 mg gllmepiride throughout study Baseline insulin doses based on FBG; titrated at every visit Target HbA1c ≤7.5%	Symptoms consistent with hypoglycemia that require assistance of another person, associated with blood glucose <50 mg/ dL, and followed by prompt recovery with carbohydrate, IV glucose, or glucagon	Allocation concealment: Yes Blinding: No Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Yes
Garber 2009,[187] **2011**[51] United States 126 sites Mexico 12 sites Industry	RCT 52 weeks+ 52 week open label	Inclusion criteria: Type 2 diabetes, age 18-80, BMI<45, had received diet or OHA therapy (up to half of the highest dose) for at least 2 months, HbA1c between 7% and 11% (diet) or between 7% and 10% if on OHA Exclusion criteria: Insulin treatment during previous 3 months, treatment with systemic corticosteriods, hypoglycemia unawareness or recurrent severe hypoglycemia, and impaired liver function	N=746 Age: 53 years % male: 49.7 Race/Ethnicity (%): White=78.2 Black=12.6 Asian=3.5 Other=5.1 Weight: 204.4 BMI: 33.1 Duration of diabetes: 5.4 years HbA1c: 8.3%	Liraglutide 1.2 mg SC qd (251; 149 ext) Liraglutide 1.8 mg SC qd (246;154 ext) Glimepiride 8mg qd (248; 137 ext)	Major: Plasma glucose < 3.1 and required 3rd party assistance	Allocation concealment: Yes Blinding: Yes Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes
Goh 2009[115] Singapore NR	Prospective Cohort Patient Questionnaire at the Tan Tock Seng Hospi-tal (medical records were used to fill out incomplete questionnaires) 28 days	Inclusion criteria: Patients with isolated hypoglycemia, no co-existing acute medical issue requiring a hospital stay of > 24 hours. Neurological signs and symptoms with which patients first presented must have been completely resolved with the reversal of hypoglycemia	N=203 % male: 36.9 Race/Ethnicity (%): Chinese=67.5 Malay=18.2 Indian=12.3 Other=2.0 %Type 2 diabetes: 94.6 Previous symptomatic hypoglycemia: 21.2%	N/A	Admission to the ER	Population: No Outcomes: No Measurement: No Confounding: No Intervention: N/A

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Goldstein 2007[181] Multinational Industry	RCT 24 weeks	Inclusion criteria: Ages 18 to 78, type 2 diabetes, on or not on an oral anti-hyperglycemic agent at screening Exclusion criteria: Type 1 diabetes, unstable cardiac disease, significant renal impairment, elevated liver enzymes	N=1091 Age: 53.5 years % male: 49.4 Race/Ethnicity (%): White: 51.7 Black: 6.9 Hispanic: 27.2 Asian: 5.7 Other: 8.5 BMI: 32.1 Type 2 (%): 100 Duration of diabetes: 4.5 years HbA1c: 8.8%	1) Sitagliptin 100 mg OD 2) Metformin 500 mg BID 3) Metformin 1,000 mg BID 4) Sitagliptin 50 mg + Metformin 500 mg BID 5) Sitagliptin 50 mg + Metformin 1,000 mg BID 6) Placebo All patients received counseling on diet and exercise throughout the study	Loss of consciousness or requirement for medical assistance	Allocation concealment: Unclear Blinding: Yes Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Partially
Greco 2010[128] Italy NR	Case Series Chart analysis 8 years	Inclusion criteria: Patients admitted to the hospital with severe hypoglycemia between January 1, 2001 and December 31, 2008	N=99/5377 medical admissions due to diabetes attributed to severe hypoglycemia Age (median): 84.7 % male: 36.4 BMI: 27.8 Duration of diabetes:15.7 years	N/A	Symptomatic episode requiring assistance of another person and treatment with intravenous glucose or glucagon injection. Confirmed by blood glucose of 50mg/dl	Population: Yes Outcomes: Yes Measurement: No Confounding: No Intervention: N/A
Gürlek 1999[116] Turkey NR	Retrospective Cohort Chart Review Mean: 3.3 year	Inclusion criteria: Attended outpatient clinic weekly or biweekly for 1 year; taking conventional insulin therapy (1-2 injections), no oral medications	N=165 (baseline data reported for 114 with type 2 diabetes) Age: 58.9 years % male: 44.7 BMI: 29.8 Duration of diabetes: 12.9 years	N/A	Patient unable to take yes action themselves OR Coma requiring parenteral glucose administered in hospital setting	Population: No Outcomes: No Measurement: Yes Confounding: No Intervention: N/A
Haak 2005[33] Multinational 5 European countries 63 sites Industry	RCT 26 weeks	Inclusion criteria: Type 2 diabetes for ≥12 months, age ≥35, HbA1c in past 12 months, on insulin for ≥ 2 months Exclusion criteria: Received OHAs within 2 months of the trial; pregnant or breast feeding; proliferative retinopathy; uncontrolled hypertension; recurrent major hypoglycemia; impaired renal or hepatic function; cardiac problems; total daily basal insulin dose >100 IU/day	N=505 Age: 60.4 years % male: 51.1 Race/Ethnicity (%): White=99 Asian-Pacific Islander=1 Weight (lbs): 191.1 BMI: 30.4 Duration of diabetes: 13.2 years HbA1c: 7.9%	Detemir (341) NPH (164)	Patient unable to treat him/herself	Allocation concealment: No Blinding: No Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Harsch 2002[121] Germany NR	Cross-sectional Anonymous questionnaire randomly distributed N/A	Inclusion criteria: Patients with diabetes (Type 1, Type 2, or unclassified); driving at least 1000 km annually, driver's license for at least 1 year, treated with potentially hypoglycemia-inducing medication for at least 1 year	**Oral Antidiabetic (OA) group** (116/122 type 2) Age: 64.2 years Duration of diabetes: 8.6 years Recent HbA1c: 7.9% Impaired visual function related to diabetes: 8.2% Antihypertensive treatment: 52.5% CNS-relevant medication: 5.7% **Conventional Insulin Therapy (CT) group** (108/151 type 2): Age: 58.8 years Duration of diabetes: 11.7 years Recent HbA1c: 7.9% Impaired visual function related to diabetes: 20.5% Antihypertensive treatment: 38.4% CNS-relevant medication: 5.3%	N/A	Patients instructed to report hypoglycemia during driving and hypoglycemia-induced accidents with hypoglycemia as a range of events from impaired psycho-physiological performance, requiring immediate self-treatment to interruption of driving events requiring external assistance	Population: No Outcomes: Yes Measurement: No Confounding: No Intervention: N/A
Heine 2005[42] 13 countries 82 centers Industry	RCT 26 weeks	Inclusion criteria: Inadequate glycemic control on max dose SU and metformin, age 30-75, HbA1c 7-10%, BMI 25-45, stable body weight Exclusion criteria: Participated in a study 30 days prior, experienced > 3 severe hypoglycemic episodes in the past 6 months, undergoing therapy for malignant disease other than basal or squamous cell skin cancer, class III or IV cardiac disease, serum creatinine > 1.5 mg/dL (men) or 1.2 mg/dL (women), symptoms of liver disease, on long term glucocorticoid therapy, prior use of weight loss drugs, treated for > 2 consecutive weeks with insulin within 3 months prior to screening	N=549 Age: 59 years % male: 56 Race/Ethnicity (%): White=80 Black=1 Asian=1 Hispanic=16 Other=2 BMI: 31 Duration of diabetes: 10 years HbA1c: 8.3%	Intervention: exenatide 5 ug bid for 4 wks then 10Ug bid till end of study Control: glargine 10U/hs then adjusted by algorithm to achieve FBS < 100 Metformin and SU maintained at pre-study doses	Patient required assistance of another person and had a BS< 50mg/dl	Allocation Concealment: Yes Blinding: No Intention to Treat Analysis (ITT): No Withdrawals/dropouts adequately described: Unclear

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Hemmelgarn 2006[135] Canada NR	Nested case control N/A	Inclusion criteria: Aged 67-84 with valid driver's license in Quebec; resident for at least 2 years before June 1 1990; followed until death, end of study (May 31 1993), date of event, age 85 years, or emigration from province Exclusion criteria: Residence in a long-term care setting during the study period; previous hosp within past 60 days; hosp of 30 or more days any time in previous year	Cases: Had an injurious MVA (N=5579) Age: 74 years % male: 80 Controls: Random sample of 6% of the subjects from the cohort (N=13,300) Age 73 years % male: 73	N/A	N/A	Population: Yes Outcomes: No Measurement: No Confounding: No Intervention: N/A
Henderson 2003[76] Scotland Government/ Foundation	Cross-sectional Survey of randomly selected patients attending outpatient diabetes clinic	Inclusion criteria: Type 2 diabetes; 2 or more injections of insulin daily for at least 1 year	N=215 Age: 68 years (median)	N/A	Required external assistance to effect recovery	Population: Yes Outcomes: No Measurement: No Confounding: No Intervention: N/A
Hepburn 1993[99] Scotland NR	Cross-sectional Questionnaire given to sequentially selected patients at daily diabetic clinics (one location)	Inclusion criteria: type 2 diabetes, treated with dietary modification and oral agents for at least 2 years before start of insulin therapy; treated with insulin for at least 1 year	N=104 Age: 63 years % male: 50 BMI: 27 Duration of diabetes: 12 years Duration of insulin therapy: 4 years HbA1c: 10.5%	N/A	Patient unable to take appropriate restorative action and required assistance of another person for treatment (home or hospital) to administer either oral or parenteral glucose or glucagon by injection	Population: Yes Outcomes: Yes Measurement: No Confounding: Yes Intervention: N/A
Hermanns 2005[122] Germany NR	Cross-sectional Questionnaires given to Diabetes Center inpatients (addressed hypoglycemia in past 12 months)	Inclusion criteria: Referred for inpatient treatment (mostly for treatment of late complications or difficulty achieving glycemic control); age 18-75 yrs	N=388 (51 had severe hypoglycemia) Age: 35% 18-48 yrs, 35% 49-62 yrs, 30% >62 yrs % male: 62 Type 2: 63% Duration of diabetes: 31% <6 yrs, 37% 7-16 yrs; 32% >16 yrs HbA1c: 31% <7.5%, 34% 7.5-8.3%, 36% >8.3	N/A	Requiring assistance	Population: Yes Outcomes: Yes Measurement: No Confounding: Yes Intervention: N/A

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Holman 2009;[43] Holman 2007[111] United Kingdom 58 sites Industry	RCT 3 years	Inclusion criteria: 18 years and older, 12 mo or longer history of diabetes, not on insulin; HbA1c 7-10% on maximal doses of metformin and SU for at least 4 months; BMI≤40; Exclusion criteria: History of TZD therapy or triple OHA therapy	N=708 Age: 61.7 years Duration of diabetes (median): 9 years	Biphasic insulin aspart bid before meals; (n=235) Prandial insulin aspart tid before meals; (n=239) Basal insulin detemir qhs (n=234)	Third party assistance required	Allocation concealment: Yes Blinding: Outcomes assessment (endpoints) Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes
Holstein 2001[17] (subset of Holstein 2003) Germany Industry	Prospective Cohort Region of Germany with 200,000 residents 4 years	Inclusion criteria: All emergency room patients from only hospital in area (n=30,768); this publication focuses only on SU-associated hypoglycemia	N=45 Age: 83.5 years % male: 36.3 Duration of diabetes: 7.2 years BMI: 23.6 HbA1c: 5.2% Note: non-diabetic range 3.4-4.9%	N/A	Symptomatic event requiring treatment with IV glucose or glucagon and confirmed by blood glucose measurement of <2.8 mmol/L	Population: Yes Outcomes: Yes Measurement: Yes Confounding: Yes Intervention: Yes
Holstein 2003[107] Germany, Austria, Switzerland NR	Case series Cases reported by randomly chosen MDs and members of German Diabetes Assoc. at acute care hospitals	Responses received from 24/400 MDs (6%)	N=93 episodes Age: 77.7 years % male: 41 BMI: 24.7 Duration of diabetes: 9.1 years HbA1c: 5.3% Note: non-diabetic range 3.4-4.9%	N/A	Symptomatic event requiring administration of IV glucose or glucagon and confirmed by blood glucose < 2.8 mmol/l	Population: No Outcomes: Yes Measurement: No Confounding: No Intervention: N/A

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Holstein 2003[109] Germany NR	Population-based case series N/A	Inclusion criteria: All episodes of severe hypoglycemia in all patients presenting in the emergency department of one hospital, 1997-2000	N=148 (56%) cases of severe hypoglycemia in 121 patients with type 2 diabetes Age: 76 years % male: 36 BMI: 25.7 Duration of diabetes: 17 years Renal failure (CrCl<60 ml/min): 54% HbA1c: 6.2% Note: non-diabetic range 3.4-4.9%	N/A	Symptomatic event requiring administration of IV glucose or glucagon injection that relieved symptoms and confirmed by blood glucose measurement	Population: Yes Outcomes: Yes Measurement: Yes Confounding: No Intervention: N/A
Holstein 2009[102] Germany NR	Case-control Tertiary care hospital N/A	Inclusion criteria: Type 2 diabetes, on sulfonylureas Exclusion criteria: On insulin	Cases: 43 (mean glucose level at time of event: 32) Controls: 54	N/A	Symptomatic event requiring therapy with IV glucose confirmed by blood glucose < 50 mg/dl	Population: No Outcomes: Yes Measurement: Yes Confounding: Yes Intervention: N/A
Holstein 2011[103] Germany Industry	Case-control Clinic Lippe-Detmold, a large tertiary-care hospital in East Westphalia, Germany, January 2000 -December 2009	Inclusion criteria: Patients attending the ED of Lippe-Detmold Clinic and taking sulfonylurea	N=203 Age: 78.4 years % male: 52.7 BMI: 26.9 Duration of diabetes:11.3 years HbA1c: 6.9%	Patients on sulfonylurea: Patients experiencing severe hypoglycemia (n=102) Patients with no severe hypoglycemia (n=101)	Symptomatic event requiring treatment with intravenously administered glucose and confirmed by blood glucose measurement of <50 mg/dl	Population: No Outcomes: Yes Measurement: Yes Confounding: Yes Intervention: N/A

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Honkasalo 2010[77] Finland Foundation	Retrospective Cohort Local ambulance registries, local healthcare unit databases, patient questionnaires 12 months	N/A	N=1065 patients with type 2 diabetes Age: 65.4 years	N/A	Required the help of another person to recover from a hypoglycemic episode.	Population: No Outcomes: No Measurement: No Confounding: No Intervention: N/A
Hypertension in Diabetes IV 1996[188] United Kingdom Government/ Industry/ Foundation	RCT 5 years	Inclusion criteria: Non-insulin dependent diabetes Exclusion criteria: Required strict blood pressure control or beta blockade; severe vascular disease, severe concurrent illness; pregnant women	N=758 Age: 57 years % male: 53 Race/ethnicity (%): Caucasian=87% Asian=5% Afro-Carribean=8% BMI: 29 Duration of diabetes: 3.2 years HbA1c: 6.8% Smoking: 22% current	Tight blood pressure control (<150/85 mmHg) (N=497) Less tight control (<180/105 mmHg) (N=261) Part of UKPDS	Requiring medical assistance or admission to hospital	Allocation concealment: Unclear Blinding: Unclear Intention to treat analysis (ITT): Not for hypoglycemic reactions Withdrawals/dropouts adequately described: No
Kendall 2005[56] United States 91 sites Industry	RCT 30 weeks	Inclusion criteria: Age 22-77: taking metformin and SU; FPG <13.3, BMI 27-45, HbA1c: 7.5 to 11%; metformin at least 1500 mg/d and SU at maximally effect dose for 3 months; weight stable for 3 months; no abnormal labs; women postmenopausal , surgically sterile or on OCs for 3 months Exclusion criteria: Other significant medical conditions or use of other oral glucose lowering drugs or weight loss drugs within 3 months; on steroids, drugs affect GI motility, transplantation or invest drugs	N=733 Age: 56 years % male: 58 Race/Ethnicity (%): White=68 Black=11 Weight (lbs):215.6 BMI: 34 Type 2 (%):100 Diabetes duration: 8.9 years HbA1c: 8.5% ACE inhibitor: 50%	Exenatid 5ug bid N=245 Exenatide 10ug bid N=241 Placebo N=247	Required the assistance of a third party	Allocation concealment: Unclear Blinding: Yes Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Kennedy 2006[37] **GOAL HbA1c** United States 2,164 sites Industry	RCT 24 weeks	Inclusion criteria: Men and women, ≥18 years of age, diagnosis of type 2 diabetes for ≥1 year, inadequate glycemic control (A1c >7.0%) despite diet, exercise, OHAs; candidate for insulin; stable doses of current medications for ≥2 months before randomization Exclusion criteria: Severe heart failure; significant renal or hepatic disease; pregnancy or lactation; malignancy in last 5 years (except treated basal cell carcinoma); dementia; hypersensitivity to insulin glargine; any other condition that could interfere with study completion; treated with metformin with impaired renal function (modified after 498 randomized to allow continuation in study if metformin was discontinued)	N=5,721 Age: 57 years % male: 49 Race/Ethnicity (%): White=71 Black=16 Hispanic=10 Other=3 BMI: 34.3 Type 2 (%): 100 Duration of diabetes: 8.5 years HbA1c: 8.9%	1) Insulin glargine usual titration and laboratory HbA1c testing; n=1,978 2) Insulin glargine usual titration and point-of-care (POC) HbA1c testing; n=1,975 3) Insulin glargine active titration and laboratory HbA1c testing; n=1,967 4) Insulin glargine active titration and POC HbA1c testing; n=1,973	Patient required assistance and 1) there was prompt response to treatment (e.g., glucose or glucagon) or 2) SMBG level <36 mg/dl	Allocation concealment: Yes Blinding: No Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Yes
Labad 2010[123] Scotland Government	Cross-sectional Lothian Diabetes Register 12 months	Inclusion criteria: Individuals between 60 and 74 years old with a confirmed diagnosis of type 2 diabetes Exclusion criteria: Non-type 2 diabetes, non-English speakers, or unable to read large print.	N=1066 Age: 67.9 years % male: 51.3 Race/Ethnicity (%): White=95.3 Other=4.7 Duration of diabetes: 9.1 years HbA1c: 7.4% History of severe hypoglycemia: 10.8% MI: 14.1% Angina: 28% Cerebrovascular disease: 8.7%	N/A	Needing assistance by another person	Population: Yes Outcomes: No Measurement: Yes Confounding: Yes Intervention: N/A

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Lee 2006[114] United States Industry	Retrospective pre-post cohort Medical and pharmacy claims data from PharMetrics database January 1, 2001 - April 30, 2005	Inclusion criteria: Age >18 years; multiple claims indicating a diagnosis of type 2 diabetes and use of insulin therapy; initiated treatment with insulin analogue pen device July 1, 2001 to December 31, 2002; data for at least 6 months before index date and at least 2 years of continuous enrollment after	N=1156 Age: 45.4 years % male: 53.8 Metabolic disease: 8.2% Neuropathy: 8.2% nephropathy: 7.6% retinopathy: 7.2% CVD: 6.7%	Conversion to insulin pen therapy Target HbA1c: N/A	No clear definition ED visits, hospitalizations, MD visits related to hypoglycemia	Population: Yes Outcomes: No Measurement: Yes Confounding: Yes Intervention: Yes
Leese 2003[25] Scotland Industry	Retrospective cohort DARTS/ MEMO registry N/A	Inclusion criteria: Type 1 or 2 diabetes in the registry who were alive in 1997 and who were either still alive in 1998 or had died but had not emigrated from the area during the one year study period	N=977 w/ type 1 and 7678 w/ type 2 Type 2: Age: 65 years % male: 52 Duration of diabetes: 8 years	N/A	Required emergency treatment from primary care, ambulance, or other emergency services; severe defined as blood sugar < 3.5 mmol/L requiring treatment with glucagon, IV dextrose or paramedic confirmation of low blood sugar with rapid recovery following treatment	Population: Yes Outcomes: Yes Measurement: Yes Confounding: No Intervention: N/A
Leiter 2005[124] Canada 4 sites Industry	Cross-sectional Questionnaire to patients with scheduled clinic visit	Inclusion criteria: Male or female; ages 18 years and older; type 1 or 2 diabetes; treated with insulin alone or with OHAs for at least 1 yr	N=335 (97% of patients screened) N=133 with type 2 Age: 60 years BMI: 32 HbA1c: 7.5%	N/A	Required external assistance and plasma glucose <2.8 mmol/L	Population: No Outcomes: Yes Measurement: Yes Confounding: N/A Intervention: N/A

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Liebl 2009[48] PREFER Europe 107 sites Industry	RCT 26 weeks	Inclusion criteria: Adults; BMI≤40; on 1 or 2 OHAs with or without insulin; HbA1c ≥ 7.0% and ≤ 12% Exclusion criteria: Cardiac disease, impaired hepatic or renal failure, proliferative retinopathy, recent treatment with 3 or more OHAs or use of short-acting or pre-mixed insulin in past 6 months	N=719 Age: 60 years % male: 57 BMI: 31 Type 2 (%): 100 HbA1c: 8.5%	Basal-bolus with insulin detemir and insulin aspart (N=541) Premixed analogue insulin with biphasic insulin aspart (n=178) target HbA1c not specified	Patient unable to treat themselves	Allocation concealment: Unclear Blinding: No Intention to treat analysis (ITT): No (1 dose) Withdrawals/dropouts adequately described: Yes
Lundkvist 2005[125] Sweden Industry	Cross-sectional Interviews of patients at primary care centers	Inclusion criteria: Age≥ 35; type 2 diabetes, treatment with OHA and/or insulin	N=309 115 w/ hypoglycemia; 194 without Age: 65 years Microvascular complication: 39% Macrovascular complication: 28%	NA	Required assistance of a third party to rectify the situation	Population: No Outcomes: No Measurement: No Confounding: Yes Intervention: N/A
Marre 2009[175] 21 countries 116 sites Industry	RCT 26 weeks	Inclusion criteria: Treated with OHAs for ≥ 3 months; 18-80 years old; HbA1c 7—10%; BMI ≤ 45; Exclusion criteria: Insulin use within 3 months; impaired liver or renal function; uncontrolled HTN; cancer or any drugs apart from OHAs likely to affect glucose concentrations	N=1041 Age: 56 years % male: 50 Weight (lbs): 180.4 BMI: 30 Type 2 (%): 100 Duration of diabetes: 6.5 years HbA1c: 8.5%	**Glimepiride, 2-4mg/day PLUS:** a) Liraglutide 0.6 SC and rosiglitazone b) Liraglutide 1.2 SC and rosiglitazone c) Liraglutide 1.8 SC and rosiglitazone d) Liraglutide and rosiglitazone 4mg/day HbA1c<7%	Self-measured blood glucose = 3.0 mmol/l	Allocation concealment: Unclear Blinding: YesIntention to treat analysis (ITT): No (1 dose) Withdrawals/dropouts adequately described: Yes
Marre 2009[18] PREDICTIVE France Industry	Prospective Cohort Patient medical records 52 weeks	Inclusion criteria: Patients prescribed insulin detemir by physician, including those who switched from treatment with other basal insulin and insulin-naïve patients Exclusion criteria: Patients unlikely or unable to comply with the study protocol; patients not classified as diabetes type 1 or 2	N=1772 Type 1 diabetes (n=643) Type 2 diabetes (n=1129) Age: 57 years % male: 50 Weight (lb): 172.6 BMI: 28.2 Type 2 (%): 63.7 Duration of diabetes: 15.5 years Major hypoglycemia: 6.7% HbA1c: 8.6%	N/A	Severe CNS symptoms consistent with hypoglycemia; subject unable to treat himself/ herself and third-party intervention is needed; has one of the following: a) Blood glucose <2.8 mmol/l (50 mg/dl) b) Reversal of symptoms after food intake, glucagon or intravenous glucose	Population: No Outcomes: Yes Measurement: Yes Confounding: No Intervention: Yes

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Marrett 2009;[81] **Marrett 2011**[87] United States Industry	Cross-sectional 2007 Health and Wellness Survey	Inclusion criteria: Those who reported being treated with one or more OHAAs any time during the previous 6 months Exclusion criteria: Patients who reported insulin use within the same previous 6 months	N=1984 Age: 58.1 % male: 56.7 BMI: 34.5 Duration of diabetes: 7.3 years Microvascular: 22.5% Heart attack: 8% Angina: 8.5% Stroke: 4.3% Peripheral Vascular Disease: 0.96% CHF: 4.3%	N/A	Required the assistance of others to manage symptoms or requiring medical assistance	Population: Yes Outcomes: Yes Measurement: No Confounding: No Intervention: N/A
Matthews 2010[49] Multinational Industry	RCT 2 years	Inclusion criteria: Men, non-fertile women and women of child-bearing potential using medically approved birth control; aged 18–73 years; Type 2 diabetes inadequately controlled (HbA1c 6.5–8.5%) by metformin monotherapy	N=3118 Age: 57.5 years % male: 53.5 Race/Ethnicity (%): White=86.8 Black=1.2 Asian=2.9 Hispanic=8.4 Other=0.7 Weight (lbs): 196.2 BMI: 31.8 Duration of diabetes: 5.7 HbA1c: 7.3% Current Smokers: 16.6%	Vidagliptin 50 bid Glimepiride starting at 2 mg Groups added to metformin therapy	Any episode requiring assistance of another party	Allocation concealment: No Blinding: Yes Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: No

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Meneghini 2007[176] PREDICTIVE United States 1083 sites Industry	RCT 26 weeks	Inclusion criteria: Type 2 diabetes; ≥18 years old; HbA1c ≤12%; BMI ≤45; likely to benefit from initiation of detemir, addition of detemir to other therapy, change to detemir, or continuation of detemir Exclusion criteria: Any glucose lowering medication not indicated in combination with detemir; anticipate starting on another medication known to interfere with glucose metabolism (e.g., steroids); proliferative retinopathy or maculopathy; history of hypoglycemia unawareness or recurrent major hypoglycemia; pregnant; nursing; had serious illness	N=4937 Age: 59 years % male: 52 Race/Ethnicity (%): White=77 Black=17 Asian=2 Other=5 BMI: 33.8 Type 2 (%): 100 Duration of diabetes: 11.4 years HbA1c: 8.5%	Randomization by study site (n=1083) to: a) Intervention: self-adjustment of insulin according to algorithm b) Control: adjustment by investigator according to standard of care Everyone was on detemir qhs as basal insulin; other medications as needed No target HbA1c	Symptoms of low blood sugar that resolved with oral carbohydrates, glucagon or IV glucose AND blood sugar < 56 AND patient was unable to treat himself	Allocation concealment: Unclear Blinding: No Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Yes
Miller 2001[100] United States Government	Cross Sectional Diabetes Clinic of the Grady Health System, Inc, Atlanta, Ga. April 1, 1999 – October 31, 1999	Inclusion criteria: Type 2 diabetes with follow-up data > 2 months	N=1055 Age: 60.9 years % male: 28.2 Race/Ethnicity (%): White=3.6 Black=93.8 Other=2.6 BMI: 33.0 Duration of diabetes: 10.8 years HbA1c: 7.6%	N/A	Loss of consciousness or other major alteration of mental status caused by hypoglycemia that required the assistance of another person to treat the condition	Population: Yes Outcomes: Yes Measurement: Yes Confounding: Yes Intervention: N/A
Moen 2009[75] United States Government/ Foundation	Retrospective cohort Veterans Health Administration fiscal year 2005 acute inpatient data files 12 months	Inclusion criteria: At least one acute care hospitalization between Oct 1, 2004 – Sept 30, 2005 and at least one outpatient measure of serum creatinine between week 1 and 1 year before hospitalization	N=243,222	N/A	Severity denoted by categorical glucose measures: ≥60 and <70 mg/dl; ≥50 and <60 mg/dl; <50 mg/dl	Population: Yes Outcomes: Yes Measurement: Yes Confounding: Yes Intervention: N/A

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Murata 2005[19] United States Government (VA)	Prospective cohort Mean: 41 weeks	Inclusion criteria: Type 2 taking at least 1 dose of long acting insulin daily; did not self-titrate insulin; stable for 2 months. Exclusion criteria: History of ETOH or SUD, chronic liver disease, pancreas insufficiency, chronic infectious disease, endocrinopathy, creatinine > 3, on corticosteroids or immunosuppressant drugs, insulin pump, life expectancy < 1 yr	N=344 Age: 66 years % male: 96 BMI: 32 Diabetes duration: 15 years Insulin treatment: 8 years Also on OHA: 48% HbA1c: 8.0%	N/A	Blood sugar≤ 60 with symptoms of affected mental function or requiring assistance of others	Population: Yes Outcomes: No Measurement: No Confounding: No Intervention: N/A
Nauck 2007;[177] **Seck 2010**[50] Multinational Industry	RCT 52 wks, then f/u for another year	Inclusion criteria: Age 18-78; Type 2 diabetes; not currently on an OHA or on an OHA other than metformin monotherapy at a dose ≥1500 mg/day or on metformin in combination with another OHA; HbA1c >6.5% and < 10%	N=1172 Age: 56.7 years % male: 59.2 Race/Ethnicity (%): White=73.9 Black=6.5 Hispanic=7.6 Asian=8.4 Other=3.6 Weight(lbs): 197.2 BMI: 31.3 Duration of diabetes: 6.4 years HbA1c: 7.7%	Sitagliptin 100mg qd Glipizide starting at 5 mg qd Groups added to metformin therapy	Required nonmedical assistance Required medical assistance	Allocation concealment: Unclear Blinding: Yes Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Yes
Nauck 2009[53] **(LEAD-2)** 21 Countries, 170 sites Industry	RCT 26 weeks	Inclusion criteria: Type 2 diabetes; age 18-80 yrs; HbA1c 7-11% (if prestudy OHA monotherapy ≥3 months) or 7-10% (if prestudy combination OHA therapy ≥3 months); BMI ≤ 40 Exclusion criteria: Insulin use during previous 3 months	N=1087 Age: 57 years % male: 58 Race/Ethnicity (%): White=87 Black=3 Asian/Pacific Islander=9 Other=1 BMI: 31 Duration of diabetes: 7.6 years HbA1c: 8.4%	Liraglutide (once-daily) 1) 0.6 mg (n=242) 2) 1.2 mg (n=240) 3) 1.8 mg (n=242) Glimepiride (once-daily): 4 mg (n=242) Placebo (n=121)	Required third-party assistance	Allocation concealment: No Blinding: Yes (reported to be double-blind) Intention to treat analysis (ITT): No (excluded 4 who did not receive a treatment dose) Withdrawals/dropouts adequately described: Yes

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Nichols 2010[26] United States Industry	Retrospective cohort database of patients newly started on insulin 49 months	Inclusion criteria: Type 2 diabetes, 18 or older with no prior insulin use who then were started on insulin between 1999-2004 Exclusion criteria: No HbA1c in the 6 months prior to insulin initiation or only had 1 insulin prescription filled	N=3332 Age: 60 years % male: 49 Duration of diabetes: 6.8 years BMI: 34 HbA1c: 9.3% Hypertension: 61% Current smokers: 12% CVD: 25% Nephropathy: 10% Retinopathy: 17%	N/A	Defined as ICD-9 251.0 and 251.2 during an outpatient visit	Population: Yes Outcomes: Yes Measurement: Yes Confounding: No Intervention: Yes
Olansky 2011[178] United States 229 sites Industry	RCT 44 weeks	Inclusion criteria: Type 2 diabetes; age 18-78; HbA1c ≥7.5% on diet; on no OHA for previous 4 months	N=815 Age: 49.7 years % male: 56.5 BMI: 33.4 Duration of diabetes: 3.4 years HbA1c: 9.9%	Sitagliptin 50/metformin 500 bid titrated up to 50/1000 bid (n=625) Metformin 500 bid titrated up to 1000 bid (N=621)	Required nonmedical or medical assistance	Allocation concealment: No Blinding: Yes Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Yes
Panikar 2003[117] India NR	Prospective Cohort 6 months of triple drug therapy	Inclusion criteria: Duration of type 2 diabetes ≥ 5 years and being treated with insulin Exclusion criteria: Known renal failure or increased serum creatinine levels >1.5 mg/dl; cardiac abnormality-history of symptomatic angina, cardiac insufficiency or history of myocardial infarction or abnormal ECG; SGOT/SGPT more than two times upper limit of normal; more than 60 ml alcohol/ day	N=124 Age: 57.1 years % male: 47 Weight (lb): 149.7 Type 2 (%): 100 HbA1c: 11.5%	Triple drug combination of: pioglitazone 15 mg/d glibenclamide 5 mg metformin 500 mg three times a day Each in addition to insulin	"Significant hypoglycemia" Not defined in paper	Population: Yes Outcomes: Yes Measurement: No Confounding: No Intervention: Yes

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Pencek 2009[20] United States 116 sites Industry	Prospective cohort 6 months	Inclusion criteria: MDs selected patients they thought would benefit from pramlinitide	N=1297 Age: 48.7 years % male: 38.6 Race/Ethnicity (%): White=84.7 Black=9.6 Hispanic=3.8 Other=1.2 Weight (lbs): 214.6 BMI: 34.1 Duration of diabetes: 18.5 HbA1c: 8%	N/A	Patient reported as self-treatable or requiring assistance (either of another person (PASH) or of a medical (MASH))	Population: No Outcomes: Yes Measurement: No Confounding: No Intervention: N/A
Pettersson 2011[82] Sweden multicenter Industry	Cross-sectional Medical record review and self administered questionnaire	Inclusion criteria: Type 2 diabetes; age≥35; metformin and SU for at least 6 months Exclusion criteria: Type 1 diabetes; HIV or hepatitis; gestational diabetes; any treatment with insulin; any treatment with akarbos, repaglinid during last 6 months	N=430 Age: 69 years % male: 61 BMI: 28.7 Microvascular events: 20% Macrovascular events: 33% Major medical events: 23%	N/A	Severe: Needed the assistance of others to manage symptoms Very Severe: Needed medical attention	Population: Yes Outcomes: No Measurement: Yes Confounding: No Intervention: N/A
Pratley 2010[179] 11 European countries 158 sites Industry	RCT Open label 26 weeks	Inclusion criteria: Type 2 diabetes; age 18-80; HbA1c 7.5 - 10.0%; BMI < 45; metformin for at least 3 months Exclusion criteria: Treatment with any OHA except metformin within 3 months of trial; recurrent major hypoglycemia or hypoglycemic unawareness; present use of any drug except metformin that could affect glucose; impaired renal or hepatic function; clinically significant cardiovascular disease; or cancer	N=675 Age: 55.3 years % male: 52.9 Race/Ethnicity (%): White=86.6 Hispanic=16.2 Black=7.2 Asian Pacific Islander=2.0 Other=4.2 Weight (lbs): 206.4 BMI: 32.8 Duration of diabetes: 6.2 years HbA1c: 8.4%	Lirgulitide 1.2 mg qd (225) Lirgulitide 1.8 mg qd (221) Sitagliptin 100 mg qd (219)	Required third party assistance	Allocation concealment: Yes Blinding: No Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Yes

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Quilliam 2011[27] United States Industry	Case-control Health care claims from the 2004 to 2008 MarketScan database (Ann Arbor, Michigan)	Inclusion criteria: Adults; 18+ years of age with at least 2 outpatient or inpatient claims for diabetes during 2004 to 2008 taking at least 1 OHA Exclusion criteria: At least 12 months of continuous eligibility within a non-capitated health plan after the initial fill date of an OHA, and those with 1 medical claim (inpatient or outpatient) for type 1 or gestational diabetes during the study period	N=14,729 Age: 54.8 years % male: 53.5	Cases: patients with hypoglycemic events (n=1339) Controls: patients without hypoglycemic events but with similar exposure status (n=13,390)	Requiring inpatient medical intervention	Population: Yes Outcomes: No Measurement: Yes Confounding: Yes Intervention: N/A
Quilliam 2011[183] United States Industry	Retrospective cohort Health care claims from the 2004 to 2008 MarketScan database	Inclusion criteria: Type 2 diabetes; age 18+; at least 2 claims for diabetes during study period; taking at least 1 OHA Exclusion criteria: At least 12 months continuous eligibility; 1 claim for type 1 or gestational diabetes	N=536,581 Age: 18-34 (3.3%) 35-49 (25.7%) 50-64 (70.8% 65+ (0.1%) % male: 54% Insulin Use: 6.0% Macrovascular complications: 7.0% Microvascular complications: 4.3%	N/A	Required medical intervention	Population: Yes Outcomes: No Measurement: Yes Confounding: Yes Intervention: N/A

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Raskin 2009[31] United States 100 sites Industry	RCT 26 weeks	Inclusion criteria: Adults with type 2; currently on OHA medication monotherapy (at least 2 months) or dual therapy; HbA1c between 7.5 and 11% inclusive (monotherapy) or between 7.0 and 10% inclusive (dual therapy) Exclusion criteria: Pregnant or nursing women; significant disease history; any investigational drug within 4 weeks of screening; treatment with TZD or systemic corticosteroids within 2 months of screening; history of hypoglycemic unawareness or recurrent severe hyperglycemia	N=561	Repaglinide/metformin BID Repaglinide/metformin TID Rosiglitazone /metformin BID	Required the assistance of others	Allocation concealment: Unclear Blinding: No (open-label) Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Yes
Rašlová 2004[112] 8 countries 31 sites Industry	Randomized, open-label trial 22 week treatment	Inclusion criteria: Men and women ≥18 years; BMI ≤40 kg/m^2; HbA1c <12.0%; history of type 2 diabetes ≥1 year Exclusion criteria: Significant medical disorder; hypoglycemic unawareness or recurrent major hypoglycemia; pregnant or breast-feeding women; allergy to insulin	N=395 Age: 58.2 years % male: 42.1 Race/Ethnicity (%): Caucasian=99.7 Non-Caucasian=0.3 Weight (lbs): 177.7 BMI: 29.2 Type 2 (%): 100 Duration of diabetes: 14.1 years HbA1c: 8.1%	Insulin detemir (IDet) (100U/mL) in combo with insulin aspart (IAsp) (n=195) NPH insulin (NPH) (100IU/mL) in combo with regular human insulin (HIS) (n=199)	Individual unable to treat him/herself	Allocation Concealment: No Blinding: Yes- Intention to Treat Analysis (ITT): No Withdrawals/ Dropouts: Yes
Ratner 2002[34] United States 37 sites Industry	RCT 52 weeks	Inclusion criteria: Age 26-76; type 2 diabetes; on insulin for at least 6 months; HbA1c 7.5-13%, body weight +/-60% of desirable according to Met Life tables Exclusion criteria: IHD; uncontrolled HTN; GI or renal disease (CR > 2); unstable diabetic retinopathy; treatment with drugs known to affect gastric motility or glucose metabolism	N=538 Age: 56 years % male: 60 Race/Ethnicity (%): White=58 Black=9 Hispanic=7 Other=1 Unknown=25 BMI: 31 Duration of diabetes: 12 years HbA1c: 9.2%	Mealtime (tid) injections of placebo, or 30, 75, or 150 ug of pramlintide Target HbA1c < 8%	Events requiring assistance of another individual, or administration of glucagon, or IV glucose. Were then rated mild, moderate, severe by PI	Allocation Concealment: Unclear Blinding: Yes Intention to Treat Analysis (ITT): No (1 dose) Withdrawals/Dropouts adequately described: Yes

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Rayman 2006[45] Multinational 90 sites Industry	RCT 26 weeks	Inclusion criteria: Age ≥ 18; Type 2 DM; > 6 months continuous insulin therapy; HbA1c 6.0 - 11.0%	N=890 Age: 60 years % male: 49.7 BMI: 31.3 Duration of diabetes: 13.5 years HbA1c: 7.5%	Insulin glulisine and NPH (N=448) RHI + NPH (N=442)	Requiring assistance of another person and confirmed by blood sugar <36 mg/dl or associated with prompt recovery with oral carbohydrate, IV glucose, or glucagon	Allocation concealment: Unclear Blinding: No (open-label) Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Yes
Redelmeier 2009[129] Canada Government	Case control study Ontario Ministry of Transportation Medical Advisory Board	Inclusion criteria: Licensed drivers in Ontario 1/1/05-1/1/07 with commercial license annual review, report after crash, or diabetic patients reviewed for other reason Exclusion criteria: No HbA1c available	N=795 Age: 52 yr % male: 80 Duration of diabetes: approx 20 yrs HbA1c: ranged from 4.4-14.7%	N/A	Required outside assistance	Population: Yes Outcomes: Yes Measurement: No Confounding: Yes Intervention: N/A
Rhoads 2005[118] United States NR	Retrospective cohort MarketScan Health Productivity and Management Database (data from 5 large employers)	Inclusion criteria: Employees eligible in incur absence and/or short term disability with pharm. benefits; at least 12 mos continuous enrollment; at least 2 drug claims for same class of DM-related medications	N=442 with hypoglycemia Age: 44 years % male: 71	N/A	ICD-9-CM 250.8, 251.1, 251.2	Population: Yes Outcomes: Yes Measurement: Yes Confounding: Yes Intervention: N/A

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Riddle 2003;[41] Dailey 2009,[132] INSULIN GLARGINE 4002 United States and Canada Industry	RCT 24 week	Inclusion criteria: Men and women; ages 30-70 years; diabetes for ≥ 2 years, treated with stable dose of 1 or 2 OHAs (sulfonylurea, metformin, pioglitazone, rosiglitazone) for ≥ 3 mos; BMI 26-40 kg/m^2; HbA1c 7.5-10%; FPG ≥ 140 mg/dl at screening Exclusion criteria: Prior use of insulin except for gestational diabetes or for <1 wk; current use of α-glucosidase inhibitor or rapid-acting insulin secretagogue; use of other agents effecting glycemic control, history of ketoacidosis or self-reported inability to recognize hypoglycemia; serum alanine aminotransferase or aspratate aminotransferase > 2 times upper limit of normal	N=756 Age: 67 years % male: 56 Race/Ethnicity (%): White=84 Black=12 Asian=3 Multiracial=1 Hispanic=8 BMI: 32.4 Duration of diabetes: 8.7 years HbA1c: 8.6%	Glargine starting dose 10 IU at bedtime, titrated weekly NPH same HbA1c ≤7.0% was study outcome	Symptoms consistent with hypoglycemia during which the subject required the assistance of another person and was associated with either a glucose level <56mg/dl or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon	Allocation concealment: Yes Blinding: No Intention-to-Treat Analysis (ITT): No (1 dose) Withdrawals/dropouts adequately described: Yes
Rosenstock 2008[189] Europe and United States 80 sites Industry	RCT 52 weeks	Inclusion criteria: Insulin naïve pts with type 2 diabetes; age ≥18; diabetes for at least 1 year; BMI < 40; HbA1c 7.5 – 10%; on one or two OHA for at least 4 months at least ½ the maximal recommended dose	N=582 Age: 58.9 years % male: 57.9 Race/Ethnicity (%): White=88.1 Black=5.8 Asian Pacific Islander=2.4 Other=3.6 Weight (lbs): 192.3 BMI: 30.5 Duration of diabetes: 9.1 years HbA1c: 8.6%	Detemir (291) Glargine (291) qhs titrated to target FPG <6.0	Required assistance from a third party	Allocation concealment: No Blinding: No Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes

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Rosenstock 2001[39] United States 59 sites Industry	RCT 28 weeks	Inclusion criteria: Type 2 diabetes, age 40-80, on insulin for ≥ 3 months HbA1c 7-12%, BMI < 40 Exclusion criteria: Significant hepatic or renal dysfunction, had received treatment with an OHA within prior 3 months	N=518 Age: 59 years % male: 60 Race/Ethnicity (%): White=80 Black=40 Hispanic=22 BMI: 30.6 Type 2 (%): 100 Duration of diabetes(years): 13.7 Duration of insulin use (years): 8.4 years Symptomatic hypoglycemia during screening:27% HbA1c: 8.6%	Glargine: qd NPH: qd or bid Target HbA1c: <6.7%	Event with symptoms consistent with hypoglycemia in which the subject required assistance of another person and was either accompanied by a blood glucose of < 2.0 mmol/L or had prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration	Allocation concealment: Unclear Blinding: No Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes
Rosenstock 2009[35] United States and Canada Industry	RCT 5 years	Inclusion criteria: Age 30-70; Type 2 for ≥ 1 yr; stable dose for > 3months on OHAs or insulin alone or in combination; HbA1c 6-12% Exclusion criteria: Proliferative or severe non-proliferative retinopathy; history of laser vitrectomy or photocoagulation; use of insulin within 3 months; SBP >150 or DBP > 90; history of hypoglycemia unawareness	N=1024 Age: 55 years % male: 54 Weight (lbs): 217.8 BMI: 34 Type 2 (%): 100 Diabetes duration: 11 years Duration of insulin use (years): 5 years Renal insufficiency: 10% HbA1c: 8.4%	Insulin glargine (N=513) qd NPH insulin (N=504)bid	Symptomatic hypoglycemia requiring assistance and either with blood glucose levels of ≤3.1 mmol/l or treated with oral or injectable carbohydrate or glucagon injection	Allocation concealment: Unclear Blinding: No Intention to treat analysis (ITT): No (1 dose) Withdrawals/dropouts adequately described: Yes

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Russell-Jones 2009[54] (LEAD-5 met+SU) 17 Countries, 107 sites Industry	RCT 26 weeks	Inclusion criteria: Type 2 diabetes; age 18-80; treated with OHAs for ≥3 months before screening; HbA1c 7.5-10% if on oral monotherapy or 7-10% if on combination therapy; BMI ≤45 Exclusion criteria: Insulin use within 3 months prior to trial; impaired hepatic or renal function; clinically significant CV disease; proliferative retinopathy or maculopathy; hypertension (≥180/100 mmHg) or cancer; pregnant; recurrent hypoglycemia or hypoglycemia unawareness; seropositive for hepatitis B antigen or hepatitis C antibody; using any other medications that could affect blood glucose levels	N=576 Age: 57.5 years % male: 56.6 Race/Ethnicity: NR Weight (kg): 85.3 BMI: 30.5 Duration of diabetes: 9.4 years HbA1c: 8.3%	Randomized if received glimepiride (4 mg) and metformin (2 g) for at least 3 weeks and had fasting glucose of 7.5 to 12.8 mmol/l after 6 week run-in Liraglutide once-daily (1.8 mg) (blinded) (n=230) Liraglutide placebo once-daily (blinded) (n=114) Insulin glargine once-daily (open label) (n=232) All in combination with metformain and glimepiride (open label)	Requiring third-party assistance	Allocation concealment: Yes Blinding: Partial, participants, investigators, study monitors for liraglutide and placebo groups (see interventions) Intention to treat analysis (ITT): No (excluded 5 who did not receive a treatment dose) Withdrawals/dropouts adequately described: Yes
Saloranta 2002[59] 12 Countries, 103 sites Industry	RCT 24 weeks	Inclusion criteria: Men and women, age 30 or older; type 2 diabetes for ≥6 weeks; maintained on diet alone for ≥6 weeks before screening; FPG 7.0-8.3 mmol/L Exclusion criteria: Type 1 diabetes; pancreatic injury; acute metabolic or significant diabetic complications	N=675 Age: 60.2 years % male: 62.5 Race/Ethnicity (%): Caucasian=95.6 Black=1 Asian=1.3 Other=2.1 BMI: 28.9 Duration of diabetes: 3.6 years HbA1c: 6.5%	Nateglinide 30, 60, or 120 mg (maintain diet and exercise during study) Goal HbA1c <6.0%	Requiring outside assistance	Allocation concealment: Unclear Blinding: Yes - double Intention to treat analysis (ITT): Unclear Withdrawals/dropouts adequately described: No
Sarkar 2010[78] United States Government	Cross-sectional Survey of patients from Kaiser Permanente northern California 62% Response Rate	Inclusion criteria: Type 2 diabetes on medications; age 30-75	N=14,357 Age: 58 years % male: 51 Race/Ethnicity (%): White=22 Black=17 Latino=23 Asian=20 Other/mixed=20 Duration of diabetes: 10 years HbA1c: 7.6%	N/A	Participant report of having a "severe low blood sugar reaction, such as passing out or needing help to treat the reaction"	Population: Yes Outcomes: Yes Measurement: No Confounding: Yes Intervention: N/A

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Sato 2010[106] Japan NR	Case-control Seirei Hamamatsu General Hospital January 2005 – October 2009	Inclusion criteria: Type 2 diabetes treated with sulfonylurea Exclusion criteria: Patients with factitious hypoglycemia owing to the mistaken use of medicine or attempted suicide, severe acute infection, heart failure, acute coronary syndrome, hepatic dysfunction, endocrine disorders, or renal failure	N=157 Age: 66 years % male: 59.9 BMI: 24 Duration of diabetes: 8.9 years HbA1c: 7.8%	Case: Admission to hospital with severe hypoglycemia (n=32) Control: Outpatients without severe hypoglycemia (n=125)	Characteristic symptoms and a plasma glucose level of less than 50 mg/dl which required intravenous glucose administration	Population: No Outcomes: No Measurement: No Confounding: No Intervention: N/A
Schernthaner 2004[57] Europe Industry	RCT 27 weeks	Inclusion criteria: Type 2 diabetes, >35 years old, treated for at least 3 months with diet alone or in combination with metformin or an α-glucosidase inhibitor HbA1c 6·9-11·5%, able to perform home blood glucose monitoring Exclusion criteria: Contraindication to study drugs, no effective contraception in women with child-bearing potential, elevated transaminases more than threefold the upper normal range	N=845 Age: 60.5 years % male: 51.5 Weight (lbs): 183.6 BMI: 30.6 Duration of diabetes: 5.7 years HbA1c: 8.3% Macrovascular: 21.4% Microvascular: 10.5%	Gliclazide modified release (MR) Glimepiride Both arms either as monotherapy or with pts current therapy maintained at a stable dose	Symptomatic episodes requiring external assistance owing to severe impairment in consciousness or behavior, with BGL < 3 mmol/L	Allocation concealment: Unclear Blinding: Yes Intention to treat analysis (ITT): No (1 dose) Withdrawals/dropouts adequately described: Yes
Shen 2008[101] United States NR	Cross-sectional National Inpatient Sample database	Inclusion criteria: Discharge diagnosis of diabetes Exclusion criteria: Age < 18, pregnancy, skin diagnoses, transfers to other hospitals, discharges with "missing values"	N=787,836 Age: 66 years % male: 46	N/A	"Acute hypoglycemic condition" as a discharge diagnosis	Population: Yes Outcomes: Yes Measurement: Yes Confounding: Yes Intervention: N/A
Shorr 1997[97] United States Government	Retrospective Cohort Tennessee Medicaid enrollees January 1, 1985, through December 31, 1989	Inclusion criteria: All Tennessee Medicaid enrollees aged 65 years and older who used insulin or oral hypoglycemic drugs from 1985 through 1989 and experienced severe hypoglycemia; 1 full year of Medicaid enrollment was required	N=586 Age: 78 years % male: 18 Race/Ethnicity (%): White=48 Non-white=52	N/A	Neuroglycopenic or autonomic symptoms, with a concomitant blood glucose determination of <50 mg/dL)	Population: Yes Outcomes: Yes Measurement: Yes Confounding: Yes Intervention: N/A

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Sotiropoulos 2005[108] Greece NR	Case series Clinical records at a single hospital	Inclusion criteria: Patients admitted due to severe hypoglycemia	N=207 Age: 62 years % male: 41 Duration of diabetes: 7.4 years HbA1c: 6.8%	N/A	Comatose or pre-comatose on arrival at ED; glucose < 50, and needing IV glucose	Population: Yes Outcomes: Yes Measurement: No Confounding: Yes Intervention: N/A
Stahl 1999[28] Switzerland NR	Case series Medical records for ER admissions at the University Hospital, Basle Switzerland 12 years	Inclusion criteria: Type 2 diabetes treated with long versus short-acting sulfonylurea Exclusion criteria: Insulin treatment	N=28 Age: 71.8 years % male: 46.4 Duration of diabetes: 10.2 years	Long- acting sulfonylurea (n=16) Short-acting sulfonylurea (n=12)	Episodes of hypoglycemia leading to hospital admission	Population: No Outcomes: Yes Measurement: No Confounding: Yes Intervention: Yes
Standl 2006[180] 11 European countries, 113 centers Industry	RCT 24 weeks	Inclusion criteria: men or women, age 18-80 years, type 2 diabetes diagnosed at least 3 years prior to study entry, on oral anti-diabetics for at least 6 months with poor control (HbA1c ≥7.5% and ≤10.5%, FBG ≥120 mg/dl), BMI ≤35 kg/m^2	N=624 Age: 61.8 years % male: 54.5 BMI: 28.5 Type 2 (%): 100 Duration of diabetes: 9.9 years HbA1c: 8.8%	AM Glargine titrated to target FBG ≤ 100 mg/dl and AM glimepiride (6 to 9 am) PM Glargine n=312; titrated to target FBG ≤ 100 mg/dl and AM glimepiride (6 to 9 am)	Symptoms consistent with hypoglycemia during which the person required the assistance of another person and was associated with a blood glucose level <50 mg/dl or with prompt recovery after oral carbohydrate, IV glucose or glucagon administration	Allocation concealment: Unclear Blinding: No Intention to treat analysis (ITT): No Withdrawals/dropout adequately described: No
Stepka 1993[98] Poland NR	Retrospective Cohort Medical records from GI and Metabolic Diseases of one hospital, 1975 - 1989	Inclusion criteria: Diabetic patients admitted for serious hypoglycemia	N=137 Age: 66.4 years Type 2: 73.7% Treated with insulin: 26.3%	N/A	Requiring immediate aid in a health care institution	Population: Yes Outcomes: Yes Measurement: No Confounding: Yes Intervention: N/A

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Stork 2007[130] Netherlands Foundation	Case Control University Medical Center Utrecht, Netherlands	Inclusion criteria: Adults ages 20 to 65 with a diabetes duration of 2 years, absence of cardiovascular disease or neuropathy, visual acuity > 16/20 in both eyes, drivers license Exclusion criteria: Medication use that would influence hypoglycemia counter-regulation.	N=20 (Type 2 diabetes) Age: 51.6 years % male: 80 Weight (lbs): 196.7 BMI: 28.3 Duration of diabetes: 8.7 years HbA1c: 7.9%	Type 1 diabetes with impaired hypoglycemic awareness Type 1 diabetes with normal hypoglycemic awareness Type 2 diabetes with normal awareness	N/A	Population: No Outcomes: Yes Measurement: No Confounding: No Intervention: Yes
Sugarman 1991[96] United States NR	Retrospective Cohort Medical records for all hospital discharges from Navajo Area Indian Health Service facilities October 1st 1983 to September 30th 1988	Exclusion criteria: Children, intentional drug overdose, non-diabetic	113 diabetic patients with 130 admissions (126 admissions among 109 patients who had been prescribed hypoglycemic agents) Race/ethnicity: Native American (100%) Duration of diabetes: 11.9 years (based on data from 108 patients)	N/A	Definition not given - all patients had been admitted to a hospital	Population: Yes Outcomes: Yes Measurement: Yes Confounding: No Intervention: N/A
UK Hypoglycaemia Study Group (UKHSG) 2007[190] United Kingdom 6 centers Government	Prospective cohort study 9–12 months	Inclusion criteria: Type 2 diabetes; patients with type 1 diabetes for < 5 years or > 15 years. Exclusion criteria: HbA1c >9%, measured centrally by an HPLC; severe diabetic complications, e.g., binocular visual acuity <6/12, major amputation, severe peripheral sensory neuropathy; treatment with metformin or acarbose alone; seizures unrelated to hypoglycemia; concurrent malignant disease; severe systemic diseases unrelated to diabetes; pregnancy Insulin users had to be taking two or more injections daily	N=274 Age: 57.2 years % male: 68.2 BMI: 29.8 Type 2 (%): 43 HbA1c: 7.5%	Subjects were given hypoglycemia reporting forms, on which they were asked to document the time, duration, symptoms, glucose level (if checked) and treatment required during any episode of hypoglycemia	Requiring help for recovery	Population: Yes Outcomes: No Measurement: No Confounding: No Intervention: N/A

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
UKPDS 33 1998[21] United Kingdom 23 sites Government/ Foundation/ Industry	RCT Median: 11 years	Inclusion criteria: Newly diagnosed with diabetes (confirmed with FPG > 6mmol/l); age 25 to 65 years Exclusion criteria: Ketouria > 3 mmol/l; myocardial infarction in the previous year; current angina or HF; >1 major vascular episode;, serum creatinine > 175 umol/l; retinopathy requiring photocoagulation; malignant hypertension; uncorrected endocrine abnormality; occupation precluding insulin therapy; severe concurrent illness; inadequate comprehension	N=3867 Age: 59 years % male: 59 Race/Ethnicity (%): Caucasian=78 Afro-Caribbean=12 Asian=10 Weight (lbs): 178.2 BMI: 29.1 Type 2 (%): 100 HbA1c: 7.3%	FPG goal of 6 mmol/L. (n=2729); these patients received dietary advice; sulfonylureas used were: chlorpropamide 100-500mg; glibenclamide 2.5-20mg; glipizide 2.5-40mg. FPG goal of15 mmol/L. (n=1138)	Requiring third-party assistance or hospitalization	Allocation Concealment: Yes Blinding: Unclear Intention to Treat Analysis (ITT): Yes Withdrawals/dropouts adequately described: Unclear
UKPDS 34 1998[29] United Kingdom 23 sites Government/ Foundation/ Industry	RCT 10 years	Inclusion criteria: Newly diagnosed with diabetes (confirmed with FPG > 6mmol/l); age 25 to 65 years Exclusion criteria: Ketouria > 3 mmol/l; myocardial infarction in the previous year; current angina or HF; >1 major vascular episode; serum creatinine > 175 umol/l; retinopathy requiring photocoagulation; malignant hypertension; uncorrected endocrine abnormality; occupation precluding insulin therapy; severe concurrent illness; inadequate comprehension	N=743 Age: 59 years % male: 59 Race/Ethnicity (%): White=78 Afro-Caribbean=12 Asian=10 Weight (lbs): 178.2 BMI: 29.1 Type 2 (%): 100 HbA1c: 7.3%	Of 1704 overweight pts 743 were randomized: Diet (N=411) Intense glucose control (w/ metformin) (N=342)	Required third party help or medical intervention	Allocation Concealment: Yes Blinding: Unclear Intention to Treat Analysis (ITT): Yes Withdrawals/dropouts adequately described: Unclear
Valensi 2009[22] **IMPROVE** 11 countries Industry	Prospective Cohort N/A	Inclusion criteria: Type 2 dm newly started on BIASP30/70	N=52,419 Age: 55 years % male: 57 Weight (%): 156.2 BMI: 26 Duration of diabetes: 7 years HbA1c: 9.3%	N/A	Severe CNS symptoms; patient unable to self-treat; accompanied by blood sugar < 50 or symptoms reversed after carbohydrate intake, glucagon or IV glucose	Population: Yes Outcomes: No Measurement: No Confounding: No Intervention: N/A

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Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Vexiau, 2008[126] France 98 primary care clinics Industry	Cross-sectional Survey of MDs and patients	Inclusion criteria: ≥ 35 years old, type 2, on SU and metformin for at least 6 months Exclusion criteria: Using insulin, type 1, being treated for hepatitis or HIV, h/o gestational diabetes	N=400 Age: 62 years % male: 53 Weight (lbs): 178.2 Duration of diabetes > 7 years: 46% Current smoking: 14% HbA1c: 7.2%		Severe-needing third party assistance Very severe-needing medical attention	Population: No Outcomes: No Measurement: No Confounding: Yes Intervention: N/A
Weir, 2011[147] Canada Government	Case-control Ontario Health Administrative database January 2002 – March 2008	Inclusion criteria: Outpatients 66 years and older; diabetes mellitus; prescriptions for glyburide, insulin or metformin	N=2650	Normal renal function: Case (N=204) Control (N=802) Impaired renal function: Case (N=354) Control (N=1290)	Presenting to the hospital or emergency room with an admission diagnosis of hypoglycemia	Population: No Outcomes: No Measurement: Yes Confounding: No Intervention: N/A
Whitmer, 2009[94] United States Government	Cohort Registry data from Kaiser Permanente (KP) N/A	Inclusion criteria: Enrollees in KP as of January 2003; no prior diagnosis of dementia, MCI, or memory loss; history of type 2 diabetes;age ≥ 55 years old	N=16,667 Age: 65 years % male: 55 Race/Ethnicity (%): White=63 Black=11 Hispanic=11 Asian=12 Duration of diabetes: 9.6 years At least 1 episode of hypoglycemia: 8.8% HbA1c: 8.1%	NA	Hospitalization and ED codes for hypoglycemia before 2003	Population: Yes Outcomes: Yes Measurement: Yes Confounding: Yes Intervention: N/A

Author Date Country Funding Source	Study Design Data Sources Length of Follow-up	Inclusion/Exclusion Criteria	Patient Characteristics	Intervention/ Control Target HbA1c	Definition of Severe Hypoglycemia	Study Quality
Williams-Herman, 2009[113] 18 countries 140 sites Industry	RCT 54 weeks	Inclusion criteria: 18-78years old; not on an OHA; HbA1c ≥7.5% to ≤ 11% after a run-in period w/ no meds; good compliance during second placebo run in period	N=1091 Age: 53.5 % male: 57 BMI: 32 Duration of diabetes: 4 years HbA1c: 8.5%	a) Metformin 1000 mg bid (n=78) b) Sitagliptin 100 mg qd (n=106) c) Metfromin 500 mg bid (n=122) d) Metformin 1000 mg bid (n=137) e) Sitagliptin 50 bid + metformin 500 bid (n=148) f) Sitagliptin 50 bid +metformin 100mg bid (n=157) Target HbA1c< 7%	Requiring medical intervention or exhibiting markedly depressed level of consciousness, including loss of consciousness, or seizure	Allocation concealment: Unclear Blinding: Yes Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: Yes
Zargar, 2009[131] India NR	Retrospective Cohort Hospital records of admissions to Sher-i-Kashmir Institute of Medical Sciences 9 years	Inclusion criteria: Death certificate mentioning diabetes as underlying or contributory factor	N=741 Age: 58.8 years	N/A	Hypoglycemia noted as a cause of, or contributing cause of death	Population: No Outcomes: Yes Measurement: No Confounding: Yes Intervention: N/A
Zinman, 2009[182] United States and Canada 96 sites Industry	RCT 26 weeks	Inclusion criteria: 18-80 years old; HbA1c 7-11% on pre-study OHA for ≥ 3 months; BMI ≤ 45 Exclusion criteria: Use of insulin during previous 3 months	N=533 Age: 55 years % male: 57 Race/Ethnicity (%): White=82 Black=12 Asian=2 Hispanic=15 Other=3 BMI: 33 Type 2 (%):100 Duration of diabetes: 9 years HbA1c: 8.5%	Group 1 (n= 178) 1.2 mg ligragulatide qd sc Group 2 (178) 1.8 mg lig qd sc Group 3 (n=177) placebo PLUS metformin and rosiglitazone in all 3 groups	Requiring third party assistance or medical intervention	Allocation concealment: Yes Blinding: Yes Intention to treat analysis (ITT): Yes Withdrawals/dropouts adequately described: Yes

AE = Adverse Event; BMI = Body Mass Index; CABG = Coronary Artery Bypass Grafting; CHF = Congestive Heart Failure; CK = Creatinine Kinase; CNS = Central Nervous System; CV = Cardiovascular; CVA = Cerebrovascular Accident; d/c = Discontinued; ER = Emergency Room; ESRD = End-stage Renal Disease; ETOH = Alcohol; GI = Gastrointestinal; GP = General Practitioner; HbA1c = Hemoglobin A1c; HTN = Hypertension; LVH = Left Ventricular Hypertrophy; MI = Myocardial Infarction; N/A = Not Applicable; NR = Not Reported; OHA = Oral Hypoglycemic Agent; RCT = Randomized Controlled Trial; SMBG = Self-monitored Blood Glucose; SU = Sulfonylurea; SUD = Substance Use Disorder; TZD = Thiazolidinedione; SU = Sulfonylurea

Table 2. Characteristics of Studies Included in Extended Analysis for Key Question #1

Author/Year/ Country/ Funding Source	Study Design Data sources Length of Follow-up	Population	Definition of Hypoglycemia	Results	Study Quality
Alvarez-Guisasola, 2008[85] 7 European countries Industry	Cross-sectional Questionnaire	N=1709 Type 2, age > 30, who had had a SU or TZD added to metformin in the previous 5 years	Self-report of episodes in past year, rated: 1. no interruption in activities 2. interrupt in activities but no help required 3. needed assistance of others 4. needed medical attention	38% reported one or more episodes of any severity; 26.8% reported level 3 and 5.1% reported level 4	Population: Yes Outcomes: No Measurement: No Confounding: Yes Intervention: N/A
Akram, 2006[84] Denmark Danish MRC and industry	Cross-sectional Questionnaire	N=401 of 671 asked to participate Type 2, exclusions: on SUs, on dialysis, concomitant malignancy, pregnancy, inability to complete questionnaire	Severe: required assistance of another person	66/401 (16.5%) had at least one severe event in the past year	Population: No Outcomes: Yes Measurement: No Confounding: Yes Intervention: N/A
Chan, 2010[73] China, Taiwan, Malaysia, Thailand Industry	Cross-sectional Questionnaire	N=2257 Type 2, older than 30, on OHA for at least 6 months	Self-report of episodes in past 6 months, rated: 1. no interruption in activities 2. interrupt in activities but no help required 3. needed assistance of others 4. needed medical attention	66 + 94 (160) of 2257 reported one or more severe or very severe events (7%)	Population: No Outcomes: Yes Measurement: No Confounding: No Intervention: N/A
Donnelly, 2005[72] Scotland Industry	Prospective cohort	267 Type 1 and 2 (N=173)	Required 3d party assistance, self report by diary	5 type 2 patients had one or more severe events over 1 month (5/173=2.8%)	Population: No Outcomes: No Measurement: Yes Confounding: Yes Intervention: N/A
Henderson, 2003[76] Edinburgh Government	Cross-sectional Questionnaire	N=215 type 2 diabetics treated with insulin at one clinic	Required external assistance; approx estimates of number of episodes in past year	32 (15%) people reported one or more severe episodes in past year	Population: No Outcomes: Yes Measurement: No Confounding: No Intervention: N/A
Honkasalo, 2010[77] Finland Foundation	Cross-sectional Questionnaire, EMRs, ambulance records	N=680 Patients over age 18 with Type 1 or Type 2 DM (n=480) all on insulin living in two communities	Needs the help of another person to recover	53/480 T2DM patients (12.3%) had one or more severe (self reported) episodes over 1 year; 10/53 required ambulance or emergency care	Population: No Outcomes: Yes Measurement: No Confounding: No Intervention: N/A

Author/Year/ Country/ Funding Source	Study Design Data sources Length of Follow-up	Population	Definition of Hypoglycemia	Results	Study Quality
Jennings, 1989[80] England Industry	Cross-sectional Questionnaire	N=219 Age 40-65 with type 2 attending a single clinic who were treated with OHAs	Symptoms associated with a blood sugar reading of < 3 mmol and precipitated by reduced carbohydrate intake or increased exertion; relieved by carbohydrates; occurred after the institution of OHA therapy; and no other explanation for the hypoglycemic episode	In past 6 months: 41/203 (20%) patients on SU; 0/16 patients on metformin	Population: No Outcomes: Yes Measurement: No Confounding: No Intervention: N/A
Lecomte, 2008[79] France NR	Cross-sectional Claims data and survey of patients and providers	Random sample of 10,000 adults (36% responded) Treated for diabetes and living in France sent a questionnaire	Required the help of another person	26.5 % of 635 T2D on insulin and 6.3% of 2689 T2DM on OHA reported one or more severe episode in 2001	Population: No Outcomes: Yes Measurement: No Confounding: No Intervention: N/A
Lee, 2010[88] United States Industry	Retrospective cohort Administrative claims data	400 on NPH and 1698 on glargine T2DM patients < 65 years old, NOT pregnant, and were in the database for 6 months pre and 6 months post index date; index date was first prescribed for glargine or NPH	ICD 9 codes 251.0x, 251.1x, 251.2x, 250.3x. A hypoglycemic-related hospitalization event was defined by at least one claim with the codes above during a hospitalization	NONE in either group	Population: Yes Outcomes: No Measurement: Yes Confounding: Yes Intervention: N/A
Marrett, 2011[87] United States Industry	Population based survey	N=1984 Type 2 diabetes treated with one or more OHA in past 6 months but NOT on insulin	Severe—needed assistance of others Very severe—needed medical assistance	In past 6 months , 13% reported severe and 4% reported very severe episodes	Population: Yes Outcomes: Yes Measurement: No Confounding: Yes Intervention: N/A
Moen, 2009[81] United States Government	Retrospective cohort	N=243,222 VHA database of patients with CKD who had a t least one hospitalization in 2004-2005 and at least one outpatient measurement of CR between 1week and 1 year before they were hospitalized	Among 92,003 CKD patients with diabetes, 9264 had at least one glucose < 50 in the database		Population: Yes Outcomes: Yes Measurement: Yes Confounding: Yes Intervention: N/A
Neil, 2007[74] United States Government (VA)	Patient survey	N=11,529 Type 2 diabetics on SU but not insulin	Required assistance of another person	5965 responses to this question 538/5965 (9%) identified the episode as severe	Population: Yes Outcomes: Yes Measurement: No Confounding: Yes Intervention: Yes

Author/Year/ Country/ Funding Source	Study Design Data sources Length of Follow-up	Population	Definition of Hypoglycemia	Results	Study Quality
Pettersson, 2011[82] Sweden (multicenter) Industry	Cross-sectional Patient survey	N=430 Patients with type 2 dm, age 35 or older, on metformin and SU for past 6 months	1. Mild: no interruption in activities 2. Moderate: interrupt in activities but no help required 3.Severe: needed assistance of others 4. Very severe: needed medical attention.	17% reported level 2; 1% reported level 3 and 1% reported level 4 hypoglycemic episode within past 6 months	Population: No Outcomes: Yes Measurement: No Confounding: No Intervention: N/A
Sarkar, 2010[78] United States Government	Cross-sectional patient survey linked with medical records	N=14,357 Adults with type 2 diabetes treated with OHAs past year	Survey question: In the past year, how many times have you had SEVERE low blood sugar reaction such as passing out or needing help to the treat the reaction?	1579 (11%) reported at least one episode; Insulin: 59% Mixed OHAs 23% Secretagogues alone: 13% Metformin alone: 5% 129/1579 (8%) had evidence of a documented ER visit or hospitalization for hypoglycemia in the prior year	Population: Yes Outcomes: Yes Measurement: No Confounding: Yes Intervention: N/A
Stargardt, 2009[83] Germany 92 clinics Industry	Patient survey	N=392 Type 2, 35 years old or older, treated in prior 6 months with either a combination of metformin and a glitazone or met and a SU	1. No interruption in activities 2. interrupt in activities but no help required 3. needed assistance of others 4. needed medical attention.	w/in previous 6 months 9/392 reported severe (#3) and 6/392 reported very severe (#4)	Population: No Outcomes: No Measurement: No Confounding: No Intervention: N/A
Willliams, 2011[86] United States Industry	Cross-sectional Patient survey	N=10374 Patients with T2DM currently on one or more OHAs but not insulin invited…of whom **2074** completed the survey	If you answered yes to: In the prior 2 weeks did you have either “symptoms of low blood sugar” or “low blood sugar in the middle of the night” some most or all of the time	286/2074 (14%)	Population: Yes Outcomes: Yes Measurement: No Confounding: Yes Intervention: N/A

CKD = Chronic Kidney Disease; EMRs = Electronic Medical Records; ER = Emergency Room; HbA1c = Hemoglobin A1c; N/A = Not Applicable; NR = Not Reported; OHA = Oral Hypoglycemic Agent; RCT = Randomized Controlled Trial; SU = Sulfonylurea; T2DM = Type 2 diabetes mellitus; TZD = Thiazolidinedione; SU = Sulfonylurea

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Table 3. Incidence of Severe Hypoglycemia by Treatment Arms

Table 3a. Intensive versus Standard Glycemic Control Studies

Study and year	Study type	Study duration	Intervention Control	Hypoglycemia Incidence % (n/N)	Risk ratio [95% CI]
Duckworth (VADT) 2009[5]	RCT	5.6 yrs	Intensive control Standard control	8.5 (76/892) 3.1 (28/899)	2.74 [1.79 to 4.18]
ACCORD 2008[3]	RCT	3.5 yrs	Intensive control Standard control	16.6 (849/5128) 5.3 (274/5123)	3.10 [2.72 to 3.53]
ADVANCE 2008[4]	RCT	5 yrs	Intensive control Standard control	2.7 (150/5571) 1.5 (81/5669)	1.88 [1.44 to 2.46]
UKPDS 33 1998*[21]	RCT	10 yrs	Intensive control Standard control	1.1 (33/3071) 0.7 (8/1138)	1.53 [0.71 to 3.30]
Abraira (VA-CSDM) 1995[30]	RCT	2.3 yrs	Intensive control Standard control	6.7 (5/75) 2.6 (2/78)	2.60 [0.52 to 12.99]
		Totals	Intensive control Standard control	7.6 (1113/14737) 3.0 (393/12907)	2.40 [1.76 to 3.27]

*Data obtained from Hemmingsen B, Lund SS, Gluud C, Vaag A, Almdal T, Hemmingsen C,Wetterslev J. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2011, Issue 6. Art. No.: CD008143. DOI: 10.1002/14651858.CD008143.pub2.

Table 3b. Insulin Studies

Study and year	Study type	Study duration	Intervention(s) Control	Hypoglycemia Incidence % (n/N)
A. Regular insulin and Lispro studies: fast-short acting				
Anderson, 1997[47] (crossover study)	RCT	26 wks	Regular human insulin phase	0.6 (4/722)
			Insulin lispro phase	0.1 (1/722)
B. Insulin aspart studies: rapid-acting				
Holman, 2009[43] (4T study)	RCT	3 yrs	Prandial insulin aspart	2.1 (5/239)
			Biphasic insulin aspart	2.6 (6/235)
			Insulin detemir (basal)	0.9 (2/234)
C. Biphasic insulin: intermediate- and fast-acting mixture				
Berntorp, 2011[15]	Prospective cohort	26 wks	Biphasic insulin aspart	0.2 (2/1154)
Buse, 2011[36]	RCT	2.5 yrs	Insulin lispro 75/25 mix	4.2 (20/473)
			Insulin glargine (long-acting)	2.9 (12/419)
Holman 2009[43] (4T study)	RCT	3 yrs	Biphasic insulin aspart	2.6 (6/235)
			Prandial insulin aspart	2.1 (5/239)
			Insulin detemir (basal)	0.9 (2/234)
Liebl, 2009[48]	RCT		Biphasic insulin aspart	0/178
			Insulin detemir and insulin aspart	0.9 (5/537)
Valensi (IMPROVE) 2009[22]	Prospective cohort	26 wks	Biphasic insulin aspart	0.13 (69/52,419) 0.008 events per patient-year
D. Mixed fast and long-acting insulins studies				
Liebl, 2009[48]	RCT	26 wks	Insulin detemir and insulin aspart	0.9 (5/537)
			Biphasic insulin aspart	0/178
Rayman, 2006[45]	RCT	26 wks	Regular human insulin + NPH	1.6 (7/442)
			Insulin glulisine + NPH	0.5 (2/448)
Dailey, 2004[46]	RCT	26 wks	Regular human insulin + NPH	1.2 (5/441)
			Insulin glulisine + NPH	1.4 (6/435)
E. NPH insulin studies: intermediate acting				

Study and year	Study type	Study duration	Intervention(s) Control	Hypoglycemia Incidence % (n/N)
Rosenstock, 2009[35]	RCT	5 yrs	NPH insulin	11.1 (55/504)
			Insulin glargine	7.6 (38/513)
Rayman, 2007[45]	RCT	26 wks	NPH (basal therapy) + regular human insulin	1.6 (7/442)
			NPH (basal therapy) + insulin glulisine	0.5 (2/448)
Haak, 2005[33]	RCT	26 wks	Insulin detemir	<2% both arms (numbers not given)
			NPH insulin	
Dailey, 2004[46]	RCT	26 wks	NPH (basal therapy) + regular human insulin	1.2 (5/441)
			NPH (basal therapy) + insulin glulisine	1.4 (6/435)
Fritsche, 2003[44]	RCT	24 wks	NPH insulin + glimepiride (G) 3 mg	2.6 (6/232)
			Bedtime Insulin glargine + G	1.8 (4/227)
			Morning Insulin glargine + G	2.1 (5/236)
Riddle, 2003[41]	RCT	24 wks	Adjunct NPH insulin to 1-2 oral antiglycemic agents (sulfonylurea, metformin, or glitazone)	1.8 (7/389)
			Adjunct Insulin glargine to 1-2 oral antiglycemic agents (sulfonylurea, metformin, or glitazone)	2.5 (9/367)
Rosenstock, 2001[39]	RCT	28 wks	NPH insulin	2.3 (6/259)
			Insulin glargine	0.4 (1/259)
F. Insulin detemir studies: long-acting				
Holman, 2009 (4T study)[43]	RCT	3 yrs	Insulin detemir (basal)	0.9 (2/234)
			Insulin aspart (prandial)	2.1 (5/239)
			Biphasic insulin aspart	2.6 (6/235)
Liebl, 2009[48]	RCT	26 wks	Insulin detemir and insulin aspart	0.9 (5/537)
			Biphasic insulin aspart	0/178
Rosenstock, 2008[40]	RCT	52 wks	Insulin detemir	1.7 (5/291)
			Insulin glargine	2.7 (8/291)
Meneghini (PREDICTIVE) 2007[176]	RCT	26 wks	Insulin detemir - Algorithm care	0.26 events per patient years
			Insulin detemir - Standard care	0.20 events per patient years
Haak, 2005[33]	RCT	26 wks	Insulin detemir	<2% in both arms (numbers NR)
			NPH insulin	
Marre (PREDICTIVE) 2009[18]	Prospective cohort	52 wks	Insulin detemir	0.3 (4/1129)
G. Insulin glargine studies: long-acting				
Buse, 2011[36]	RCT	2.5 yrs follow-up	Insulin glargine (long-acting)	2.9 (12/419)
			Insulin lispro 75/25 mix	4.2 (20/473)
Rosenstock, 2009[35]	RCT	5 yrs	Insulin glargine (long-acting)	7.6 (38/513)
			NPH insulin (intermediate acting)	11.1 (55/504)
Russell-Jones, 2009[54]	RCT	26 wks	Insulin glargine (long-acting) added to metformin and sulfonylurea)	0/232
			Liraglutide added to metformin and sulfonylurea)	2.2 (5/230)
			Placebo added to metformin and sulfonylurea)	0/114

Study and year	Study type	Study duration	Intervention(s) Control	Hypoglycemia Incidence % (n/N)
Rosenstock, 2008[40]	RCT	52 wks	Insulin glargine	2.7 (8/291)
			Insulin detemir	1.7 (5/291)
Kennedy, 2006[37]	RCT	24 wks	Insulin glargine, usual and active titration	3 (228/7607)
			Insulin glargine, usual titration	0.09 events per patient-year
			Insulin glargine, active titration	0.14 events per patient-year
Standl, 2006[180]	RCT	24 wks	Insulin glargine, morning administration + Glimepiride (G) 2-4 mg	1.3 (4/299)
			Insulin glargine, bedtime administration + G 2-4 mg	0.7 (2/281)
Davies, 2005[38]	RCT	24 wks	Insulin glargine algorithm 1 (investigator led)	0.9 (21/2315)
			Insulin glargine algorithm 2 (performed by study subjects)	1.1 (25/2273)
Heine, 2005[42]	RCT	26 wks	Adjunct Insulin glargine (long-acting) added to oral therapy (metformin and sulfonylurea	1.5 (4/267)
			Adjunct Exenatide added to oral therapy (metformin and sulfonylurea)	1.4 (4/282)
Fritsche, 2003[44]	RCT	24 wks	Bedtime Insulin glargine + G	1.8 (4/227)
			Morning Insulin glargine + G	2.1 (5/236)
			NPH insulin (intermediate acting) +G	2.6 (6/232)
Riddle, 2003[41]	RCT	24 wks	Insulin glargine (long-acting)	2.5 (9/367)
			NPH insulin (intermediate acting)	1.8 (7/389)
Rosenstock, 2001[39]	RCT	28 wks	Insulin glargine (long-acting)	0.4 (1/259)
			NPH insulin (intermediate acting)	2.3 (6/259)
H. Non-specific Insulin studies				
UK Hypoglycemia Group 2007[190]	Prospective cohort	9-12 mos	Treated with insulin for <2 years	~7.0* (*6*/89)
			Treated with insulin for >5 years	~25.0* (*19*/77)
			Sulfonylurea	7.0 (8/108)
Murata, 2005[19]	Prospective cohort	41 wks	Long-acting insulin	5.5 (19/344)
Nichols, 2010[26]	Retrospective cohort	49 mos	All types (regular, quick-acting, NPH, mixed, etc.) Hypoglycemia requiring a medical contact occurred in 1.9% of patients in the first year of insulin use, but by the fifth year the rate had fallen to 0,4%. No cases of required hospitalization.	
Asche, 2008[23]	Retrospective cohort	395 days of followup	Insulin with sulfonylurea	2.8 (3/106)
			Insulin with thiazolidinedione	4.3 (8/187)
			Sulfonylurea monotherapy	2.6 (55/2117)
			Thiazolidinedione monotherapy	1.7 (12/702)
			Metformin	0/2326
Leese, 2003[25]	Retrospective cohort	NR	Insulin	7.3 (66/901) 11.8/100 patient yrs [95% CI 9.5 to 14.1]

*extracted from graph

Table 3c. Sulfonylurea Studies

Study and year	Study type	Study duration	Intervention (daily dose) Control	Hypoglycemia Incidence % (n/N)
Arechavaleta, 2011[52]	RCT	30 wks	Adjunct Glimepiride 1-6 mg added to metformin	1.5 (8/519)
			Adjunct Sitagliptin 100 mg added to metformin	0.2 (1/516)
Garber, 2011[51]	RCT	52 wks	Glimepiride 8 mg	0/248
			Liragultide 1.2 mg	0/251
			Liragultide 1.8 mg	0/247
Matthews, 2010[49]	RCT	2 yrs	Adjunct Glimepiride 2-6 mg added to metformin	1.8 (15/1546)
			Adjunct Vildagliptin 100 mg added to metformin	0/1553
Seck, 2010;[50] Nauck, 2007[177]	RCT	2 yrs	Adjunct Glipizde 5 mg added to metformin	Non-med. Assist. 1.5 (9/584) Med. Assist. 1.5 (9/584)
			Adjunct Sitagliptin 100 mg added to metformin	Non-med. Assist. 0.2 (1/588) Med. Assist. 0.2 (1/588)
Marre, 2009[175]	RCT	52 wks	Glimepiride 2-4 mg + liragultide 0.6 mg	0/233
			Glimepiride 2-4 mg + liragultide 1.2 mg	0/228
			Glimepiride 2-4 mg + liragultide 1.8 mg	1.7 (4/234)
			Glimepiride 2-4 mg	0/114
			Rosiglitazone 8 mg + Glimepiride 2-4 mg	0/232
Nauck, 2009[53] LEAD-2	RCT	26 wks	Glimepiride 4 mg plus Metformin	0/242
			Liragultide 0.6 mg plus Metformin	0/242
			Liragultide 1.2 mg plus Metformin	0/241
			Liragultide 1.8 mg plus Metformin	0/242
			Placebo plus Metformin	0/121
Russell-Jones, 2009[54] LEAD-5	RCT	26 wks	Insulin glargine (long-acting) added to metformin and sulfonylurea)	0/232
			Liraglutide added to metformin and sulfonylurea)	2.2 (5/230)
			Placebo added to metformin and sulfonylurea)	0/114
Chou, 2008[55]	RCT	28 wks	Glimepiride (G) 1–4 mg	0/225
			Rosiglitazone (R) 4-8 mg	0/232
			R to 4 mg + G to 4 mg (Regimen A)	0.4 (1/225)
			R to 8 mg + G to 4 mg (Regimen B)	0.9 (2/219)
Standl, 2006[180]	RCT	24 wks	Glimepiride 2-4 mg + Insulin glargine, morning administration +	.3 (4/299)
			Glimepiride 2-4 mg + Insulin glargine, bedtime administration	0.7 (2/281)
Heine, 2005[42]	RCT	26 wks	Adjunct Exenatide 20 µg added to oral therapy (metformin and sulfonylurea)	1.4 (4/282)
			Adjunct Insulin glargine added to oral therapy (metformin and sulfonylurea)	1.5 (4/267)

Study and year	Study type	Study duration	Intervention (daily dose) Control	Hypoglycemia Incidence % (n/N)
Kendall, 2005[56]	RCT	30 wks	Adjunct Exenatide 20 µg to oral therapy (metformin and sulfonylurea)	0/241
			Adjunct Exenatide 10 µg to oral therapy (metformin and sulfonylurea)	0.4 (1/245)
			Adjunct Placebo to oral therapy (metformin and sulfonylurea)	0/247
Drouin, 2004[32]	RCT	10 mos	Gliclazide modified release 30–120 mg	0/401
			Gliclazide 80–120 mg	0.3 (1/399)
Schernthaner, 2004[57]	RCT	27 wks	Glimepiride 1–6 mg	0/440
			Gliclazide 30–120 mg	0/405
Fritsche, 2003[44]	RCT	24 wks	Glimepiride 3 mg + NPH insulin	2.6 (6/232)
			Glimepiride 3 mg + Bedtime Insulin glargine	1.8 (4/227)
			Glimepiride 3 mg + Morning Insulin glargine	2.1 (5/236)
UK Hypoglycemia Group[190]	Prospective cohort	9-12 mos	Sulfonylurea	7.0 (8/108)
			Treated with insulin for <2 years	~7.0* (*6*/89)
			Treated with insulin for >5 years	~25.0* (*19*/77)
Holstein, 2001[17]	Prospective population-based cohort	4 yrs	Overall	5.6/100,000 inhabitants/yr
			Glimepiride 2 mg	0.3 (6/1768) 0.86/1000 person yrs
			Gilbenclamide 7 mg	2.2 (38/1721) 5.6/1000 person yrs
Asche, 2008[23]	Retrospective cohort	395 days of followup	Sulfonylurea monotherapy	2.6 (55/2117)
			Sulfonylurea with Insulin	2.8 (3/106)
			Thiazolidinedione with insulin	4.3 (8/187)
			Thiazolidinedione monotherapy	1.7 (12/702)
			Metformin	0/2326
Bodmer, 2008[24] N=50,048 of which 73 had severe hypoglycemia	Retrospective cohort with nested case control	NR/NA	Sulfonylurea	110/100,000 person yrs (22 patients on monotherapy [16 gliclazide, 5 glibenclamide, 1 glimepiride], 11 combined with metformin)
Leese, 2003[25]	Retrospective cohort	NR/NA	Sulfonylurea	0.8 (23/2823) 0.09/100 patient yrs [95%CI 0.6 to 1.3]
Stahl, 1999[28]	Retrospective case series	12 yrs	Long-acting Sulfonylureas	2.7 (16/594) (15 glibenclamide, 1 chlorpropamide)
			Short-acting Sulfonylureas	0.9 (12/1334)
			Glibornuride	*0.9 (10/1138)*
			Gliclazide	*1.0 (2/196)*
			Any Sulfonylurea	1.5 (28/1928)

* Not reported, estimated from figure

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Table 3d. Metformin (Biguanides) Studies

Study and year	Study type	Study duration	Intervention (daily dose) Control	Hypoglycemia Incidence % (n/N)
Arechavaleta, 2011[52]	RCT	30 wks	Metformin with adjunct glimepiride 1-6 mg	1.5 (8/519)
			Metformin with adjunct sitagliptin 100 mg	0.2 (1/516)
Matthews, 2010[49]	RCT	2 yrs	Metformin with adjunct glimepiride 2-6 mg	1.8 (15/1546)
			Metformin with adjunct vildagliptin 100 mg	0/1553
Olansky, 2011[178]	RCT	44 wks	Metformin up to 2000 mg	0/625
			Metformin and sitagliptin up to 100 mg	0/621
Aschner, 2010[60]	RCT	24 wks	Metformin 2000 mg	0/522
			Sitagliptin 100 mg	0.4 (2/528)
Pratley, 2010[179]	RCT	26 wks	Metformin with adjunct sitagliptin 100 mg	0/219
			Metformin with adjunct liragultide 1.2 mg	0.4 (1/225)
			Metformin with adjunct liragultide 1.8 mg	0/221
Seck, 2010;[50] Nauck, 2007[177]	RCT	2 yrs	Metformin with adjunct Sitagliptin 100 mg	Non-med. Assist. 0.2 (1/588) Med. Assist. 0.2 (1/588)
			Metformin with adjunct Glipizde 5 mg	Non-med. Assist. 1.5 (9/584) Med. Assist. 1.5 (9/584)
Nauck, 2009[53] LEAD-2	RCT	26 wks	Liragultide 0.6 mg plus Metformin	0/242
			Liragultide 1.2 mg plus Metformin	0/241
			Liragultide 1.8 mg plus Metformin	0/242
			Glimepiride 4 mg plus Metformin	0/242
			Placebo plus Metformin	0/121
Raskin, 2009[31]	RCT	26 wks	Metformin 2000 mg and repaglinide bid (maximum dose 4 mg)	0/177
			Metformin tid (doses 1000,500,1000 mg) and repaglinide tid (maximum doses 4,2, and 4 mg)	0/178
			Metformin 2000 mg and rosiglitazone bid (maximum dose 4 mg)	0/206
Russell-Jones, 2009[54] LEAD-5	RCT	26 wks	Insulin glargine (long-acting) added to metformin and sulfonylurea)	0/232
			Liraglutide added to metformin and sulfonylurea)	2.2 (5/230)
			Placebo added to metformin and sulfonylurea)	0/114
Williams-Herman, 2009;[113] Goldstein, 2007[181] *Patients could be on oral meds*	RCT	54 wks	Metformin (M) 500 mg	1.1 (2/182)
			Metformin 1000 mg	0/182
			Sitagliptin 100 mg	0/179
			Sitagliptin 50 mg + Metformin 500 mg	0/190
			Placebo/ Metformin 1000 mg	0/176
Zinman, 2009	RCT	26 wks	Metformin (M) 2 g + rosiglitazone (R) 8 mg and liraglutide 1.2 mg	0/178
			M+R and liraglutide 1.8 mg	0/178
			M+R and placebo	0/177

Study and year	Study type	Study duration	Intervention (daily dose) Control	Hypoglycemia Incidence % (n/N)
Bolli, 2008[172]	RCT	24 wks	Adjunct Pioglitazone 30 mg + metformin ≥ 1500 mg	0/281
			Adjunct Vildagliptin 100 mg + metformin ≥ 1500 mg	0/295
Heine, 2005[42]	RCT	26 wks	Adjunct Exenatide 20 µg added to oral therapy (metformin and sulfonylurea)	1.4 (4/282)
			Adjunct Insulin glargine added to oral therapy (metformin and sulfonylurea)	1.5 (4/267)
Kendall, 2005[56]	RCT	30 wks	Adjunct Exenatide 20 µg to oral therapy (metformin and sulfonylurea)	0/241
			Adjunct Exenatide 10 µg to oral therapy (metformin and sulfonylurea)	0.4 (1/245)
			Adjunct Placebo to oral therapy (metformin and sulfonylurea)	0/247
UKPDS 28 1998[191]	RCT	3 yrs	Adjunct metformin to 2250 mg + sulfonylurea	0.3 (1/291)
			Sulfonylurea	0/300
Bodmer, 2008[24] N=50,048 of which 73 had severe hypoglycemia	Retrospective cohort with nested case-control	NR/NA	Metformin	60/100,000 person yrs (3 patients on monotherapy, 11 combined with sulfonylurea)
Asche, 2008[23]	Retrospective cohort	395 days of followup	Metformin	0/2326
			Sulfonylurea monotherapy	2.6 (55/2117)
			Sulfonylurea with Insulin	2.8 (3/106)
			Thiazolidinedione monotherapy	1.7 (12/702)
			Thiazolidinedione with insulin	4.3 (8/187)
Leese, 2003[25]	Retrospective cohort	NR/NA	Metformin or diet	0.05/100 patient yrs [95% CI 0.01 to 0.2]

Table 3e. Dipeptidyl-Peptidase-4 Inhibitors (DPP-4) Studies

Study and year	Study type	Study duration	Intervention (daily dose) Control	Hypoglycemia Incidence % (n/N)
Arechavaleta, 2011[52]	RCT	30 wks	Adjunct Sitagliptin 100 mg added to metformin	0.2 (1/516)
			Adjunct Glimepiride 1-6 mg added to metformin	1.5 (8/519)
Matthews, 2010[49]	RCT	2 yrs	Adjunct Vildagliptin 100 mg added to metformin	0/1553
			Adjunct Glimepiride 2-6 mg added to metformin	1.8 (15/1546)
Olansky, 2011[178]	RCT	44 wks	Sitagliptin up to 100 mg and metformin up to 2000 mg	0/625
			Metformin up to 2000 mg	0/621
Aschner, 2010[60]	RCT	24 wks	Sitagliptin 100 mg	0.4 (2/528)
			Metformin 2000 mg	0/522

Study and year	Study type	Study duration	Intervention (daily dose) Control	Hypoglycemia Incidence % (n/N)
Pratley, 2010[179]	RCT	26 wks	Adjunct Sitagliptin 100 mg added to metformin	0/219
			Adjunct Liragultide 1.2 mg added to metformin	0.4 (1/225)
			Adjunct Liragultide 1.8 mg added to metformin	0/221
Seck 2010;[50] Nauck, 2007[177]	RCT	2 yrs	Adjunct Sitagliptin 100 mg added to metformin	Non-med. Assist. 0.2 (1/588) Med. Assist. 0.2 (1/588)
			Adjunct Glipizde 5 mg added to metformin	Non-med. Assist. 1.5 (9/584) Med. Assist. 1.5 (9/584)
Williams-Herman, 2009;[113] Goldstein, 2007[181] *Patients could be on oral meds*	RCT	54 wks	Sitagliptin 100 mg	0/179
			Sitagliptin 50 mg + Metformin 500 mg	0/190
			Sitagliptin 50 mg + Metformin 1000 mg	0/182
			Metformin 500 mg	1.1 (2/182)
			Metformin 1000 mg	0/182
			Placebo/ Metformin 1000 mg	0/176
Bolli 2008/2009[172, 173]	RCT	24 wks	Adjunct Vildagliptin 100 mg + metformin ≥ 1500 mg	0/295
			Adjunct Pioglitazone 30 mg + metformin ≥ 1500 mg	0/281
Aschner, 2006[136] *Patients could be on oral meds*	RCT	24 wks	Sitagliptin 100 mg	0/238
			Sitagliptin 200 mg	0/250
			Placebo	0/253

Table 3f. Glucagon-like Peptide-1 (GLP-1) Analogs Studies

Study and year	Study type	Study duration	Intervention (daily dose) Control	Hypoglycemia Incidence % (n/N)
Garber, 2011[51]	RCT	52 wks	Liragultide 1.2 mg	0/251
			Liragultide 1.8 mg	0/247
			Glimepiride 8 mg	0/248
Pratley, 2010[179]	RCT	26 wks	Adjunct Liragultide 1.2 mg added to metformin	0.4 (1/225)
			Adjunct Liragultide 1.8 mg added to metformin	0/221
			Adjunct Sitagliptin 100 mg added to metformin	0/219
Marre, 2009[175]	RCT	52 wks	Liragultide 0.6 mg + glimepiride 2-4 mg	0/233
			Liragultide 1.2 mg + glimepiride 2-4 mg	0/228
			Liragultide 1.8 mg + glimepiride 2-4 mg	1.7 (4/234)
			Glimepiride 2-4 mg	0/114
			Rosiglitazone 8 mg + Glimepiride 2-4 mg	0/232
Nauck, 2009[53] LEAD-2	RCT	26 wks	Liragultide 0.6 mg plus Metformin	0/242
			Liragultide 1.2 mg plus Metformin	0/241
			Liragultide 1.8 mg plus Metformin	0/242
			Glimepiride 4 mg plus Metformin	0/242
			Placebo plus Metformin	0/121

Study and year	Study type	Study duration	Intervention (daily dose) Control	Hypoglycemia Incidence % (n/N)
Russell-Jones, 2009[54] LEAD-5	RCT	26 wks	Liraglutide added to metformin and sulfonylurea)	2.2 (5/230)
			Insulin glargine (long-acting) added to metformin and sulfonylurea)	0/232
			Placebo added to metformin and sulfonylurea)	0/114
Zinman, 2009[182]	RCT	26 wks	Liragultide 1.2 mg plus Metformin (M) 2 g + rosiglitazone (R) 8 mg	0/178
			Liragultide 1.8 mg and M + R	0/178
			Placebo and M + R	0/177
Heine, 2005[42]	RCT	26 wks	Adjunct Exenatide 20 µg added to oral therapy (metformin and sulfonylurea)	1.4 (4/282)
			Adjunct Insulin glargine added to oral therapy (metformin and sulfonylurea)	1.5 (4/267)
Kendall, 2005[56]	RCT	30 wks	Adjunct Exenatide 20 µg to oral therapy (metformin and sulfonylurea)	0/241
			Adjunct Exenatide 10 µg to oral therapy (metformin and sulfonylurea)	0.4 (1/245)
			Adjunct Placebo to oral therapy (metformin and sulfonylurea)	0/247

* One event in the liraglutide1.8 mg group occurred after regular insulin was infused during the extension period (post 52 weeks)

Table 3g. Bari 2D, Insulin Sensitization versus Insulin Provision

Study and year	Study type	Study duration	Intervention Control	Hypoglycemia Incidence % (n/N)
BARI 2D*[58]	RCT	5.3 yrs	Insulin sensitization therapy	5.9 (68/1153)
			Insulin-provision therapy	9.2 (106/1154) P=0.003

* Medication use among all patients was as follows: metformin 54%; sulfonylurea 53%; insulin 28%; any thiazolidinedione 19%; rosiglitazone 10%.

Table 3h. Amylin Analog Studies

Study and year	Study type	Study duration	Intervention Control	Hypoglycemia Incidence % (n/N)
Ratner, 2002[34]	RCT	52 wks	Adjunct Pramlintide 30 µg tid to insulin therapy (some patients were also on oral agents)	1.6 (2/122)
			Adjunct Pramlintide 75 µg tid to insulin therapy (some patients were also on oral agents)	0.7 (1/136)
			Adjunct Pramlintide 150 µg tid to insulin therapy (some patients were also on oral agents)	1.4 (2/144)
			Adjunct Placebo to insulin therapy (some patients were also on oral agents)	1.5 (2/136)

Study and year	Study type	Study duration	Intervention Control	Hypoglycemia Incidence % (n/N)
Pencek, 2010[20]	Prospective cohort	6 mos	Adjunct Pramlintide to insulin therapy (some patients were also on oral agents)	<u>Patient-ascertained severe hypoglycemia</u> 1) adjustment period (0–3 months) 2.8% (n=531); 2) maintenance period (>3–6 months) 0.4% (n=387)
				<u>Medically-assisted severe hypoglycemia</u> 1) adjustment period (0–3 months) 0.4% (n=531); 2) maintenance period (>3–6 months) 0.3% (n=387)

Table 3i. Glinide Studies

Study and year	Study type	Study duration	Intervention Control	Hypoglycemia Incidence* % (n/N)
Raskin, 2009[31]	RCT	26 wks	Repaglinide bid (maximum dose 4 mg) / metformin 2000 mg	0/177
			Repaglinide tid (maximum doses 4,2, and 4 mg)/metformin tid (doses of 1000,500,1000 mg)	0/178
			Rosiglitazone bid (maximum doses 4 mg)/ metformin 2000 mg	0/206
Saloranta, 2002[59] Serious events rare (Not reported) *Diet alone subjects*	RCT	24 wks	Nateglinide 30 mg tid	0/166
			Nateglinide 60 mg tid	0/175
			Nateglinide 1200 mg tid	0/171
			Placebo tid	0/163

* Requiring assistance from an outside party

Table 3j. Thiazolidinedione Studies

Study and year	Study type	Study duration	Intervention (daily dose) Control	Hypoglycemia Incidence % (n/N)
Marre, 2009[175]	RCT	26 wks	Rosiglitazone 8 mg + Glimepiride 2-4 mg	0/232
			Glimepiride 2-4 mg + liragultide 0.6 mg	0/233
			Glimepiride 2-4 mg + liragultide 1.2 mg	0/228
			Glimepiride 2-4 mg + liragultide 1.8 mg	1.7 (4/234)
			Glimepiride 2-4 mg	0/114

Study and year	Study type	Study duration	Intervention (daily dose) Control	Hypoglycemia Incidence % (n/N)
Raskin, 2009[31]	RCT	26 wks	Rosiglitazone bid (maximum dose 4 mg) / metformin 2000 mg	0/206
			Repaglinide bid (maximum dose 4 mg) / metformin 2000 mg	0/177
			Repaglinide tid (maximum doses 4,2, and 4 mg)/metformin tid (doses 1000-500-1000 mg)	0/178
Zinman, 2009[182]	RCT	26 wks	Rosiglitazone (R) 8 mg + Metformin (M) 2 g and liraglutide 1.2 mg	0/178
			R + M and liraglutide 1.8 mg	0/178
			R + M and placebo	0/177
Bolli, 2008[172]	RCT	24 wks	Adjunct Pioglitazone 30 mg + metformin ≥ 1500 mg	0/281
			Adjunct Vildagliptin 100 mg + metformin ≥ 1500 mg	0/295
Chou, 2008[55] *Drug-naive subjects*	RCT	28 wks	Glimepiride (G) 1–4 mg	0/232
			Rosiglitazone (R) 4-8 mg	0/225
			R to 4 mg + G to 4 mg (Regimen A)	0.4 (1/225)
			R to 8 mg + G to 4 mg (Regimen B)	0.9 (2/219)
Dormandy, 2005[174] (PROactive)	RCT	34.5 mos	Adjunct Pioglitazone 15-45 mg + other glucose lowering drugs	0.73 (19/2605)
			Adjunct Placebo + other glucose lowering drugs	0.42 (11/2633)
Asche, 2008[23]	Retrospective cohort	395 days of followup	Thiazolidinedione monotherapy	1.7 (12/702)
			Thiazolidinedione with insulin	4.3 (8/187)
			Sulfonylurea monotherapy	2.6 (55/2117)
			Sulfonylurea with Insulin	2.8 (3/106)
			Metformin	0

Table 3k. Studies in Which Patients are on a Variety of Medications

Study and year	Study type	Study duration	Intervention Control	Hypoglycemia Incidence % (n/N)
Davis, 2010[16]	Prospective community-based cohort	6.4 yrs	Several, not described	8.4 (52/616) 1.7 per 100 patient-years
Quilliam, 2011[183]	Retrospective cohort of working-age patients	Patients who were represented for at least one year in a database	The most common classes of OHAs were metformin (75.7%), sulfonylureas (42.3%), and thiazolidinediones (33.3%). Insulin use in addition to OHA use was relatively infrequent, (6.0%)	3.5 (653/18,657) 1.5 per 100 patient-years

Table 3l. Management (Self vs. GP or Nurse Management) Studies

Study and year	Study type	Study duration	Intervention Control	Hypoglycemia Incidence % (n/N)
Barnett, 2008[171]	RCT	27 wks	Gliclazide - self-monitoring of blood glucose (SMBG)	0/311
			Gliclazide – Non-SMBG	0/299
Meneghini (PREDICTIVE) 2007[176]	RCT	26 wks	Insulin detemir - Algorithm care	0.26 events per patient years
			Insulin detemir - Standard care	0.20 events per patient years

Table 4. Risk Factor Data Table for Key Question #2

Study Location Funding Age/Sex	Study Design Analysis Definition of Severe # of Patients	Risk Factors for Severe Hypoglycemia OR Patient Characteristics If No Formal Risk Factor Analysis				
Akram, 2006[84]	Cross-sectional survey	**Univariate analysis (RAE – risk of any event, RRE – risk of repeated events)**				
			RAE OR 95% CI	p value	RRE RR 95% CI	p value
Denmark	Multivariate	Age	1.01 0.99–1.04	0.366	0.98 0.97–1.00	0.030
		Diabetes duration	1.02 0.98–1.06	0.400	0.96 0.94–0.98	< 0.001
Danish Research Medical Council	The need for assistance from another person to treat the condition in the preceding year	Diabetes duration prior to insulin start	0.98 0.93–1.02	0.403	0.93 0.91–0.96	< 0.001
		Duration of insulin therapy	1.07 1.01–1.13	0.018	0.99 0.96–1.02	0.370
		Impaired awareness	2.66 1.55–4.56	< 0.001	1.18 0.87–1.59	0.229
		Insulin regimens:				
66/men and women	401 surveys completed, 66 at least one event, 178 total episodes, overall incidence of severe hypoglycemia 0.44 episodes/ person year	Twice daily	2.89 0.67–12.6	0.157	0.45 0.25–0.87	0.017
		Three times daily	2.07 0.27–16.1	0.489	0.18 0.04–0.82	0.027
		Four times daily	4.81 1.05–22.1	0.043	0.54 0.28–1.03	0.059
		Retinopathy (untreated)	0.99 0.56–1.78	0.979	0.63 0.45–0.86	0.004
		Peripheral neuropathy (asymptomatic)	1.64 0.80–3.39	0.181	2.00 1.33–2.99	0.001
		Peripheral neuropathy (symptomatic)	1.69 0.92–3.11	0.089	1.42 0.97–2.07	0.071
		Hypertension	0.57 0.33–0.97	0.039	1.40 1.03–1.90	0.033
		Hypertension therapy:				
		RAS blocking	0.89 0.31–2.54	0.826	0.65 0.39–1.08	0.096
		Non-RAS blocking drugs	1.55 0.65–3.71	0.323	0.38 0.24–0.59	< 0.001
		Combination of both	0.63 0.27–1.43	0.266	0.65 0.44–0.95	0.027
		Macrovascular complication (stroke, MI)	1.14 0.57–2.27	0.719	1.78 1.28–2.48	0.001
		Metformin	0.51 0.25–1.01	0.052	1.05 0.72–1.55	0.789
		Marital status (married)	2.57 1.32–5.01	0.006	1.19 0.80–1.79	0.393
		Exercise (strenuous)	0.49 0.19–1.31	0.154	2.06 1.33–3.18	0.001
		Smoking	0.74 0.38–1.46	0.389	1.43 1.02–2.02	0.041
		Use of tranquilizers	1.66 0.93–2.98	0.087	1.57 1.17–2.12	0.003
		Multivariate analysis - *Risk of any event*				
		Impaired awareness 3 fold increased risk of any event				
		Long duration of DM (per 10 years) 2 fold increased risk of any event				
		Being married 2 fold increased risk of any event				
		Rate of severe hypoglycemia (risk of repeated events)				
		Peripheral neuropathy 3x increased rate				
		Long duration of DM (per 10 years) prior to insulin therapy 3x decreased rate				
		Tx with RAS blocking drugs ½ rate of severe hypoglycemia				

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Study Location Funding Age/Sex	Study Design Analysis Definition of Severe # of Patients	Risk Factors for Severe Hypoglycemia OR Patient Characteristics If No Formal Risk Factor Analysis
Alvarez Guisasola, 2008[85] Multicenter (7 countries) Industry 63/men and women	Observational, cross-sectional, multicentre study Unadjusted Based on answer to question "Have you ever felt symptoms of hypoglycemia (low blood sugar) in the past year? (iii) felt you needed assistance of others to manage symptoms (iv) needed medical attention, ambulance, ER, saw doctor or nurse	**Patient reported outcomes and HbA1c goal status** Characteristic — patients at goal — patients not at goal — p value Hypoglycemic symptoms who felt the need for assistance, including medical attention, to manage symptoms 5.8 (11/190) — 4.8 (22/462) — 0.0152* *This p value was combined with other hypoglycemia symptom severities
Asplund, 1991[105] Sweden NR 75/men and women	Case-control 2 – matched on gender and age Median BG 1.7 mmol/l 11 patients comatose,3 reduced consciousness, five fully alert but with signs/symptoms of hypoglycemia and sought medical attention 422 patients on glipizide, - 19 with severe hypoglycemia 844 controls	Duration of diabetes (months): Cases 36 (14-48); Controls 75 (52-108); P value 0.004 Duration of sulfonylurea treatment (months): 14 (6-43); 51 (34-75); 0.004 Duration of glipizide treatment (months): 12 (3-26); 41.5 (26-59); <0.001 Glipizide dose (mg day): 10 (5-15); 10 (5-15); NS Number of concomitant drugs (excluding glipizide): 5 (3.5-5); 2 (1-1); <0.001 Cardiac Disorders, Renal Disorders, Liver Disorders, Cerebral Disorders all more common in hypoglycemia group Only significant in renal disease: OR 4.0 95% CI 1.2-13.1 Circulatory disease 14/19 (74%) Hepatic failure (moderate) 2/19 (11%) Other meds taken by cases: Diuretic 13/19 (68%);Cardiac clycosides 6/19; Benzodiazepines 5/19; NSAIDS 4/19; beta-blocker 4/19; salicylates 4/19 Significant drug ORs (cases vs. controls): Any diuretic OR=8.5 (CI 1.7-29.3) Benzodiazepines OR=10.0 (CI 1.4-71.8)

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Study Location Funding Age/Sex	Study Design Analysis Definition of Severe # of Patients	Risk Factors for Severe Hypoglycemia OR Patient Characteristics If No Formal Risk Factor Analysis
Bodmer, 2008[24] **UK based General practice Research Database** UK Industry 61/men and women	Nested case control within retrospective cohort Unadjusted for severe hypoglycemia, adjusted for generic hypoglycemia Hypoglycemia leading to an emergency hospitalization or death 2,025 case subjects, 7,278 matched controls 73 out of 2,025 had severe hypoglycemia	"Numbers too small for a meaningful model." – formal risk analysis not performed Of 73 case subjects 35 were on insulin (26 were on insulin only and 9 used insulin in combination with an oral antidiabetes drug) 22 used sulfonylureas only 3 metformin only 11 a combination of sulfonylureas and metformin 2 were past users of antidiabetes drugs. Among 22 users of sulfonlyureas only, 16 used gliclazide, 5 glibenclamide, and 1 glimepiride, and 17 used a high dose and 5 a low dose.
Bruce, 2009[92] **Fremantle (older patients with cognitive impairment/ dementia)** Australia Government (Initial Fremantle) and Government/ Industry (this study) 76/men and women	Prospective Cohort Univariate and multivariate Cox proportional hazards; Negative binomial regression model *Severe hypoglycemia* Answer yes to "Have you ever had to go the hospital because of a hypoglycemic attack?" or "Have you ever had a serious hypoglycemic attack that made you go unconscious?" *Health service use for hypoglycemia (HSH)(used as severe hypoglycemia during followup)* An event requiring ambulance and/or emergency department attendance and/or hospitalization for hypoglycemia as the primary diagnosis 302, 27 had HSH during followup	At study entry: No significant independent associations between dementia and any measure of hypoglycemia, however: Cognitive impairment without dementia: Self reported severe hypoglycemia (OR 2.96 (1.05-8.33)) Doctor verified neuroglycopenia (OR 5.10 (1.46-17.87)) HSH (OR 9.65 (1.65-56.60)) <u>Significant Risk Factors</u> **Time to first HSH** HR 95% CI / p value Dementia 3.02 (1.07-8.53) 0.037 Insulin therapy 2.77 (1.18-6.46) 0.019 Low BMI 5.94 (1.85-19.06) 0.003 Inability to self manage medications 4.19 (1.43-12.25) 0.009 History of self reported severe hypoglycemia 3.51 (1.15-10.76) 0.028 **Frequency of HSH** RR 95% CI / p value Dementia 20.26 (6.00-68.44) <0.001 Insulin therapy 14.60 (3.49-61.12) <0.001 Renal Impairment 4.70 (1.02-21.70) 0.048

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Davis, 2010[16]	Prospective cohort	**Univariate associates**	**HR (95% CI)**	**p value**
	Univariate and multivariate	Age 65 yr or older	1.15 (0.65-2.02)	0.63
Fremantle (everyone)		Male sex	0.97 (0.56-1.67)	0.90
	An episode in which a patient with a subnormal blood/plasma/serum glucose required health service use and hypoglycemia was the primary diagnosis	BMI <29.0 kg/m^2	0.97 (0.56-1.68)	0.92
		Education attainment higher than primary level	1.65 (0.78-3.51)	0.19
Australia		English ability (not fluent)	0.53 (0.19-1.48)	0.23
		Any exercise in past 2 wks	0.60 (0.34-1.04)	0.07
Government (Initial Fremantle) and Industry (this study)		Daily alcohol consumption of three or more standard drinks	1.38 (0.55-3.46)	0.50
		GAD ab positive	4.41 (1.75-11.10)	0.002
	616	Diabetes duration > or equal to 8 yr	2.92 (1.60-5.32)	<0.001
	52 had 66 episodes of severe hypoglycemia	FSG >or equal to 8.0 mmol/liter	1.32 (0.73-2.38)	0.35
		AbA1c > or equal to 7.0%	2.11 (1.13-3.95)	0.020
		Sulfonylurea treatment (vs. lifestyle/other oral agents)	2.50 (1.16-5.38)	0.019
67/men and women		Insulin treatment (+/- oral agents)	4.29 (2.44-7.55)	<0.001
		Time on insulin (increase of 1 yr)	1.42 (1.24-1.63)	<0.001
		Blood glucose self monitoring	1.01 (0.48-2.15)	0.98
		History of severe hypoglycemia	6.59 (2.62-16.60)	<0.001
		eGFR <60 ml.min per 1.73 m^2	2.90 (1.68-5.00)	<0.001
		Peripheral neuropathy	2.89 (1.60-5.21)	<0.001
		Orthostatic hypotension	1.74 (0.99-1.15)	0.34
		QTc interval (increase of 10 msec^0.5)	1.05 (0.95-1.15)	0.34
		Five or more prescribed medications	1.84 (1.07-3.17)	0.028
		Anticoagulant therapy	2.93 (1.06-8.13)	0.039
		Regular aspirin use (> or equal to 75 mg/d)	1.31 (0.74-2.31)	0.36
		NSAID treatment	1.29 (0.61-2.74)	0.51
		Allopurinol treatment	1.62 (0.65-4.08)	0.30
		Fibrate treatment	1.86 (0.74-4.67)	0.19
		Beta-blocker treatment	1.26 (0.63-2.51)	0.51
		Hospitalized in 1998	1.77 (1.03-3.05)	0.039
		Independent associates	**HR (95% CI)**	**p value**
		Time on insulin (increase of 1 yr)	1.33 (1.15-1.53)	<0.001
		History of severe hypoglycemia	5.66 (2.21-14.50)	<0.001
		eGFR <60 ml/min per 1.73 m^2	2.39 (1.37-4.15)	0.002
		Peripheral neuropathy	2.44 (1.33-4.47)	0.004
		Education attainment higher than primary level	2.34 (1.09-5.04)	0.029

Study Location Funding Age/Sex	Study Design Analysis Definition of Severe # of Patients	Risk Factors for Severe Hypoglycemia OR Patient Characteristics If No Formal Risk Factor Analysis		
Davis, 201193 Patients taken from Fremantle Australia Government (Initial Fremantle) and Industry (this study) 67/men and women	Followup of Fremantle Prospective cohort patients Multivariate Requiring documented health service use 602 patients ACE genotyped, 49 patients reported 63 episodes of SH	Independent baseline predictors of time to first severe hypoglycemic event and frequency of severe hypoglycemia during follow-up **Time to first event** Time on insulin (increase of 1 yr) History of severe hypoglycemia eGFR _ 60 ml/min per 1.73m2 Peripheral neuropathy Educational attainment beyond primary level ACE *DD* genotype ACE-I use **Frequency** *Logit model* Time on insulin (increase of 1 yr) eGFR _ 60 ml/min per 1.73m2 Peripheral neuropathy Educational attainment beyond primary school level *Count model* HbA1c (increase of 1%) FSG (increase of 1 mmol/liter) ACE *DD* genotype	**Hazard ratio (95% CI)** 1.33 (1.15–1.53) 5.48 (2.05–14.64) 2.63 (1.46–4.73) 2.57 (1.36–4.84) 2.82 (1.25– 6.38) 2.35 (1.13–1.53) 1.77 (0.99 –3.13) **Incidence rate ratio (95% CI)** 0.34 (0.18–0.66) 0.18 (0.06–0.50) 0.18 (0.06–0.49) 0.17 (0.04–0.87) 1.36 (1.08 –1.71) 0.83 (0.73– 0.94) 1.80 (1.00 –3.24)	**p value** 0.001 0.001 0.001 0.004 0.013 0.006 0.052 **p value** 0.001 0.001 0.001 0.033 0.009 0.004 0.050
Duran-Nah, 2008[104] Mexico NR 59/men and women	Case control Multivariate Blood glucose < or equal to 72 in presence of neurological clinical picture consistent with a severely confused mental state or worse, non-arousable, should respond to IV glucose 92 (cases) patients with hypoglycemia and 188 without (controls)	**Variable** Age (years) Diabetes duration (years) Illiteracy-primary Attending physician (FP) Chronic renal failure (yes) Missed meals (yes) Previous hypoglycemia (yes) Combined therapy (yes) Polypharmacy use (yes)	**OR (95% CI)** 0.95 (0.88-0.09) 1.110 (1.05-1.2) 3.7 (1.4-10.0) 2.8 (1.02-7.9) 3.0 (1.2-7.7) 19.8 (9.1-43.1) 2.9 (1.3-6.5) 5.2 (2.3-11.8) 4.9 (0.7-35.1)	**p value** 0.008 0.001 0.009 0.04 0.01 <0.001 0.01 <0.01 0.11

Study Location Funding Age/Sex	Study Design Analysis Definition of Severe # of Patients	Risk Factors for Severe Hypoglycemia OR Patient Characteristics If No Formal Risk Factor Analysis			
Fadini, 2009[95]	Retrospective Cohort	**Characteristic**	**OHAs**	**Insulin**	**p value**
		Age, years	79.7 (11.4)	74.7 (10.1)	0.009
Italy	Unadjusted	Male sex (%)	46.0	41.3	0.66
		Institutionalized (%)	7.9	4.8	0.73
NR	Hypoglycemia that led to hospitalization	First blood glucose (mg/dl)	38.2 (11.2)	39.7 (11.5)	0.33
		Coma (%)	54.0	30.2	0.002
77/men and		Fall (%)	25.4	17.5	0.27
women	126 episodes	Duration of hypoglycemia (h)	8.1 (8.9)	3.9 (4.3)	0.001
	(63 OHA, 63 Insulin)	HbA1c (%)	6.75 (1.0)	8.1 (2.1)	<0.001
		Serum creatinine (mmol/l)	106.6 (45.4)	120.6 (115.9)	0.64
	Precipitating events: low carb	eGFR >60 ml/min/1.73 m2	37	43	0.63
	intake without change in therapy	eGFR 30–59 ml/min/m2	21	16	0.32
	n=71, errors in administration of	eGFR 15–29 ml/min/m2	5	1	0.09
	insulin n=19	eGFR <ml/min/m2	0	3	0.08
	No association with other typical	0–4 years from diagnosis(%)	39.7	26.9	0.13
	risk factors (such as education)	5–9 years from diagnosis (%)	17.5	9.5	0.19
		10–19 years from diagnosis (%)	17.4	19.1	0.82
	In-hospital outcomes:	20+ years from diagnosis (%)	25.4	44.5	0.03
	Acute coronary syndrome	Obesity (%)	30.2	23.8	0.27
	17.5% OHA, 19.0% Insulin, p=0.85	Dyslipidemia (%)	19.0	12.7	0.74
		Hypertension (%)	79.4	79.4	0.78
	Duration of stay	Coronary artery disease (%)	39.7	31.7	0.53
	9.8 days OHA, 8.0 days Insulin,	Peripheral artery disease (%)	47.6	38.1	0.27
	p=0.05	Retinopathy (%)	9.5	27.0	0.007
		Known neuropathy (%)	6.3	17.5	0.023
	Death at follow-up	Liver disease (%)	3.2	25.4	0.001
	31.7% OHA, 52.4% Insulin p=0.02	Cancer (%)	12.7	22.2	0.25
		COPD (%)	22.2	11.1	0.19
		Rheumatoid arthritis (%)	0.0	3.2	0.25
		Dementia (%)	3.2	4.8	0.44
		Beta-blockers (%) (selective (%))	19.0 (19.0)	15.9 (12.7)	0.56
		ACE inhibitors (%)	58.7	61.9	0.52
		Aspirin (%)	57.1	41.3	0.46
		NSAIDs (%)	1.6	3.2	0.41
		Cimetidine (%)	0.0	1.6	0.25
		CNS depressants (%)	15.9	17.5	0.49

Study Location Funding Age/Sex	Study Design Analysis Definition of Severe # of Patients	Risk Factors for Severe Hypoglycemia OR Patient Characteristics If No Formal Risk Factor Analysis
Henderson, 2003[76] Scotland NR 68/men and women	Cross-sectional Unadjusted Required external assistance, symptoms suggestive of hypoglycemia that had resolved following treatment with oral carbohydrate, or had required treatment with parenteral glucose or glucagon 215 interviews, 60 episodes by 32 people 0.28 episodes per patient per year	Frequency of severe hypoglycemia increased with: Age ($p<0.05$ $r=0.2$) Duration of diabetes ($p<0.05$, $r=0.2$) Duration of insulin therapy ($p<0.05$, $r=0.2$) Impaired awareness (9 fold higher rate) – not associated with age duration of DM, or duration of tx with DM Normal awareness: 0.22 episodes/patient/year Impaired awareness 2.15 episodes/patient/year No association with: Lower HbA1c Higher insulin dose
Hepburn, 1992[99] Scotland NR 63/men and women	Cross-sectional Unadjusted Episode during which the patient was unable to take appropriate restorative action and required the assistance of another person for treatment (either at home or in the hospital) to administer either oral or parenteral glucose, or glucagon by injection 104 type 2 DM patients	$r=0.39$ ($p<0.001$) - # episodes and duration of insulin All patients with partial awareness (n=6) and 3 of 80 (4%) with normal awareness had severe hypoglycemia in past year Characteristic — No Severe Hypoglycemia (n=62) — Severe hypoglycemia (n=25) Age (years) — 62 ± 8 — 64 ± 11 Body mass index — 28 ± 5 — 26 ± 4 Duration of diabetes (yrs) — 11 — 13 Duration of insulin therapy (yrs) — 2 — 6 Daily insulin dose (U/kg) — 0.6 — 0.7 Glycated hemoglobin (%) — 10.4 — 10.7
Holman, 2009[43] **Treat to Target in Type 2 DM (4-T)** UK Industry 62/men and women	RCT Third party assistance needed 708 patients	Hypoglycemic events (no/patient/year) — Biphasic — Prandial — Basal All patients Grade 3 — 0 — 0 — 0 Patients with an HbA1c of less than or equal to 6.5% Grade 3 — 0 — 0 — 0

Study Location Funding Age/Sex	Study Design Analysis Definition of Severe # of Patients	Risk Factors for Severe Hypoglycemia OR Patient Characteristics If No Formal Risk Factor Analysis
Holstein, 2009[102] Germany NR 78/men and women	Case Control Multivariate A symptomatic event requiring treatment with IV glucose and confirmed with a BG of <50 mg/dl (<2.8 mmol/l) 43/97 had severe hypoglycemia All on sulfonylurea and no insulin	Characteristic / Control (n=54) / Severe Hypoglycemia (n=43) / p value Sex (male / female): 28 / 26 / 20 / 23 / 0.60 * Age (years): 80.1 ± 8.8 / 75.2 ± 10.4 / 0.01 BMI (kg / m 2): 26.80 ± 4.73 / 26.72 ± 4.67 / 0.94 Creatinine (mg/ dl): 1.83 ± 1.23 / 1.53 ± 0.93 / 0.18 Creatinine clearance (ml / min): 38.89 ± 18.85 / 48.91 ± 23.65 / 0.02 HbA 1c (%): 7.15 ± 0.96 / 6.73 ± 1.28 / 0.07 Age at onset of diabetes (years): 69.1 ± 12.3 / 66.1 ± 14.3 / 0.30 Diabetes duration (years): 10.8 ± 8.1 / 8.6 ± 11.3 / 0.30 Co-medication (number of all drugs): 7 ± 2 / 6 ± 3 / 0.08 Metformin treatment (number of patients): 22 / 13 / 0.28 * *Variable* / *Univariate analysis OR and p value* / *Multivariate analysis and p value* Gender: 0.81 (0.36 – 1.80) 0.60 / 0.79 (0.30 – 2.07) 0.63 Age (years): 0.95 (0.91 – 0.99) 0.02 / 0.92 (0.88 – 0.98) 0.005 Diabetes duration (years): 0.97 (0.93 – 1.03) 0.31 / 0.96 (0.91 – 1.01) 0.11 Sulfonylurea daily dose (mg): 1.16 (0.99 – 1.36) 0.07 / 1.25 (1.03 – 1.52) 0.02 HbA 1c (%): 0.69 (0.45 – 1.04) 0.08 / 0.67 (0.42 – 1.05) 0.08 *KCNJ11* (E23K): 0.54 (0.30 – 0.98) 0.04 / 0.68 (0.34 – 1.35) 0.27
Holstein, 2003[107] 3 countries NR 78/men and women	Case series Unadjusted A symptomatic event requiring administration of IV glucose or glucagon 93 episodes, 37 on glimepiride, 56 on glibenclamide	Glimepiride (n=37) / Glibenclamide (n=56) / Treatment Differences (95% CI) / p value Age (years): 77.1±11.2 (43–93) / 78.1±9.6 (43–97) / -1.0 (-6.0; 4.0) / 0.721 Female sex (%): 57% (21/37) / 61% (34/56) / -4.0% (-24.4; 16.5) / 0.830 Body mass index: 24.6±4.5 (16.9–38.4) / 24.8±4.5 (17.8–36.9) / -0.2 (-2.6; 2.2) / 0.942 Duration of diabetes (years): 7.0±7.0 (0–32) / 10.5±8.7 (0–33) / -3.5 (-7.4; 0.4) / 0.095 HbA1c (HPLC; non-diabetic range 3.4–4.9%): 5.4±0.7 (4.6–7.7) / 5.2±0.9 (3.7–7.5) / 0.2 (-0.2; 0.6) / 0.345 Initial blood glucose (mmol/l): 1.9±0.66 (0.78–2.9) / 1.8±0.89 (0–3.7) / 0.1 (-0.24; 0.6) / 0.443 Co-medication (number of drugs): 6.2±3.0 (0–15) / 3.6±3.0 (0–16) / 2.60 (1.2; 4.0) / <0.001 Creatinine-clearance (ml/min): 38±23 (10–87) / 54±32 (8–180) / -16.0 (-30.1; -1.9) / 0.016 Possible causes identified for 75 of 93 (81%): missed meals (59%), alcohol (15%), increased activity (5%), incorrect dosing (1%)

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Study Location Funding Age/Sex	Study Design Analysis Definition of Severe # of Patients	Risk Factors for Severe Hypoglycemia OR Patient Characteristics If No Formal Risk Factor Analysis
Holstein, 2003[109] Germany Industry 84/men and women	Case series A symptomatic event requiring an IV glucose or glucagon injection that relieved symptoms and was confirmed by blood glucose measurement 30,768 patients in ED, 264 cases of SH Rate 1.5 episodes per 100 patients in insulin treated DM2 0.4 episodes per 100 for overall DM2	Characteristic in type 2 DM (n=148) with SH Age (year) 76 +/- 12 (44-95) Percent female 64% (95/148) BMI 25.7 +/- 4.8 (15.8-39.7) Initial blood glucose (mg/dl) 34 +/- 16 (0-61) Diabetes duration 17 +/- 11 (0-40) HbA1c% 6.2 +/- 1.8 (3.9-15.5) Renal failure (cr clearance less than 60 ml/min) 54% (80/148) Comorbidity (number of concomitant diseases 3.6 +/- 2.6 (0-7) Comedication (number of drugs) 3.3 +/- 3.0 (0-18) Patients with recurrent hypoglycemia in the study period 12% (14/121)

Characteristic	CT (n=78)	SU (n=45)	CT+SU (n=25)	pvalue CT vs SU	pvalue CT vs CT+SU	pvalue SU vs CT+SU
Age (year)	76 +/- 11)	79 +/- 13	72 +/- 10	0.176	0.109	0.023
Percent female	63%	62%	44%	1.000	0.109	0.209
BMI	25.0 +/- 5.1	24.4 +/- 5.0	24.4 +/- 3.3			
Diabetes duration (years)	19+/-10	12+/-10	16+/-10	<0.001	0.195	0.113
Initial blood glucose	38+/-19	31+/16	34+/-16	0.040	0.345	0.455
HbA1c %	6.7+/-2.0	5.4+/-0.9	6.6+/-1.8	<0.001	0.824	<0.001
Insulin dose	37+/-18		27+/-20		0.017	
Frequency and dose of glibenclamide		n=38, 6.1+/- 3.1	n=18, 7.2+/-1.1			
Frequency and dose of glimepiride		n=6, 2.5+/-0.8	n=7 2.1+/-0.6			
Comedication (number of drugs)	3.7 +/- 2.5	3.8 +/- 2.8	5.2 +/- 3.6	0.838	0.022	0.075
Renal failure (cr cl < 60 ml/min)	53% (41/78)	58% (26/45)	52% (13/25)	0.707	1.000	0.802

Attributed causes for 68/148 (46%) episodes in type 2 patients: missed meals (59%), incorrect dosing (19%), alcohol (13%), increased activity (9%)

Study Location Funding Age/Sex	Study Design Analysis Definition of Severe # of Patients	Risk Factors for Severe Hypoglycemia OR Patient Characteristics If No Formal Risk Factor Analysis
Holstein, 2011[103] Germany NR 77/men and women	Case control Multivariate Symptomatic event requiring treatment with IV glucose and was confirmed by BG <50 mg/dl 102 cases of SH, 101 controls	Basic characteristics of type 2 diabetic patients with sulfonylurea-induced hypoglycemia versus control group Variable — Severe hypoglycemia (n = 102) — Control (n = 101) — p value Sex (female/male) — 45/57 — 51/50 — 0.36 Age (years) — 77.4 ± 9.2 — 79.3±9.2 — 0.13 Body mass index (kg/m2) — 26.7±5.5 — 27.0±4.4 — 0.76 Serum creatinine (mg/dl) — 1.55±0,87 — 1.72±1.03 — 0.19 Creatinine clearance (ml/min) — 45.8±22. — 6 38.0±18.1 — 0.02 HbA1c (%) — 6.5±1.2 — 7.2±1.3 — 0.0004 Co-medication (number of drugs) — 7.0±2. — 8 7.4±2.8 — 0.28 Duration of diabetes (years) — 11.0±9.9 — 11.5±8.3 — 0.71 Patients with glimepiride mean daily dose 76 (74.5%) 2.8±1.6 mg 81 (80.2%) 2.3±1.3 mg 0.33 (chi2) 0.04 (t-test) Patients with glibenclamide mean daily dose 25 (24.5%) 6.1±3.7 mg 1 8 (17.8%) 5.0±3.6 mg 0.2 (chi2) 0.3 (t-test) Patients with gliquidone mean daily dose 1 (1.0%) 30 mg 2 (2%) 60 mg 0.62 Additional treatment with metformin mean daily dose 37 (36%) 1731±602 mg 43 (43%) 1715±494 mg 0.36 (chi2) 0.90 (t-test) Additional treatment with insulin mean daily dose 29 (28%) 36.4±22 I.E. 20 (20%) 36.8±21.5 I.E. 0.15 (chi2) 0.96 (t-test) Co-medication with other CYP2C9 main substrates 24 (24%) 33 (49%) 0.001 (chi2) Co-medication with other drugs being at least one CYP2C9 substrate 39 (39%) 32 (47%) 0.30 (chi2) Risk factors for severe hypoglycemia in 102 sulfonylurea-treated type 2 diabetic patients with severe hypoglycemia versus control group (n=101) Variable — Relative risk (95% CI) — p value HbA1c (%) — 1.56 (1.20–2.04) — 0.001 Dose of sulfonylurea — 1.00 (0.96–1.04) — 0.95 CYP2C9-genotypes *2/*2, *2/*3, and *3/*3 — 0.58 (0.14–2.50) — 0.47 Co-medication with other CYP2C9-main substrates — 0.34 (0.17–0.65) — 0.001 Co-medication with other drugs being at least one CYP2C9-substrate — 0.72 (0.39–1.34) — 0.30 Co-medication with insulin — 1.61 (0.84–3.09) — 0.15 Co-medication with angiotensin-converting enzyme inhibitor — 1.35 (0.77–2.34) — 0.29 Co-medication with analgetics — 1.21 (0.59–2.50) — 0.60 Co-medication with gyrase inhibitors — 0.99 (0.20–5.03) — 0.99 Presence of coronary heart disease — 2.38 (1.35–4.18) — 0.003 Presence of heart failure — 1.46 (0.84–2.55) — 0.18 Presence of dementia — 1.97 (0.94–4.15) — 0.09 Previous participation at structured diabetes education — 1.09 (0.59–2.00) — 0.79 Kind of accommodation (home vs. nursing home) — 1.29 (0.87–1.92) — 0.21

Study Location Funding Age/Sex	Study Design Analysis Definition of Severe # of Patients	Risk Factors for Severe Hypoglycemia OR Patient Characteristics If No Formal Risk Factor Analysis
Holstein, 2001[17] **Same data set as Holstein 2003 Germany above** Germany Industry 84/men and women	Prospective cohort Unadjusted A symptomatic event requiring an IV glucose or glucagon injection that relieved symptoms and was confirmed by blood glucose measurement 30,768 patients in ED, 264 cases of SH Rate 1.5 episodes per 100 patients in insulin treated DM2 0.4 episodes per 100 for overall DM2	Basic characteristics of the diabetic patients presenting with sulfonylurea-induced hypoglycemia Characteristic / Glibenclamide +glimepiride (n=1) / Glibenclamide (n=38) / Glimepiride (n=6) / Treatment difference and 95% CI glibenclamide vs glimepiride Age (years): 84 / 83.5 / 83.5 / 0 (-17.1; 9.1) Sex (% female): 0% / 63.2% / 66.7% / -3.5 (-44.1; 37.3) Diabetes duration (years): 4 / 6.0 / 16.0 / -10 (-19.0; 0.8) BMI (kg/m^2): 24.8 / 22.9 / 28.2 / -5.3 (-10.7; 1.1) Sulfonylurea dose (mg): 3.5 and 2 / 4.4 / 3.0 / 1.4 (0.6; 6.6) Initial venous blood glucose (mmol/l): 2.24 / 1.7 / 1.8 / -0.1 (-0.97; 0.95) HbA1c (HPLC; non-diabetic range 3.4–4.9%): 5.6 / 5.25 / 4.7 / 0.55 (-0.3; 1.9) Patients with impaired renal function: 1/1 (100%) / 23/38 (60.5%) / 4/6 (66.7%) / -6.1% (-46.9; 34.7) Co-medication (number of drugs): 7 / 3.0 / 3.5 / -0.5 (-3.7; 3.1) Participation in diabetes education programs (%): 0% / 3% (1/38) / 0% / Not done
HTN in DM study IV,1996[91] UK Government/ Industry 57/men and women	RCT Unadjusted Major hypoglycemic events: requiring medical assistance or hospitalization 758 patients	No difference between allocations in the proportion of patients having hypoglycemic episodes Annual rates of major hypoglycemic episodes over 5 years Time post randomization / Captopril / Atenolol / Less tight control *n*: 247 / 223 / 228 1st year: 2.5% / 0.5% / 0.8% 2nd year: 0.9% / 1.0% / 0.4% 3rd year: 0 / 1.0% / 0.8% 4th year: 1.0% / 3.1% / 0.9% 5th year: 0.5% / 1.6% / 1.8% Ever over 5 years: 4.0% / 4.9% / 3.1%
Leese, 2003[25] **DART/MEMO** Scotland Industry 65/men and women	Retrospective cohort No adjustment Any episode requiring external help 7,678 with type 2 DM	Number / HbA1c % / Age (years) / Duration of DM (years) / BMI / Sex (% male) On insulin, no hypo: 835 / 8.23 / 63.2 / 11.8 / 30.1 / 47.7 On insulin, hypo: 66 / 7.87 / 66.6 / 13.5 / 26.7 / 47.0 P value: 0.097 / 0.038 / 0.137 / <0.001 / 0.914 On sulfonylurea, no hypo: 2,800 / 7.16 / 65.4 / 6.3 / 29.6 / 52.2 On sulfonylurea, hypo: 23 / 8.00 / 65.0 / 7.2 / 28.1 / 47.8 P value: 0.064 / 0.884 / 0.517 / 0.122 / 0.687

Study Location Funding Age/Sex	Study Design Analysis Definition of Severe # of Patients	Risk Factors for Severe Hypoglycemia OR Patient Characteristics If No Formal Risk Factor Analysis		
Miller, 2010[89] **ACCORD data** 2 countries Government and industry 62/men and women	RCT Multivariate adjusted Episodes of hypoglycemia requiring emergency care or be admitted to a hospital: Hypoglycemia requiring medical assistance (HMA), or "low blood glucose" requiring any assistance, medical or non medical (HA), after March 2003: plasma glucose of less than 2.8 mmol/l (50 mg/dl) or symptoms that promptly resolved with carbohydrate also a requirement		**HR (95% CI)**	**p value**
		HMA (both intensive and standard arms)		
		Female (v male)	1.21 (1.02 to 1.43)	0.0300
		Race		<0.0001
		Non Hispanic white	1.0	
		African-American	1.43 (1.20 to 1.71)	<0.0001
		Hispanic	0.93 (0.68 to 1.27)	0.6500
		Other	0.64 (0.47 to 0.88)	0.0100
		History of CV disease (yes v no)	1.10 (0.94 to 1.28)	0.2200
		History of peripheral neuropathy (yes v no)	1.19 (1.02 to 1.38)	0.0300
		Time since diagnosis of diabetes (years)		0.7394
		< or equal to 5	1.0	
		6-10	0.98 (0.77 to 1.24)	0.8500
		11-15	1.06 (0.83 to 1.37)	0.6200
		16+	1.37 (1.09 to 1.73)	0.0100
		BMI		0.0023
		<25	1.0	
		>or equal to 25 to< 30	0.78 (0.60 to 1.02)	0.0700
		30+	0.65 (0.50 to 0.85)	<0.0001
		Albumin to creatinine ratio		<0.0001
		<30	1.0	
		30-300	1.20 (1.02 to 1.43)	0.0300
		>300	1.74 (1.37 to 2.21)	<0.0001
		Serum creatinine (micromol/l)		0.0010
		<88.4	1.0	
		88.4-114.9	1.21 (1.02 to 1.43)	0.0300
		>114.9	1.66 (1.25 to 2.19)	<0.0001
		Age (per 1 year increase)	1.03 (1.02 to 1.05)	<0.0001
Miller, 2001[100] United States Government 70/men and women	Cross-sectional Multivariate Loss of consciousness or other major alteration of mental status caused by hypoglycemia that required the assistance of another person to treat the condition 5/1055	**No significant predictors of severe hypoglycemia** Age, sex, race, diabetes duration, BMI, follow-up fasting plasma glucose level, follow-up HbA1c level, type of diabetes therapy, hypoglycemia at baseline visit, and whether diabetes medication therapy was increased at the baseline visit		

Patient Number	**Sex/Age, y**	**BMI**	**Diabetes Duration, y**	**HbA1c, %**	**Therapy Type**	**Insulin Dosage, U/kg per day**
1	F/73.7	48.1	18.7	6.3	Insulin	0.32
2	F/53.2	29.6	6.4	5.6	Insulin and metformin	0.63
3	M/68.1	34.9	18.4	8.3	Insulin	0.51
4	F/74.2	26.6	23.3	8.3	Insulin	0.44
5	M/61.5	N/A	16.4	12.1	Insulin	0.32

All black race

Study Location Funding Age/Sex	Study Design Analysis Definition of Severe # of Patients	Risk Factors for Severe Hypoglycemia OR Patient Characteristics If No Formal Risk Factor Analysis				
Quilliam, 2011[27]	Nested case control	Independent predictors of inpatient hypoglycemia admissions.				
		Variable	Cases, % (n 1339)	Controls, % (n 13,390)	Crude OR (95% CI)	Adjusted OR*(95% CI)
Marketscan Database	Multivariate	Gender				
	Hypoglycemia requiring	Female	49.2	46.3	1.00 (N/A)	1.00 (N/A)
United States	hospitalization, used ICD9 codes	Male	50.8	53.7	0.89 (0.80–0.99)	0.84 (0.73–0.96)
		Age, y				
Industry	1339 cases, 13,390 controls	18–34	1.3	2.1	1.00 (N/A)	1.00 (N/A)
		35–49	13.3	21.1	0.99 (0.60–1.63)	1.01 (0.58–1.79)
55/men and women		50–64	82.6	74.5	1.75 (1.08–2.84)	1.14 (0.66–1.97)
		_65	2.8	2.4	1.88 (1.04–3.39)	0.91 (0.46–1.81)
		Oral diabetes medications†,‡				
		Sulfonylureas: Continuous availability§	41.1	30.0	2.36 (2.06–2.70)	2.25 (1.93–2.63)
		Sulfonylureas: Intermittent availability	25.1	14.6	2.88 (2.48–3.35)	2.28 (1.90–2.74)
		Metformin: Continuous availability§	34.1	47.9	0.48 (0.42–0.55)	0.62 (0.53–0.73)
		Metformin: Intermittent availability	23.8	23.3	0.70 (0.60-0.81)	0.76 (0.64-0.92)
		Thiazolidinediones: Continuous availability§	22.9	23.8	1.00 (0.87–1.15)	1.06 (0.90–1.24)
		Thiazolidinediones: Intermittent availability	16.9	13.8	1.27 (1.09–1.49)	1.22 (1.01–1.47)
		Other OHA: Continuous availability§	4.5	3.9	1.15 (0.88–1.52)	1.11 (0.80–1.55)
		Other OHA: Intermittent availability	3.7	3.2	1.17 (0.86–1.59)	1.09 (0.75–1.59)

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Study Location Funding Age/Sex	Study Design Analysis Definition of Severe # of Patients	Risk Factors for Severe Hypoglycemia OR Patient Characteristics If No Formal Risk Factor Analysis			
Quilliam, 2011[27]			Cases, % (n 1339)	Controls, % (n 13,390)	Crude OR (95% CI)	Adjusted OR*(95% CI)
Continued		Other medications#				
		Allopurinol	5.5	2.6	2.15 (1.66–2.78)	1.54 (1.13–2.12)
		Benzodiazepine	14.6	6.2	2.57 (2.17–3.03)	1.90 (1.55–2.33)
		Beta-blocker	35.1	21.3	2.01 (1.78–2.26)	1.20 (1.03–1.40)
		Blood glucose monitoring supplies	30.9	30.6	1.02 (0.90–1.15)	0.83 (0.71–0.96)
		Fluoroquinolone	10.7	2.5	4.69 (3.82–5.77)	2.59 (1.99–3.39)
		Insulin	16.8	6.7	2.84 (2.42–3.33)	2.23 (1.83–2.72)
		NSAID	13.8	10.4	1.38 (1.17–1.63)	1.27 (1.05–1.54)
		Trimethoprim	3.3	0.9	3.81 (2.68–5.41)	1.97 (1.26–3.08)
		Comorbid conditions				
		Previous outpatient visit for hypoglycemia	12.5	0.9	16.17 (12.60–20.76)	7.88 (5.68–10.93)
		Previous ED visit for hypoglycemia	6.2	0.1	48.53 (28.80–81.78)	9.48 (4.95–18.15)
		Macrovascular complications				
		Arrhythmia	6.8	1.4	5.25 (4.05–6.81)	1.69 (1.17–2.44)
		Coronary artery disease	21.0	7.8	3.12 (2.69–3.61)	1.48 (1.21–1.81)
		Heart failure	14.0	1.5	10.99 (8.86–13.64)	2.33 (1.72–3.15)
		Stroke	3.4	0.4	9.62 (6.37–14.52)	2.78 (1.62–4.77)
		Microvascular complications				
		Acute renal failure	8.3	0.6	15.43 (11.43–20.83)	3.10 (2.05–4.67)
		Chronic renal pathophysiology	8.4	1.1	8.37 (6.49–10.81)	2.22 (1.56–3.15)
		Ulcer	6.4	1.4	4.98 (3.82–6.49)	1.71 (1.20–2.44)
		Charlson comorbidity (per 1 U change)			1.72 (1.66–1.79)	1.37 (1.32-1.44)
		*Adjusted for all factors listed in the table.				
		†As identified in pharmacy claims in the 6 months before the index date.				
		‡Nonavailability of the medication/class of medication is the referent group.				
		§Participants with continuous availability had medication coverage in each of all six 30-day periods preceding the index date.				
		_Participants with intermittent availability had medication coverage in at least 1 of the preceding 6 intervals.				
		¶Includes persons taking glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, or meglitinides.				
		#Defined as medication availability in the previous 30 days.				

Study Location Funding Age/Sex	Study Design Analysis Definition of Severe # of Patients	Risk Factors for Severe Hypoglycemia OR Patient Characteristics If No Formal Risk Factor Analysis
Sarkar, 2010[78] United States Government 58/men and women	Cross-sectional Multivariate Answer yes to the question ""In the past year, how many times have you had a SEVERE low blood sugar reaction, such as passing out or needing help to treat the reaction?" 14,357 surveys included, 1,579 reported significant hypoglycemia	Self reported Health literacy unadjusted OR (95% CI) / adjusted OR (95% CI) Problems learning 1.5 (1.3-1.8) / 1.4 (1.1-1.7) Need help reading 1.5 (1.3-1.8) / 1.3 (1.1-1.6) Not confident with forms 1.5 (1.3-1.8) / 1.3 (1.1-1.6) **p value for all <0.0001**
Sato, 2010[106] Japan NR 75/men and women	Case control study Unadjusted Stratified by age, sex, HbA1c, duration of diabetes, and medications Characteristic symptoms and a plasma glucose level of than 50 mg/dl, which required IV glucose 32 cases,125 controls	**Clinical characteristics of patients with or without severe hypoglycemia.** **Variable** / **Severe hypoglycemic group (n = 32)** / **Diabetic control group (n = 125)** / **p-value** Age 74.8 ± 8.5 / 63.7 ± 11.3 / <0.001† Sex (M/F) 12 (37%)/20 (63%) / 82 (66%)/43 (34%) / <0.001† BMI (kg/m2) 23.2 ± 4.4 / 24.2 ± 4.0 / 0.26 HbA1c‡ (%) 6.54 ± 1.1 / 8.11 ± 1.5 / <0.001† Creatinine (mg/dl) 0.88 ± 0.55 / 0.78 ± 0.28 / 0.69 eGFR§ (ml/min/1.73 m2) 71.0 ± 33.5 / 77.6 ± 23.0 / 0.29 Duration of diabetes (year) 14.9 ± 10.2 / 7.3 ± 5.8 / <0.001† Number of total drugs 6.0 ± 2.6 / 4.3 ± 2.6 / 0.001† ***Dosage of sulfonylurea*** Glimepiride (mg/day) 2.7 ± 1.7 / 1.2 ± 0.93 / <0.001† Glibenclamide (mg/day) 4.25 ± 2.5 / 4.27 ± 2.3 / 0.88 ***Comedication*** Metformin 9 (28%) / 45 (36%) / 0.4 Pioglitazone 7 (22%) / 16 (13%) / 0.16 a-glucosidase inhibitor 16 (50%) / 27 (22%) / 0.001† Insulin 6 (17%) / 18 (14%) / 0.36 *Data are expressed as mean ± standard deviation or %.* *†Significant difference (p < 0.05).* *‡At the time of the event of severe hypoglycemia in the hypoglycemic group.* *§eGFR calculated according to the Modification of Diet in Renal Disease Study equation.* *eGFR: Estimated glomerular filtration rate; F: Female; HbA1c: Hemoglobin A1c; M: Male.*

Study Location Funding Age/Sex	Study Design Analysis Definition of Severe # of Patients	Risk Factors for Severe Hypoglycemia OR Patient Characteristics If No Formal Risk Factor Analysis
Shen, 2008[101] United States NR 66/men and women	Cross Sectional Multivariate ICD-9-CM code for hypoglycemia, patients had to be admitted to hospital 787,836 discharges	Acute hypoglycemic condition Odds ratio (95% CI) African American 1.62 (1.55-1.69) Hispanic 1.24 (1.18-1.30) Asian 1.15 (1.03-1.75)
Shorr, 1997[97] United States Government 65 and older/ men and women	Retrospective cohort Multivariate Hospitalization, emergency department admission, or death associated with hypoglycemic symptoms and a blood glucose of less than 2.8 mmol/l (50 mg/dl) 586 persons with severe hypoglycemia out of 33048 person years	Covariate / Person Years / No. of events / Rate / Relative Risk (95% CI) Drug Sulfonylurea 20714 255 1.23 reference value Insulin 11978 331 2.76 2.1 (1.8-2.5) Insulin and sulfonylurea 355 12 3.38 2.9 (1.6-9.2) Age, y 65-69 10627 156 1.46 reference value 70-74 8281 130 1.57 1.1 (0.9-1.4) 75-79 7159 142 1.98 1.5 (1.2-1.9) >80 6980 170 2.43 1.8 (1.4-2.3) Sex M 5304 107 2.01 reference value F 27743 491 1.77 0.8 (0.7-1.0) Race W 21207 313 1.47 reference value B 8974 239 2.66 2.0 (1.7-2.4) County of residence Rural (non-SMSA) 9121 198 2.17 reference value Rural (SMSA) 7169 137 1.91 1.1 (0.8-1.3) Urban 16758 263 1.57 0.9 (0.7-1.1) Days since hospital discharge >366 21491 272 1.27 reference value 31-365 10096 231 2.29 1.7 (1.4-2.0) 1-30 1460 95 6.50 4.5 (3.5-5.7) Nursing home resident No 26233 444 1.69 reference value Yes 6815 154 2.26 1.0 (0.8-1.3) No. of concomitant medications 0-4 24440 395 1.61 reference value >5 8608 203 2.35 1.3 (1.1-1.5) New hypoglycemic drug therapy No 31808 559 1.75 reference value Yes 1240 39 3.15 1.4 (1.0-1.9)

Study Location Funding Age/Sex	Study Design Analysis Definition of Severe # of Patients	Risk Factors for Severe Hypoglycemia OR Patient Characteristics If No Formal Risk Factor Analysis		
Sotiropoulos, 2005[108] Greece NR 62/men and women	Case series No comparison group or risk factor adjustment Comatose or pre-comatose status (according to the Glasgow coma scale) on arrival at the emergency ward, serum glucose level < 2.8 mmol/l, and necessity for IV glucose administration for resuscitation 2858 patients admitted, 207 had severe hypoglycemia (7.2%)	Out of 207 patients with severe hypoglycemia **Characterisitic** Age (years) Duration of diabetes (years) HbA1c level (%) **Characteristic** *Sex* Male Female *Presentation* Coma Semi-coma *Usual treatment* Insulin Sulfonylureas Insulin and sulfonylureas *Follow-up in diabetes clinic* Yes No *Educational status* Illiterate Elementary Middle Higher *Diabetes knowledge* Poor Good *Causes of hypoglycaemia* Missed meal Chronic renal failure Exercise Alcohol Dosage error Unknown	**Mean (SD)** 62.1 (8.7) 7.4 (2.8) 6.8 (1.3) **No.** 85 122 146 61 72 132 3 59 148 28 117 47 15 175 30 76 54 28 20 16 34	**Range** 45–88 1–14 **%** 41.1 58.9 70.5 29.5 34.8 63.8 1.4 28.5 71.5 13.5 56.5 22.7 7.3 85.4 14.6 30.8 21.9 11.4 8.2 6.5 13.9

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Study Location Funding Age/Sex	Study Design Analysis Definition of Severe # of Patients	Risk Factors for Severe Hypoglycemia OR Patient Characteristics If No Formal Risk Factor Analysis
Stepka, 1993[98] Poland NR 66/men and women	Retrospective cohort No adjustment Requiring immediate aid in a health care institution 20,978 admissions 101 DM2 treated with insulin 36 DM2 treated with orals 10 DM3 (secondary DM)	Serum creatinine >2 mg/dL prior to hypoglycemia: (20) 20.2% of insulin treated, (1) 2.7% of oral med group Ischemic heart disease: (56) 55.5% of insulin group, (28) 80% of oral med group Leg vessel disease: (29) 28.7% of insulin group, (17) 48.6% of oral med group Polyneuropathy: (17) 16.8% of insulin group, (3) 8% of oral med group Retinopathy: (16) 15.8% of insulin group, (3) 8% or oral med group Causes (allowing for multiple causes) Physical effort: (13) 12.9% insulin, (6) 17.1% oral meds Dietary Non-compliance: (60) 59.4% insulin, (14) 40% oral meds Dosage error: (7) 7% insulin, (4) 11.4% oral meds Alcohol: (7) 7% insulin, (2) 5.7% oral meds Unknown: (12)11.9% insulin, (7) 20% oral meds
Sugarman, 1991[96] United States NR 65/men and women	Retrospective cohort Stratified by age Required admission to the hospital for hypoglycemia for NIDDM 126 hypoglycemia associated admissions 4.7 per 1000 person years	46.8% of admissions were males 9.5% had change in prescribe dose of hypoglycemic agent within 30 days prior to admission RR=2.79 (95%CI 1.6-4.9) (risk of hospitalization if prescribed glyburide vs. chlorpropamide)

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Study Location Funding Age/Sex	Study Design Analysis Definition of Severe # of Patients	Risk Factors for Severe Hypoglycemia OR Patient Characteristics If No Formal Risk Factor Analysis			
Whitmer, 2009[94]	Longitudinal Cohort		**No. (%) Hypoglycemia (n=1465)**	**Nonhypoglycemia (n=15,202)**	**p value**
	Unadjusted	Age at survey, mean(SD), y	66.32 (7.54)	64.78 (7)	<0.001
Kaiser		Education[d]			0.09
Permanente	Hospitalization and ED diagnoses	Elementary or grade school	108 (7.4)	1004 (6.6)	
Northern	of hypoglycemia using codes	High/trade/business school	607 (41.4)	5997 (39.3)	
California	251.0, 251.1, and 251.2	College/higher degree	750 (51.2)	8222 (54.1)	
Diabetes		Men	804 (54.9)	8289 (54.5)	0.79
Registry	16,667 patients	Race/ethnicity			<0.001
	1465 with hypoglycemia	White	877 (59.8)	9588 (63.1)	
United States		African American	261 (17.8)	1626 (10.7)	
		Hispanic	159 (10.8)	1667 (10.9)	
Government		Asian	125 (8.5)	1917 (12.6)	
		Native American	39 (2.6)	341 (2.2)	
65/men and		Other	4 (0.3)	63 (0.4)	
women		Duration of diabetes from self report in 1994, mean (SD), y	13.72 (9.2)	9.15 (7.9)	
		Duration of Kaiser Permanente membership, mean (SD), y	22.66 (5.32)	22.98 (5.34)	0.03
		Medical utilization rate 2003-2004, mean (SD), y	20.12 (16.60)	15.2 (12.71)	<0.001
		Time since first diabetes diagnosis in Kaiser Permanente system, mean (SD), y	15.24 (3.59)	14.52 (2.89)	<0.001
		Comorbidity			
		Heart disease	1224 (83.5)	9368 (61.6)	<0.001
		Hyperlipidemia	1298 (88.6)	13,488 (88.7)	0.89
		Hypertension	1429 (97.5)	14,557 (95.8)	0.001
		Stroke	645 (43.0)	4389 (28.9)	<0.001
		End-stage renal disease	167 (11.4)	416 (2.74)	<0.001
		HbA1c 1995-2002, mean (SD),%	8.22 (1.29)	8.08 (1.30)	<0.001

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Study Location Funding Age/Sex	Study Design Analysis Definition of Severe # of Patients	Risk Factors for Severe Hypoglycemia OR Patient Characteristics If No Formal Risk Factor Analysis
Whitmer, 2009[94] **Continued**		**No. (%)** **Hypoglycemia (n=1465)** / **Nonhypoglycemia (n=15,202)** / **p value** Diabetes treatment type 2002-2003 <0.001 Insulin only 533 (37.75) 2157 (14.19) Oral only 446 (30.44) 8615 (56.67) Insulin and oral agents 352 (24.03) 2794 (18.38) Nonpharmacological-controlled 114 (7.70) 1636 (10.70) Years of insulin use from 1994 to censored date, mean number 7.23 (2.6) 6.52 (2.94) <0.001 Frequency of hypoglycemic episodes by dementia status **No. (%)** **Dementia (n=1822)** / **Nondementia (n=14,845)** / **Age-adjusted incidence rates per 10,000 person-years (95% CI)** / **Excess attributable risk per year, % (95% CI)** Any hypoglycemia No 1572 (10.34) 13,630 (89.66) 327.60 (311.02-343.18) Yes 250 (16.95) 1215 (83.05)[b] 566.82 (496.52-637.48) 2.39 (1.72-3.01) No. of hypoglycemic episodes 0 1572 (10.34) 13,630 (89.66) 327.60 (311.02-343.18) 1 150 (14.84) 852 (85.16) 491.73 (412.60-570.80) 1.64 (0.91-2.36) 2 57 (22.26) 201 (77.74) 761.75 (561.24-962.27) 4.34 (2.36-6.32) 3 or more 43 (20.40) 162 (79.60)[b] 755.46 (526.46-984.46) 4.28 (2.10-6.44) [b]p value less than 0.001

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Study Location Funding Age/Sex	Study Design Analysis Definition of Severe # of Patients	Risk Factors for Severe Hypoglycemia OR Patient Characteristics If No Formal Risk Factor Analysis				
			Unadjusted	**Adjusted**		
			HR (95% CI)	**p value**	**HR (95% CI)**	**p value**
Zoungas, 2010[90]	RCT					
ADVANCE data	Univariate and multivariate adjusted Cox proportional regression models	Age (per year)	1.06 (1.04 - 1.08)	<0.0001	1.05 (1.03 - 1.07)	<0.0001
20 countries		Gender (female vs. male)	1.08 (0.83 - 1.40)	0.56		
		Diabetes duration (per year)	1.05 (1.03 - 1.07)	<0.0001	1.02 (1.00 - 1.04)	0.03
Government/ Industry	BGL less than 2.8 mmol/l (50 mg/dl) and the presence of typical signs and symptoms of hypoglycemia, transient dysfunction of the CNS who were unable to treat themselves (requiring help from another person)	History of Macrovascular disease (yes vs. no)	1.25 (0.96 - 1.64)	0.10	1.17 (0.89 - 1.54)	0.27
		History of Microvascular disease (yes vs. no)	2.62 (1.92 - 3.57)	<0.0001	2.14 (1.47 - 3.11)	<0.0001
		Glycated hemoglobin (per 1%)	1.08 (1.00 - 1.17)	0.05	1.04 (0.96 - 1.13)	0.35
66/men and women		Creatinine level (per µmol/L)	1.01 (1.00 - 1.01)	<0.0001	1.01 (1.00 - 1.01)	<0.0001
		Albumin to Creatinine ratio (per µg/ml)	1.001 (1.00 1.002)	<0.01	1.00 (1.00 - 1.00)	0.58
		Body Mass Index (per kg/m2)	0.95 (0.93 - 0.98)	<0.01	0.95 (0.93 - 0.98)	<0.01
		Ever smoker (yes vs. no)	1.32 (1.02 - 1.71)	0.03	1.43 (1.09 - 1.88)	0.01
		Age at completion of formal education (per year)	0.97 (0.95 - 0.99)	<0.01	0.98 (0.96 - 1.00)	0.05
		Mini Mental State Examination score (per 1/30)	0.89 (0.84 - 0.93)	<0.0001	0.93 (0.87 - 0.99)	0.01
		Sulfonylurea alone (yes vs. no)	1.09 (0.81 - 1.46)	0.58		
		Metformin alone (yes vs. no)	0.43 (0.27 - 0.69)	<0.001	0.63 (0.36 - 1.09)	0.10
		Two or more oral glucose lowering agents (yes vs. no)	1.79 (1.37 - 2.34)	<0.001	1.50 (1.10 - 2.03)	<0.01
		Any blood pressure lowering agent (yes vs. no)	0.89 (0.67 - 1.18)	0.42		
		Treatment allocation (intensive vs. standard glucose control)	1.86 (1.42 - 2.44)	<0.0001	1.88 (1.42 - 2.48)	<0.001

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Table 5. Risk Factors for Severe Hypoglycemia Reported in the Individual Studies

Study Year	Age	Gender	Diabetes Duration	A1c	Previous Hypoglycemia	Polypharmacy	Education Level	BMI	Renal Disease	Impaired Awareness	Microvascular Complications	Macrovascular complications	Dementia or psych	Time on insulin	Marital status	Smoking	Intense vs Standard contro	Metformin	Sulfonlyurea	Other agents	Insulin or insulin dose	Alcohol	Race	Other
Akram, 2006[84]	√	√	√	√					√	√	√	√		√	√	√		√			√	√		√
Alvarez Guisasola, 2008[85]				√																				
Asplund, 1991[105]			√			√			√										√					√
Bodmer, 2008[24]																								
Bruce, 2009[92]	√	√	√	√	√			√	√		√	√	√		√				√		√			√
Davis, 2010[16]	√	√	√	√	√	√	√	√	√		√			√					√		√	√		√
Davis, 2011[93]				√	√		√		√		√										√			√
Duran-Nah, 2008[104]	√		√		√	√	√		√												√			√
Fadini, 2009[95]	√	√	√	√				√	√		√	√	√								√			√
Henderson, 2003[76]	√		√	√						√				√							√			
Hepburn, 1992[99]	√		√	√				√		√				√							√			
Holman, 2009[43]				√														√	√		√			
HTN in DM IV, 1996																								√
Holstein, 2001[17]	√	√	√	√		√		√	√										√					√
Holstein, 2003[107]	√	√	√	√		√		√	√															√
Holstein, 2003[109]	√	√	√	√	√	√		√	√										√		√			√
Holstein, 2009[102]	√	√	√	√		√		√	√									√	√					
Holstein, 2011[103]	√	√	√	√		√		√	√			√	√					√	√		√			√
Leese, 2003[25]	√	√	√					√											√		√			
Miller, 2001[100]	√	√	√	√			√																√	
Miller, 2010[89]	√	√		√			√	√	√		√	√									√		√	√
Quilliam, 2011[27]	√	√			√				√		√	√						√	√	√	√			√
Sarkar, 2010[78]							√																	
Sato, 2010[106]	√		√	√		√		√	√									√	√		√			√
Shen, 2008[101]																							√	
Shorr ,1997[97]	√	√				√													√		√		√	√
Sotiropoulos, 2005[108]	√	√	√	√			√												√		√			√
Stepka, 1993[98]									√		√	√									√			
Sugarman, 1991[96]	√																		√					
Whitmer, 2009[94]	√	√	√				√		√			√	√	√				√	√		√		√	√
Zoungas, 2010[90]	√	√	√	√				√	√		√	√	√			√	√	√	√					
TOTAL (31)																								

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Table 6. Other Risk Factors in Multivariate Studies

Study, year	Other risk factors and multivariate controls
Akram, 2006[84]	*Risk Factors* Diabetes duration prior to insulin therapy (per 10 yrs) ↓, Treatment with ACE-I or ARB ↓ *Multivariate Controls* Hypertension, HTN therapy: RAS blocking, Non-RAS blocking, combination of both, Exercise, Use of tranquilizers
Bruce, 2009[92]	*Risk Factors* Inability to self manage medications ↑ *Multivariate Controls* "Clinically plausible variables"
Davis, 2010[16]	*Risk Factors* Lower FSG (less than or equal to 8.0 mmol/liter) ↑ *Multivariate Controls* English ability, Exercise in past 2 weeks, GAD antibody positive, Blood glucose self monitoring, Orthostatic hypotension, QTc interval (increase), Anticoagulant therapy, Regular ASA use, NSAID treatment, Allopurinol treatment, Fibrate therapy, Beta Blocker treatment, Hospitalized in 1998
Davis, 2011[93]	*Risk Factors* ACE-I use X, ACE DD genotype ↑ *Multivariate Controls* English ability, Exercise in past 2 weeks, GAD antibody positive, sulfonlyurea treatment, Blood glucose self monitoring, Anticoagulant therapy, Regular ASA use, NSAID treatment, Allopurinol treatment, Fibrate therapy, Beta Blocker treatment, Hospitalized in 1998 for hypoglycemia, Any hospitalization in past 12 months
Duran-Nah, 2008[104]	*Risk Factors* Attending physician (FP) ↑, Missed Meals ↑, Combined antihyperglycemic therapy ↑
Holstein, 2009[102]	*Risk Factors* KCNJ11 (E23K) gene X
Holstein, 2011[103]	*Risk Factors* Co-medication with other CYP2C9-main substrates ↑, CYP2C9-genotypes *2/*2, *2/*3, and *3/*3 X, Co-medication with other drugs being at least one CYP2C9-substrate X, Co-medication with angiotensin-converting enzyme inhibitor X, co-medication with analgesics X, Co-medication with gyrase inhibitors X, Presence of heart failure X, Previous participation at structured diabetes education X, Kind of accommodation (home vs nursing home) X *Multivariate Controls* Unspecified
Miller, 2001[100]	*Risk Factors* Follow-up fasting glucose X, Diabetes therapy increased at baseline visit X
Miller, 2010[89]	*Risk Factors* LDL level (> or equal to 2.59 mmol/l) ↓ *Multivariate Controls* Living arrangement (alone or with others), Systolic blood pressure, Use of beta blockers, Thiazolidinediones
Quilliam, 2011[27]	*Risk Factors* OADs: TZDs Continuous X, Intermittent ↑; Other OAD Continuous X, Intermittent X; Other medications: Allopurinol ↑, Benzodiazepine ↑, Beta-Blocker ↑, Blood glucose monitoring supplies ↓, Flouroquinolone ↑, NSAID ↑, Trimethoprim ↑; Charlson comorbidity (per 1 U change) ↑

Sarkar, 2010[78]	*Multivariate Controls* Non English language, Household Income, Self monitoring of blood glucose, Medication adherence
Shen, 2008[101]	*Multivariate Controls* Congestive heart failure, Depression, Hypertension, Health insurance status, Median income level
Shorr, 1997[97]	*Risk Factors* County of residence (rural vs. urban) X, Nursing home residence X, New hypoglycemia drug therapy ↑, Days since hospital discharge ↑ *Multivariate Controls* Duration of hypoglycemic drug use
Zoungas, 2010[90]	*Risk Factors* Two or more oral glucose lowering agents (yes vs. no) ↑

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Table 7. Clinical Outcomes in Patients with Severe Hypoglycemia

Study, Year	All-Cause Mortality n/N (%)	MI, nonfatal n/N (%)	Stroke, non-fatal n/N (%)	Other Neurological Events (coma, seizures) n/N (%)
RANDOMIZED TRIALS				
Abraira, 1995[30] VA CSDM Group Standard Insulin (Std) vs. Intensive Tx (Int) N=153, men only, 40-69 yrs	NR	Int: 0% Std: 0%	NR	*Loss of consciousness* Int: 0/0 (0%) Std: 2/2 (100%) or 2/78 (2.6%) overall
ACCORD, 2008[3]; Bonds, 2011[61] Standard Tx (Std) vs. Intensive Tx (Int) N=10,251, 62% male, 40-79 yrs *p<0.05	*Definite role of hypoglycemia* Int: 1/816 (0.1%) Std: 0/256 (0%) *Probable role of hypoglycemia* Int: 1/816 (0.1%) Std: 2/256 (0.8%) *Possible role of hypoglycemia* Int: 25/816 (3.1%) Std: 13/256 (5.1%)	NR	NR	NR
ADVANCE, 2008;[4] Zoungas, 2010[90] Standard Tx (Std) vs. Intensive Tx (Int) N=11,140, 58% male, 55+ yrs	Int: 0/150 (0%) Std: 1/81 (1.2%) *Median follow-up of 5 years* ≥1 episode of severe hypoglycemia: 45/231 (19.5%) No severe hypoglycemia: 986/10,090 (9.0%) Adj HR=3.27 (95%CI 2.3-4.7)	NR	NR	NR
Arechavaleta, 2011[52] Sitagliptin vs. glimepiride (with metformin) N=1035, 54% male, mean age 56 yrs	Glimipiride: 0% Sitagliptin: 0%	NR	NR	Glimepiride: 6 episodes in 3 patients required medical assistance or were accompanied by neurological symptoms Sitagliptin: 1 episode in 1 patient
Buse, 2009[110] Lispro mix 75/25 vs. Glargine N=2091, 53% male, 30-80 yrs	NR	Lispro mix 75/25: 1/22 (4.5%) Glargine: 0/12 (0%)	NR	NR
Dailey, 2004[46] Glulisine vs. Regular human insulin N=876, 53% male, 18+ yrs	Glulisine: 0% Regular Human Insulin: 0%	NR	NR	NR
Duckworth (VADT), 2009[5] Standard Tx (Std) vs. Intensive Tx (Int) N=1791 Veterans, 97% male, mean age 60.4 yrs	NR	NR	NR	*Impaired consciousness* Int 9/100 pt year Std 3/100 pt year (p<0.001) *Complete loss of consciousness* Int 3/100 pt year Std 1/100 pt year; p<0.001
Heine, 2005[42] Exanatide vs. insulin glargine N=551; 56% male, 30-75 yrs *Reported that episodes of severe hypoglycemia resolved with oral carbohydrate and none required medical assistance or resulted in withdrawal from study	Exanatide: 0% Insulin glargine: 0%*	NR	NR	NR

Study, Year	All-Cause Mortality n/N (%)	MI, nonfatal n/N (%)	Stroke, non-fatal n/N (%)	Other Neurological Events (coma, seizures) n/N (%)
Holman, 2007;[111] Holman, 2009[43] Biphasic insulin aspart vs. prandial insulin aspart vs. basal insulin detemir N=708 (578 completed 3 yr follow-up), 64% male, 18+ yrs	No deaths related to hypoglycemia at 1 year follow-up (Holman, 2007)	NR	NR	*Loss of consciousness at 3-year follow-up (Holman, 2009)* Biphasic aspart: 1/235 (0.4%) Prandial asprt: 0/239 (0%) Basal detemir: 3/234 (1.3%)
Rašlová, 2004[112] Insulin detemir + insulin aspart vs. NPH + regular human insulin (HSI) N=395, 42% male, mean age 58 yrs	Insulin detemir + aspart: 0% NPH+ HIS: 0%	NR	NR	*Coma* Insulin detemir + aspart: 0% NPH+ HIS: 1/199 (0.5%)
Riddle, 2003;[41] Dailey, 2009[132] Bedtime glargine vs. NPH N=756, 56% male, 30-70 yrs	NR	NR	NR	Glargine: 0% NPH: 0%
Russell-Jones, 2009[54] Liraglutide, liraglutide placebo, or glargine N=576, 57% male, mean age 57 years	NR	NR	NR	Coma: 0% Seizures: 0%
UKPDS 33, 1998[21] Standard Tx (Std) vs. Intensive Tx (Int) N=3867, 61% male, 25-65 yrs	Int: 1/8 (12.5%) Std: 0/33 (0%)	NR	NR	NR
Williams-Herman, 2009 Sitagliptin vs. Metformin N=1091, 48% male, mean age 54 yrs	No deaths related to hypoglycemia	None	None	NR
COHORT STUDIES				
Davis, 2010[16] N=616, mean age 67 years, 52% male; mean follow-up of 6.4 years	0% (based on 66 episodes in 52 patients)	NR	NR	NR
Fadini, 2009[95] N=126, 44% male, mean age 77 yrs Patients admitted for hypoglycemia 2001-2007; 63 on oral meds, 63 on insulin	*In-hospital:* 2/126 (1.6%) due to irreversible hypoglycemia (treatment group not reported) *Total* deaths (at median follow-up of 23.2 months; cause of death not reported) On oral agent: 31.7% On insulin: 52.4%	NR	NR	Coma On oral agent: 54% On insulin: 30.2% (NOTE: the 2 deaths were due to irreversible hypoglycemia with seizures and shock)
Gürlek, 1999[116] N=114, 45% male, mean age 59 yrs Reviewed records of patients who frequently attended outpt clinic	No deaths among patients treated in a hospital setting	NR	NR	NR
Holstein, 2001[17] All emergency room patients with severe hypoglycemia Sulfonylurea-associated hypoglycemia only (all type 2) N=45, 36% male, mean age 83.5 yrs	0/45 (0%) at time of event 16/45 (35.6%) deaths during follow-up (mean of 22.8 months after event)	NR	NR	Coma: 23/45 (51%) Disorientation: 8/45 (18%) Somnolence: 5/45 (11%) Paralysis: 4/45 (9%) Cerebral seizures: 3/45 (7%) Psychological disturbances: 2/45 (5%)

Study, Year	All-Cause Mortality n/N (%)	MI, nonfatal n/N (%)	Stroke, non-fatal n/N (%)	Other Neurological Events (coma, seizures) n/N (%)
Moen, 2009[75] N=243,222 Veterans (men and women) with at least 1 acute care hospitalization during 1 year study period and at least one glucose measurement (inpt or outpt) during study period	*Outpatient risk of death within one day of a hypoglycemic event (glucose <50 mg/dl)* OR=13.28 (9.30-19.18) for patients without chronic kidney disease (CKD) OR=6.84 (4.41-10.62) for patients with CKD (with glucose ≥ 70 mg/dl and no CKD as reference group)	NR	NR	NR
Shorr, 1997[97] N=586, 18% male, first episode of serious hypoglycemia, all age 65+, emergency room visit, hospitalization, or death	2/586 (0.3%)	3/586 (0.5%)	7/586 (1.2%)	Loss of consciousness: 49% of 598 episodes Seizures: 5% of 598 episodes Irrational behavior: 6% of 598 episodes TIA: 4/586 (0.7%)
Stepka, 1993[98] N=137, gender not reported, mean age 66 yrs Medical record data from patients hospitalized for "serious" hypoglycemia	Insulin: 7/101 (6.9%) Oral meds: 3/36 (8.3%)	NR	NR	NR
Sugarman, 1991[96] N=109 (126 admissions), 47% male, mean age 66 yrs Medical record data from hospitalizations associated with hypoglycemia in Navajo Indians with non-insulin-dependent diabetes	4/109 (3.7%) (only one death was attributed to hypoglycemia)	NR	NR	NR
OTHER STUDIES				
Asplund, 1991[105] N=19, 42% male, mean age 75 yrs, all taking glipizide Events reported to Swedish Adverse Drug Reactions Advisory Committee 1980-87	2/19 (11%) within 6 days of event Additional 1/19 (5.3%) within 23 days of event	NR	1/19 (5%) had stroke prior to hypoglycemic event with further functional impairment after event	*During event* Comatose: 11/19 (58%) Reduced conscious level: 3/19 (16%) *After event* Severe confusion: 2/19 (11%)
Ben-Ami, 1999[127] N=102, 40% male, median age 72 yrs, 90% type 2, admitted to a hospital with hypoglycemia(97%) or inpatient hypoglycemia (3%)	5/102 (5%)	Transient asymptomatic myocardial ischemia: 2/102 (2%)	NR	Seizure: 8/102 (8%) Transient right hemiplegia: 1/102 (1%)
Greco, 2010[128] admitted for severe hypoglycemia N=99, 36% male, median age 84.7 yrs (included only patients 80 or older)	0/99 (0%)	NR	NR	Coma: 19/99 (19%) Somnolence: 51/99 (51%) Reported cerebral seizures and/ or psychological disturbances in remaining patients
Hepburn, 1992[99] N=104, 50% male, mean age 63 yrs Interview with questionnaire about severe hypoglycemia in past year	NR	NR	NR	Convulsions: 3/86 (4%)

Study, Year	All-Cause Mortality n/N (%)	MI, nonfatal n/N (%)	Stroke, non-fatal n/N (%)	Other Neurological Events (coma, seizures) n/N (%)
Holstein, 2003[107] N=93 episodes, 41% male, mean age 78 yrs Physicians asked to report all episodes of severe sulfonylurea-associated hypoglycemia retrospectively or as they occurred NOTE: 6% of 400 contacted physicians responded	Glimepiride: 0/37 (0%) Glibenclaminde: 0/56 (0%)	NR	NR	*Severe brain damage* Glimepiride: 1/37 (2.7%) Glibenclaminde: (0%) *Presented with* Coma: 45% Disorientation: 18% Somnolence: 14% Cerebral seizure: 10% Local neuromuscular deficits: 8% Abnormal or inappropriate behavior: 5%
Holstein, 2003[109] Additional data from cohort described by Holstein, 2001 Insulin only (N=78) and insulin plus sulfonylurea (N=25) patients 41% male, mean age 76 yrs	0/148 (0%) in type 2 diabetic patients (1 death in non-diabetic patient with protracted spontaneous hypoglycemia)	NR	NR	NR
Sotiropoulos, 2005[108] Admitted to hospital due to severe hypoglycemia N=207, 41% male, mean age 62 yrs	0/207 (0%)	NR	2/207 (1.0%)	TIA: 2/207 (1.0%) *Presented with* Coma: 146/207 (71%) Semi-coma: 61/207 (29%) Convulsions: 3/207 (1.4%)
Stahl, 1999 N=28, 46% male, mean age 71.8 yrs Medical record data from patients admitted to emergency room for severe hypoglycemia	No hypoglycemia-related deaths (e.g., within 72 hrs of admission)	NR	NR	Coma or stupor at admission: 6/28 (21%)
Zargar, 2009[131] Patients with type 2 diabetes who were admitted to a medical center and who died with diabetes recorded on the death certificate N=693	Hypoglycemia was a cause of death in 22/693 (3.2%)	NR	NR	NR

Int = Intensive Treatment; Std = Standard Treatment; Tx = Treatment; NR = Not Reported; MI = Myocardial Infarction; TIA = Transient Ischemic Attack; CKD = Chronic Kidney Disease

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Table 8. Other Outcomes in Patients with Severe Hypoglycemia

Study, Year	Hospitalizations n/N (%)	Emergency Department Visits n/N (%)	Accidents/ Trauma n/N (%)	Quality of Life	Other Outcomes	Type of Analysis 1=unadjusted; 2=minimal adjustment; 3=multivariate
RANDOMIZED TRIALS						
Abraira, 1995[30] VA-CSDM Group Std Insulin vs. Intensive Tx N=153, men only; 40-69 yrs	Intervention: 0% Control: 0%	NR	NR	NR	NR	NA
ADVANCE, 2008[4] Standard Tx (Std) vs. Intensive Tx (Int) N=11,140, 58% male, 55+ yrs	NR	NR	NR	NR	*Permanent disability* Int: 1/150 (0.7%) Std: 1/81 (1.2%)	NA
Arechavaleta, 2011[52] Sitagliptin vs. glimepiride N=1035, 54% male, mean age 56 yrs	NR	NR	NR	NR	Glimepiride: 6 episodes in 3 patients required medical assistance (location not specified) or were accompanied by neurological symptoms Sitagliptin: 1 episode in 1 patient	NA
Heine, 2005[42] Exanatide vs. insulin glargine N=551; 56% male, 30-75 yrs *Reported that episodes resolved with oral carbohydrate and none required medical assistance or resulted in withdrawal	Exanatide: 0% Insulin Glargine: 0%	Exanatide: 0% Insulin Glargine: 0%	NR	NR	NR	NA
Raslová, 2004[112] Insulin detemir + insulin aspart vs. NPH + regular human insulin (HSI) N=395, 42% male, mean age 58 yrs	Insulin detemir + aspart: 1/195 (0.5%) NPH + HSI: 2/199 (1.0%)	NR	NR	NR	NR	NA
Riddle, 2003;[41] Dailey, 2009[46] Bedtime glargine vs. NPH N=756, 56% male, 30-70 yrs	Glargine: 0% NPH: 0%	Glargine: 0% NPH: 2/13 events in 9 patients (15.4%)	NR	NR	*Withdrawal from study due to severe hypoglycemia* Glargine: 1/9 (12%) NPH: 3/9 (33%)	NA

Study, Year	Hospitalizations n/N (%)	Emergency Department Visits n/N (%)	Accidents/ Trauma n/N (%)	Quality of Life	Other Outcomes	Type of Analysis 1=unadjusted; 2=minimal adjustment; 3=multivariate
Russell-Jones, 2009[54] Liraglutide, liraglutide placebo, or glargine N=576, 57% male, mean age 57 years	NR	NR	NR	NR	*Medical Assistance* Liraglutide: 1/5 (20%) (no serious events in placebo or glargine groups)	NA
Williams-Herman, 2009[113] Sitagliptin vs. Metformin N=1091, 48% male, mean age 54 yrs	None	None	None	None	None	NA
COHORT STUDIES						
Bruce, 2009[92] N=205 with non-demented at initial assessment and who completed second assessment (83% of non-demented patients who were alive at 18 months) All ≥ 70 years	NR	NR	NR	NR	*Cognitive decline:* 33/205 (16%) (no difference in prior hypoglycemia episode between those with decline and those without) *Severe hypoglycemia:* more likely in patients with cognitive impairment (11.6%) or dementia (20.8%) than normal (3.0%) (p<0.01)	NA
Cobden, 2007[133] Patients converting from insulin syringe to biphasic pen device N=486 (subset of Lee, 2006)	Pre-pen: 8/44 hypoglycemic events (18%) Post-pen: 21/64 events (33%)	Pre-pen: 10/44 events (23%) Post-pen: 13/64 events (20%)	NR	NR	*Physician visits* Pre-pen: 15/44 events (34%) Post-pen: 21/64 events (33%) *Outpatient visits* Pre-pen: 4/44 events (9%) Post-pen: 6/64 events (9%)	NR
Fadini, 2009[95] N=126, 44% male, mean age 77 yrs Patients admitted for hypoglycemia 2001-2007; 63 on oral meds, 63 on insulin	All patients were hospitalized (study design)	Not applicable	*Falls* Oral meds: 25.4% Insulin: 17.5%	NR	*Acute coronary syndrome* Oral meds: 17.5% Insulin: 19.0% *Duration of hospital stay* Oral meds: 9.8 days Insulin: 8.0 days	NA
Goh, 2009[115] N=203 (192 or 95% Type 2), 37% male Patients admitted to observational ward in emergency department for hypoglycemia	22/203 (16%) transferred to inpatient team for longer period of treatment	All patients were seen in emergency department (study design)	NR	NR	151 patients were contacted at 7 and 28 days after discharge; 6/151 had recurrent hypoglycemia (2 were admitted)	NA

Study, Year	Hospitalizations n/N (%)	Emergency Department Visits n/N (%)	Accidents/ Trauma n/N (%)	Quality of Life	Other Outcomes	Type of Analysis 1=unadjusted; 2=minimal adjustment; 3=multivariate
Gürlek, 1999[116] N=114, 45% male, mean age 59 yrs Reviewed records of patients who frequently attended outpt clinic	0.05 episode/ patient/year	NR	NR	NR	NR	NA
Holstein, 2001[17] All emergency room patients with severe sulfonylurea-associated hypoglycemia (type 2) N=45, 36% male, mean age 83.5 yrs	All patients were hospitalized (study design)	14/45 (31%) initial treatment in emergency department	Soft tissue injuries or fractures: 6/45 (13%)	NR	NR	NA
Lee, 2006[114] Patients converting from insulin syringe to aspart pen (n=670) or biphasic pen (n=486) (see Cobden 2007 for subset data)	Pre-pen: 13/77 hypoglycemic events (17%) Post-pen: 41/139 events (30%) OR=0.88 (0.47-1.66)	Pre-pen: 12/77 events (16%) Post-pen: 19/139 events (14%) OR=0.44 (0.21-0.92)	NR	NR	*Physician visits* Pre-pen: 29/77 events (38%) Post-pen: 39/139 events (30%) OR=0.39 (0.24-0.64) *Outpatient visits* Pre-pen: 6/77 events (8%) Post-pen: 17/139 events (12%) OR=0.79 (0.31-2.01)	**1**
Leese. 2003[25] N=160 (57% type 2) with 244 hypoglycemic episodes, 54% male, mean age 52 years	52/244 episodes (21%)	19/244 episodes (8%) emergency or primary care visit 134/244 episodes (55%) ambulance + emergency or primary care visit	NR	NR	89/244 episodes (36%) ambulance service only	
Murata, 2005[19] Insulin-treated type 2 diabetes N=344 veterans, 96% male	2/55 severe episodes in 19 patients	NR	NR	NR	NR	NA
Nichols, 2010[26] Patients starting insulin N=2417, 49% male, mean age 60 yrs	No hospitalizations in 9970 patient-years of observation	NR	NR	NR	1.9% required medical contact for hypoglycemia in 1st year of insulin use; 0.4% by 5th year	NA

Study, Year	Hospitalizations n/N (%)	Emergency Department Visits n/N (%)	Accidents/ Trauma n/N (%)	Quality of Life	Other Outcomes	Type of Analysis 1=unadjusted; 2=minimal adjustment; 3=multivariate
Panikar, 2003[117] Adding triple drug combination to insulin N=124, mean age 57 yrs, 47% male	2/28 (7.1%)	NR	NR	NR	NR	NA
Rhoads, 2005[118] N=2664, 69% male, mean age 45 yrs; insulin-treated type 1 and type 2	*Admissions per year* Hypoglycemia coding: 0.97 No hypoglycemia coding: 0.48 (p<0.01)	Visits per year Hypoglycemia coding: 0.85 No hypoglycemia coding: 0.40 (p<0.01)	NR	NR	*Short Term Disability Use* Hypoglycemia coding: 47% for mean of 19.5 days per P-Y No hypoglycemia coding: 32% for mean of 11.0 days per P-Y (both p<0.01)	NA
Shorr, 1997[97] N=586, first episode of serious hypoglycemia, all age 65+, emergency room visit, hospitalization, or death	Patients identified in hospital or emergency department	Patients identified in hospital or emergency department	Injury 10/586 (1.7%)	NR	NR	NA
Stepka, 1993[98] N=137, gender not reported, mean age 66 yrs Medical record data from patients hospitalized for "serious" hypoglycemia	NR	NR	*Bone injuries* Insulin: 10/101 (9.9%) Oral med: 0/36 (0%)	NR	NR	
Sugarman, 1991[96] N=109 (126 admissions), 47% male, mean age 66 yrs Medical record data from hospitalizations associated with hypoglycemia in Navajo Indians with non-insulin-dependent diabetes	4.7 per 1000 person-years	NR	NR	NR	NR	NA

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Study, Year	Hospitalizations n/N (%)	Emergency Department Visits n/N (%)	Accidents/ Trauma n/N (%)	Quality of Life	Other Outcomes	Type of Analysis 1=unadjusted; 2=minimal adjustment; 3=multivariate
Whitmer, 2009[94] N=16,667; 55% male, no prior diagnosis of dementia, mild cognitive impairment, or general symptom memory loss; mean follow-up of 3.8 years	NR	NR	NR	NR	*In patients who developed dementia:* History of at least one episode of severe hypoglycemia in prior 22 years: 17.0% No history of severe hypoglycemia: 10.3%	3 Positive graded association between severe hypoglycemia and risk of dementia; 2.39% increase in absolute risk of dementia per year in patients with h/o hypoglycemia compared to those without; adjusted Hazard Ratio for dementia : 1.44 (95% CI 1.25-1.66) for ≥ 1 episode vs. none
CROSS-SECTIONAL STUDIES						
Alvarez-Guisasola, 2010[119] Patients who added sulfonylurea or thiazolidinedione to metformin in past 5 years; age ≥ 30 yrs, 55% male	NR	NR	NR	*EQ-5D VAS by severity of hypoglycemic symptoms* None: 73.5 Mild: 71.0 Moderate: 65.8 Severe: 54.3 (p<0.0001) *Adjusted model* Severe symptoms associated with EQ-5D VAS (p<0.0001)	NR	3 age, gender, activity, weight, HbA1c, microvascular or cardiovascular history
Davis, 2005[120] N= 861; 58% male, 57% >65 yrs NOTE: response rate 30%	NR	NR	NR	*SF-36:* scores lower for patients with self-reported severe (vs. mild/moderate) hypoglycemia for all domains except vitality *EQ-5D:* lower scores for patients with severe (vs. mild/moderate)	*Productivity:* more days lost for severe (8.6) than mild/moderate (2.7); severity was predictor of productivity (p<0.05) *Resource use:* more contacts with health service for severe (13.2) than mild/moderate (11.5)	Adjusted for age, gender, diabetes complications, BMI, and type of diabetes

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Study, Year	Hospitalizations n/N (%)	Emergency Department Visits n/N (%)	Accidents/ Trauma n/N (%)	Quality of Life	Other Outcomes	Type of Analysis 1=unadjusted; 2=minimal adjustment; 3=multivariate
Harsch, 2002[121] Surveys distributed at random in clinics, hospitals, education or self-help mtgs NOTE: data reported for oral anti-diabetic group (OA, 95% type 2, n=122, mean age 64 yrs) and conventional insulin group (CT, 72% type 2, n=151, mean age 59 yrs)	NR	NR	*Accidents per year driven on latest therapeutic regimen* OA group: $2.05X10^{-3}$ CT group: $7.17X10^{-3}$ All type 2: $3.09X10^{-3}$ *Hypoglycemia-induced accidents per year driven* OA: 2/122 (1.6%) CT: 3/151 (2.0%) *Symptomatic hypoglycemias per year driven (all Type 2):* 0.04	NR	*Breaks in driving caused by hypoglycemia* OA group: 0.1 CT group: 0.2	NA
Hermanns, 2005[122] N=388 (63% Type 2), 62% male, 35% age 18-48 yrs, 30% age 62+ yrs	NR	NR	*NR*	Severe hypoglycemia in past 12 months associated with increased risk for clinical (OR=4.4 [1.3-14.4]) and subclinical (OR=2.7 [1.1-6.9]) affective disorder but not anxiety disorder	*NR*	NA
Labad, 2010[123] Edinburgh Type 2 Diabetes Study N=1066, 51% male, mean age 68 yrs	NR	NR	NR	NR	Lifetime history of severe hypoglycemia (at least 1 episode) associated with symptoms of anxiety (ß=0.293, p<0.001) but not depression	Adjusted for gender, depression score, marital status, treatment for depression, diabetes treatment

Study, Year	Hospitalizations n/N (%)	Emergency Department Visits n/N (%)	Accidents/ Trauma n/N (%)	Quality of Life	Other Outcomes	Type of Analysis 1=unadjusted; 2=minimal adjustment; 3=multivariate
Leiter, 2005[124] N=133 with Type 2 DM, mean age 60 yrs 19 had severe episode in past 12 months; 34 reported episode in lifetime	See Emergency Department Visits	5.5% emergency or hospital visit	NR	*Lifestyle changes sometimes or always made after severe hypoglycemic episode (of n=19 reporting severe hypoglycemia in past 12 months)* Modified insulin dose: 58% Tested blood glucose more often: 84% Greater fear of future episode: 84% Additional concerns about driving: 16% Asked someone to check on them: 58% Went home from work, school, other activity: 32% Stayed home next day: 26%	*Additional physician visits:* 2.5% *Additional consultations:* 0.4% (unclear if denominator is 19 or 34 patients)	NA
Marrett, 2009;[81] Marrett, 2011[87] (additional analysis taking frequency into account) N=1984 (201 with severe or very severe hypoglycemic symptoms), 57% male, mean age 58 Data from 2007 National Health and Wellness Survey (NHWS)	NR	NR	NR	*EQ-5D by severity (p<0.0001)* Mild: 0.83 Moderate: 0.77 Severe/very severe: 0.67 *HFS II worry by severity (p<0.0001)* Mild: 12.3 Moderate: 20.1 Severe/very severe: 27.5 *Adjusted models*: Severe/very severe positively associated with HFS II worry and negatively associated with EQ-5D (both p<0.001) *EQ-5D decreased and HFS II worry increased as frequency of episodes increased*	NR	3 age, gender, BMI, education, duration of diabetes, HbA1c, diabetes complications

Study, Year	Hospitalizations n/N (%)	Emergency Department Visits n/N (%)	Accidents/ Trauma n/N (%)	Quality of Life	Other Outcomes	Type of Analysis 1=unadjusted; 2=minimal adjustment; 3=multivariate
Pettersson, 2011[82] Patients taking metformin and sulfonylurea for past 6 months (no insulin) N=430, 61% male, mean age 69 yrs	NR	NR	NR	*EQ-5D VAS score by severity* None: 0.76 Mild: 0.73 Moderate: 0.71 Severe: 0.68 Very severe: 0.66 (p=0.01 none/mild vs. moderate or worse) *EQ-5D dimensions with significant differences (none/ mild vs. moderate or worse)* Pain/discomfort: p=0.01 Anxiety/depression: 0=0.02 *HFS-II worry score by severity* None: 4 Mild: 7 Moderate: 8 Severe: 19 Very severe: 26 (p=0.06 none/mild vs. moderate or worse)		
Sarkar, 2010[78] N=14,357, 51% male, mean age 58 yrs	129/1579 (8%) hospital or ER OR=19.0 (13.0-26.0) compared to 1.6% of participants without significant hypoglycemia	see hospitalization	NR	NR	NR	

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Study, Year	Hospitalizations n/N (%)	Emergency Department Visits n/N (%)	Accidents/ Trauma n/N (%)	Quality of Life	Other Outcomes	Type of Analysis 1=unadjusted; 2=minimal adjustment; 3=multivariate
Vexiau, 2008[126] Patients taking sulfonylurea and metformin for at least 6 months N=400, 54% male, mean age 62 yrs	NR	NR	NR	*EQ-5D summary score by symptom severity (p=0.04)* None: 0.80 Mild: 0.73 Moderate: 0.70 Severe/very severe: 0.54 *Worry score by symptom severity (p=0.02)* None: 10.2 Mild: 16.5 Moderate: 22.2 Severe/very severe: 25.3 *Severe hypoglycemia significantly associated with HFS-II worry and EQ-5D summary scores (p<0.0001)*	NR	3 Adjusted for age, gender, marital status, education, activity, duration of DM, history of microvascular events, major medical events, adequate glycemic control
OTHER STUDIES						
Asplund, 1991[105] N=19, 42% male, mean age 75 yrs, all taking glipizide Events reported to Swedish Adverse Drug Reactions Advisory Committee 1980-87	NR	NR	NR	NR	*Prolonged hypoglycemia (23-60 hours):* 5/19 (26%)	
Ben-Ami, 1999[127] N=102, 40% male, median age 72 yrs, 90% type 2, admitted to a hospital with hypoglycemia (97%) or inpatient hypoglycemia (3%)	All patients were hospitalized (study design)	Not applicable	7/102 (7%)	NR	Protracted hypoglycemia (12-72 hours): 40/102 (39%)	
Greco, 2010[128] admitted for severe hypoglycemia N=99, 36% male, median age 84.7 yrs	Median hospitalization 5.5 days (cohort defined by hospitalization)	NR	NR	NR	Protracted hypoglycemia (12-72 hrs): 61/99 (61%)	

Study, Year	Hospitalizations n/N (%)	Emergency Department Visits n/N (%)	Accidents/ Trauma n/N (%)	Quality of Life	Other Outcomes	Type of Analysis 1=unadjusted; 2=minimal adjustment; 3=multivariate
Hemmelgarn, 2006[135] All drivers 67 to 84 years old NOTE: mix of type 1 and type 2 *RR=Rate Ratio; reference is no anti-diabetic therapy in preceding year ^Sulfonylurea + Metformin; no increased risk with oral monotherapy	NR	NR	*Injurious motor vehicle crash* Any insulin: RR*=1.3 (95% CI 1.0-1.8) Insulin only: RR=1.4 (95% CI 1.0-2.0) Combined oral^: RR=1.3 (95% CI 1.0-1.7) with dose response	NR	NR	Adjusted for age, gender, previous motor vehicle crashes, place of residence
Hepburn, 1992[99] N=104, 50% male, mean age 63 yrs Interview with questionnaire about severe hypoglycemia in past year	NR	NR	*Injury (not defined):* 4/86 (5%)	NR	NR	
Holstein, 2003[107] N=93 episodes, 41% male, mean age 78 yrs Physicians asked to report all episodes of severe sulfonylurea-associated hypoglycemia retrospectively or as they occurred	NR	NR	NR	NR	*Prolonged severe hypoglycemia (>12 hr)* Glimepiride: 8/37 (22%) Glibenclamide: 5/56 (9%)	
Lundkvist, 2005[125] N=309, 60% male, mean age 65 yrs	0/7 (0%)	3 visits among 6 pts requiring healthcare for hypoglycemia in past month	NR	NR	8 nurse visits, 3 physician visits, 1 telephone contact with medical care among 6 patients requiring healthcare for hypoglycemia in past month	

Study, Year	Hospitalizations n/N (%)	Emergency Department Visits n/N (%)	Accidents/ Trauma n/N (%)	Quality of Life	Other Outcomes	Type of Analysis 1=unadjusted; 2=minimal adjustment; 3=multivariate
Redelmeier, 2009[129] N=795, 84% male, mean age 52 yrs; reported to vehicle licensing authorities for review	NR	NR	*Severe hypoglycemia in past 2 years* 34/57 (60%) who had crash 200/738 (27%) without crash OR=4.07 (2.35-7.04)	NR	NR	1
Stahl, 1999[28] N=28, mean age 71.8 yrs Medical record data from patients admitted to emergency room for severe hypoglycemia	All patients were hospitalized (study design)	NR	NR	NR	*Prolonged hypoglycemia:* 1/28 (3.6%)	1
Stork, 2007[130] Driver's license for ≥ 2 yrs; at least 8000 km driven in past year N=20 type 2, 80% male, mean age 52 yrs Induced hypoglycemia (2.7 mmol/l)	NR	NR	NR	NR	*11/20 (55%) felt hypoglycemic:* 5/11 (45%) would measure glucose 6/11 (55%) would not drive *9/20 (45%) "maybe" felt hypoglycemic:* 3/9 (33%) would drive 2/9 (22%) "maybe" drive 2/9 (22%) would measure glucose 2/9 (22%) would not drive	

NR = Not reported; N/A = Not Applicable

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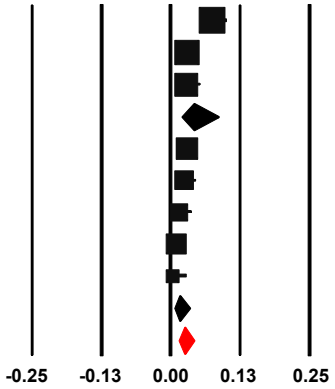
APPENDIX F. FOREST PLOTS FOR KEY QUESTION #1

Appendix F, Figure 1.

Severe hypoglycemia event rates for insulin glargine studies*

Group By Duration	Study Name	Event Rate	Lower Limit	Upper Limit	Total
long-term	Rosenstock 2009	0.074	0.054	0.100	38 / 513
long-term	Buse 2011	0.029	0.016	0.050	12 / 419
long-term	Rosenstock 2008	0.027	0.014	0.054	8 / 291
long-term		0.041	0.019	0.084	58 / 1223
short-term	Kennedy 2006	0.030	0.026	0.034	228 / 7607
short-term	Riddle 2003	0.025	0.013	0.046	9 / 367
short-term	Heine 2005	0.015	0.006	0.039	4 / 267
short-term	Davies 2005	0.010	0.008	0.013	45 / 4588
short-term	Rosenstock 2001	0.004	0.001	0.027	1 / 259
short-term		0.016	0.008	0.032	288 / 13088
Overall		0.025	0.015	0.041	346 / 14311

Event rate and 95% CI



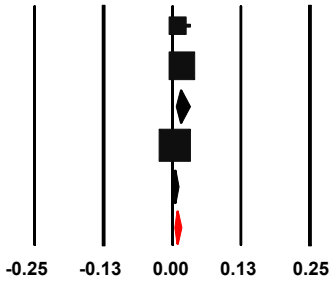
*Alone or added to OHAs

Appendix F, Figure 2.

Severe hypoglycemia event rates for insulin detemir studies

Group By Duration	Study Name	Event Rate	Lower Limit	Upper Limit	Total
long-term	Holman 4T 2009	0.009	0.002	0.034	2 / 234
long-term	Rosenstock 2008	0.017	0.007	0.041	5 / 291
long-term		0.014	0.007	0.029	7 / 525
moderate-term	Marre 2009	0.004	0.001	0.009	4 / 1129
moderate-term		0.004	0.001	0.009	4 / 1129
Overall		0.009	0.005	0.015	11 / 1154

Event rate and 95% CI

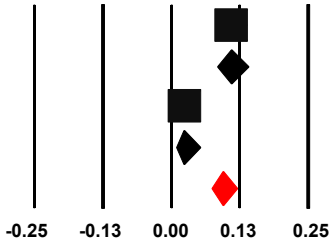


Appendix F, Figure 3.

Severe hypoglycemia event rates for NPH insulin studies

Group By Duration	Study Name	Event Rate	Lower Limit	Upper Limit	Total
long-term	Rosenstock 2009	0.109	0.085	0.139	55 / 504
long-term		0.109	0.085	0.139	55 / 504
short-term	Rosenstock 2001	0.023	0.010	0.051	6 / 259
short-term		0.023	0.010	0.051	6 / 259
Overall		0.093	0.073	0.118	61 / 763

Event rate and 95% CI

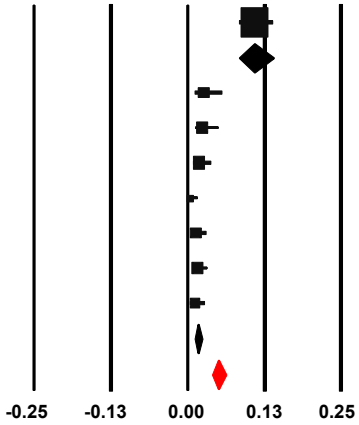


Appendix F, Figure 4.

Severe hypoglycemia event rates for NPH insulin studies*

Group By Duration	Study Name	Event Rate	Lower Limit	Upper Limit	Total
long-term	Rosenstock 2009	0.109	0.085	0.139	55 / 504
long-term		0.109	0.085	0.139	55 / 504
short-term	Frische 2003	0.026	0.012	0.056	6 / 232
short-term	Rosenstock 2001	0.023	0.010	0.051	6 / 259
short-term	Riddle 2003	0.018	0.009	0.037	7 / 389
short-term	Rayman (glulisine) 2007	0.004	0.001	0.018	2 / 448
short-term	Dailey (glulisine) 2004	0.014	0.006	0.030	6 / 435
short-term	Rayman (RHI) 2007	0.016	0.008	0.033	7 / 442
short-term	Dailey (RHI) 2004	0.011	0.005	0.027	5 / 441
short-term		0.016	0.012	0.022	39 / 2646
Overall		0.050	0.041	0.061	94 / 3150

Event rate and 95% CI



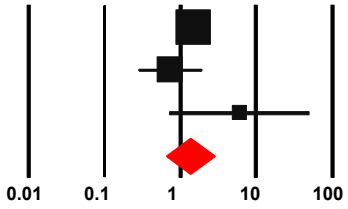
*NPH insulin as either primary therapy or in combination (Frische, sulfonylurea; Riddle oral OHAs; Rayman and Dailey, glulisine or regular insulin)

Appendix F, Figure 5.

Severe hypoglycemia events, NPH insulin versus insulin glargine studies*

Study Name	Risk Ratio	Lower limit	Upper limit	Events / Total: NPH insulin	Events / Total: Insuline glargine
Rosenstock 2009	1.473	0.993	2.186	55 / 504	38 / 513
Riddle 2003	0.734	0.276	1.950	7 / 389	9 / 367
Rosenstock 2001	6.000	0.727	49.489	6 / 259	1 / 259
	1.367	0.666	2.806	68 / 1152	48 / 1139

Risk ratio and 95% CI

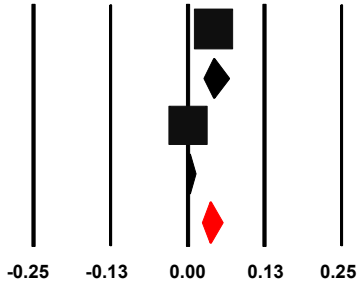


Appendix F, Figure 6.

Severe hypoglycemia event rates for insulin lispro studies

Group By Duration	Study Name	Event Rate	Lower Limit	Upper Limit	Total
long-term	Buse 2011	0.042	0.027	0.064	20 / 476
long-term		0.042	0.027	0.064	20 / 476
short-term	Anderson 1997	0.001	0.000	0.010	1 / 722
short-term		0.001	0.000	0.010	1 / 722
Overall		0.036	0.023	0.054	21 / 1198

Event rate and 95% CI



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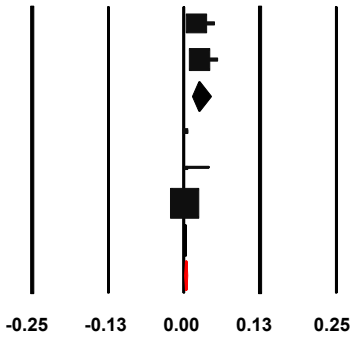
Appendix F, Figure 7.

Severe hypoglycemia event rates for insulin aspart studies

Group By Duration	Study Name	Event Rate	Lower Limit	Upper Limit	Total
long-term	Holman 4T 2009 (Prandial)	0.021	0.009	0.049	5 / 239
long-term	Holman 4T 2009 (Biphasic)	0.026	0.012	0.056	6 / 235
long-term		0.023	0.013	0.042	11 / 474
short-term	Bentrop 2011 (Biphasic)	0.002	0.000	0.007	2 / 1154
short-term	Liebl 2009 (Biphasic)	0.003	0.000	0.043	0 / 178
short-term	Valensi IMPROVE 2009 (Biphasic)	0.001	0.001	0.002	69 / 52419
short-term		0.001	0.002	0.002	71 / 53751
Overall		0.002	0.002	0.002	82 / 54225

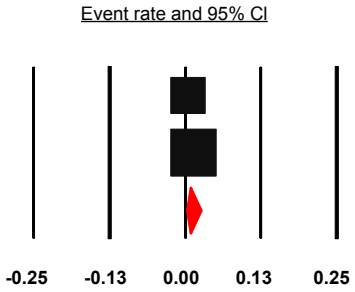


*Subjects may also have received OHAs in addition to insulin aspart.

Appendix F, Figure 8.

Severe hypoglycemia event rates for insulin glulisine (+NPH insulin) short-term (26 wks) studies

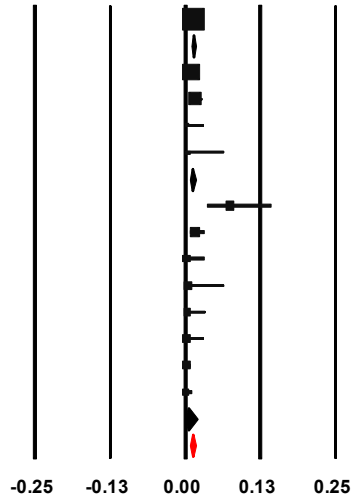
Study Name	Event Rate	Lower limit	Upper limit	Total
Rayman 2006	0.004	0.001	0.018	2 / 448
Daily 2004	0.014	0.006	0.030	6 / 435
	0.009	0.003	0.026	8 / 883



Appendix F, Figure 9.

Severe hypoglycemia rates for sulfonylurea studies*

Group By Duration	Study Name	Event Rate	Lower Limit	Upper Limit	Total
long-term	Holstein 2001	0.013	0.009	0.017	44 / 3489
long-term		0.013	0.009	0.017	44 / 3489
moderate-term	Matthews 2011	0.010	0.006	0.016	15 / 1546
moderate-term	Seck 2010	0.015	0.008	0.029	9 / 584
moderate-term	Garber 2011	0.002	0.000	0.031	0 / 248
moderate-term	Marre 2009	0.004	0.000	0.066	0 / 114
moderate-term		0.011	0.007	0.017	24 / 2492
short-term	UK Hypoglycemia Group	0.074	0.037	0.141	8 / 108
short-term	Arechavaleta 2011	0.015	0.008	0.031	8 / 519
short-term	Nauck 2009	0.002	0.000	0.032	0 / 242
short-term	Russell-Jones 2009	0.004	0.000	0.066	0 / 114
short-term	Chou 2008	0.002	0.000	0.034	0 / 225
short-term	Kendall 2005	0.002	0.000	0.031	0 / 247
short-term	Drouin 2004	0.001	0.000	0.009	1 / 800
short-term	Schernthaner 2004	0.001	0.000	0.009	0 / 845
short-term		0.005	0.001	0.019	17 / 3100
Overall		0.012	0.009	0.015	85 / 9081



*Sulfonylurea monotherapy and combined sulfonylurea and metformin studies

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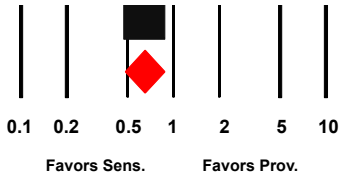
Appendix F, Figure 10.

Severe hypoglycemia events for BARI 2D study, insulin sensitization versus insulin provision

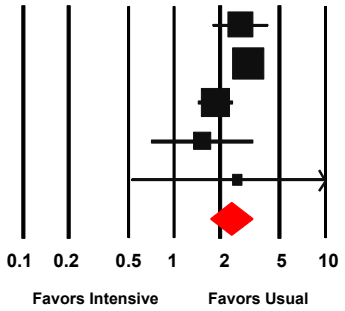
Study name	Risk ratio	Lower limit	Upper limit	Events/Total Sensitization	Events/Total Provision
BARI 2D 2009	0.642	0.479	0.861	68 / 1153	106 / 1154
	0.642	0.479	0.861	68 / 1153	106 / 1154



Appendix F, Figure 11.

Severe hypoglycemia events for intensive glycemic control versus usual care studies

Study name	Risk ratio	Lower limit	Upper limit	Events/Total Intensive control	Events/Total Usual care
VADT 2009	2.736	1.792	4.177	76 / 892	28 / 899
ACCORD 2008	3.096	2.717	3.527	849 / 5128	274 / 5123
ADVANCE 2008	1.884	1.442	2.463	150 / 5571	81 / 5669
UKPDS-33 1998	1.529	0.708	3.299	33 / 3071	8 / 1138
VA-CSDM 1995	2.600	0.520	12.993	5 / 75	2 / 78
	2.396	1.757	3.268	1113 / 14737	393 / 12907



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