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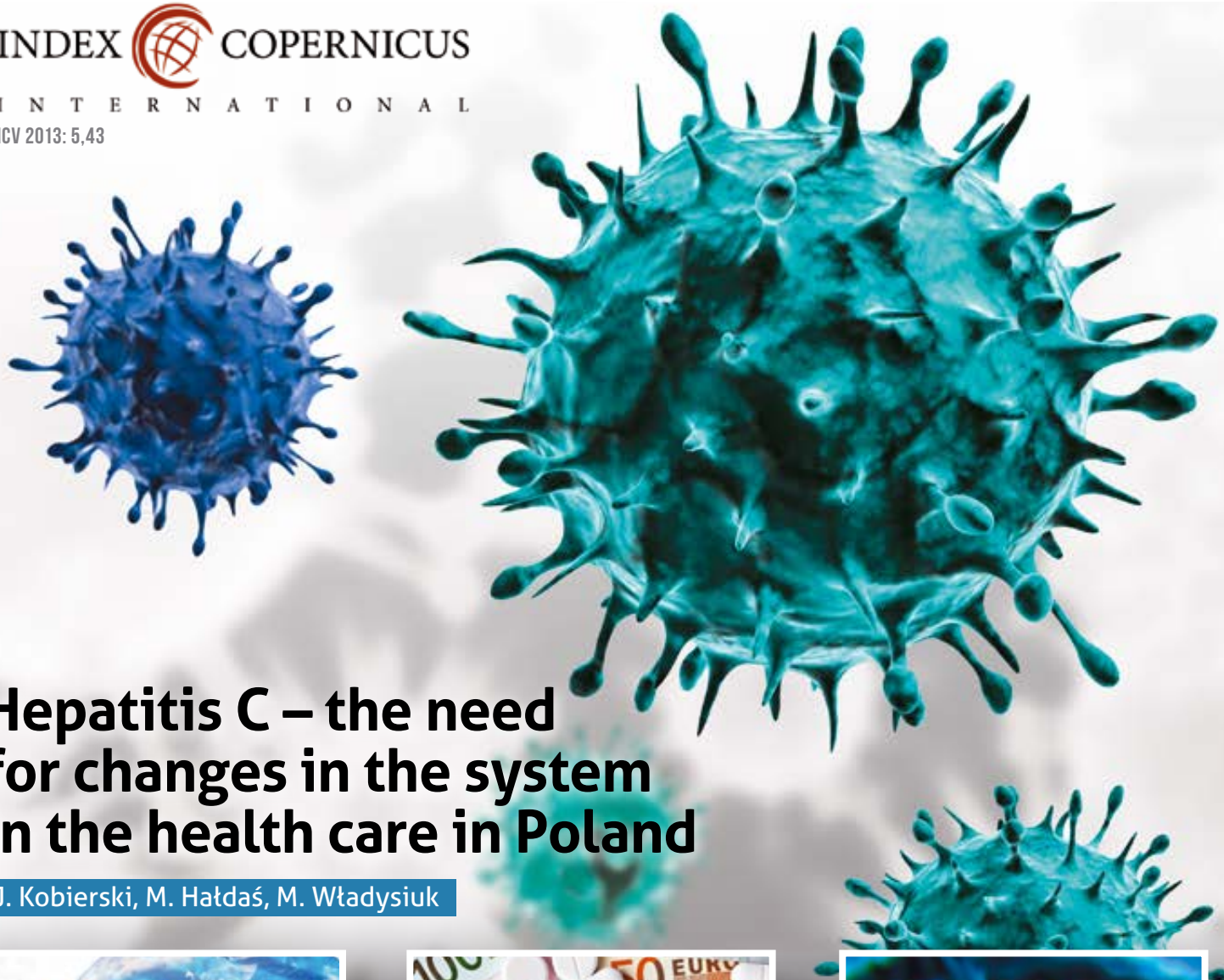

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Risk of severe hypoglycaemia for various treatment regimens – a systematic review and meta-analysis of observational studies

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ABSTRACT

Background: **Previous publications show that diabetes mellitus (DM) is a grave medical and economic problem, largely due to complications. The objective is to evaluate real-life risk of severe hypoglycaemic events (SHEs) among diabetic patients (type 1 and 2, T1&2) for various therapies.**

Methods: **We conducted a systematic review of observational studies in MEDLINE, Embase, and The Cochrane Library databases. Observational, retrospective or prospective, studies (with at least 100 participants) in children and adults were included, with focus on: time horizon, number of patients, number of SHEs, and number of patients experiencing SHEs.**

In T1 DM we distinguished basal-bolus/pre-mix insulin and insulin pump, and in T2 DM we singled out basal-bolus/pre-mix insulin, basal supported oral therapy with insulin as the basal component, sulfonylurea, and other antidiabetic medications.

We used a Poisson model implemented in Bayesian framework in WinBugs to estimate the SHE.

Results: **We identified 55 relevant studies encompassing 245,028 patients (103,741.81 patient-years). Annual SHE rates varied in T1DM from 0.18 (95%CI: 0.13–0.25) for insulin pump up to 1.1 (0.57–2.71) for basal-bolus with human basal insulin, and in T2DM from 0.006 (0.001–0.008) for oral antidiabetic drugs (excl. SU) up to 0.56 (0.16–9.65) for basal-bolus with human insulin as the basal component.**

Conclusions: **Our results confirm that available treatment regimens differ in SHEs risk in real-life setting. Still SHEs are also driven by other factors, e.g. lifestyle, which may impact treatment selection.**

BACKGROUND

Not only is diabetes mellitus (DM) an expensive medical condition, but it is also a multidimensional one, leading to wide range of complications that themselves may be clinically important or associated with high resource consumption. One of these is hypoglycaemia, that is often related to antidiabetic drugs and might affect patients compliance, quality of life and treatment outcomes. Most of hypoglycaemic events are not documented, however severe hypoglycaemic events (SHEs) require assistance of another person, and can be even fatal, although rarely. Antidiabetic drugs are associated with various rates of hypoglycaemia, and the burden of hypoglycaemia is determined mainly by drug use patterns and patients' adherence, but also diet and exercise. A review of the importance of hypoglycaemia from the perspective of the clinical process (clinical inertia, patient's adherence) and the list of possible causes and risk factors can be found e.g. in Ahrén[1].

IN POLAND, AMONG THE MOST FREQUENTLY PRESCRIBED DRUGS ARE THE ONES FOR THE TREATMENT OF CARDIOVASCULAR RELATED DISEASES, INCLUDING ANTIHYPERTENSIVE DRUGS.

Hypoglycaemia is now being frequently used in cost-effectiveness modelling in DM[e.g. 2,3] and often constitutes an important part either strongly influencing the resulting incremental cost-effectiveness ratios[e.g. 4,5] or being an outcome measure [e.g. 6]. Hypoglycaemia has also been subject to cost-of-illness studies, e.g. Jönsson et al.[7] for T2 DM in Sweden. The body of evidence in such studies is limited as–to the best of our knowledge–no systematic review and meta-analysis of severe hypoglycaemia risk has been performed. E.g. in their study Jönsson et al. assumed the rates of SHE based on five studies only[8-12]. The above observations motivate our research to try to estimate real-life risk of SHE based on best available evidence. The aim of the present study is to collect real-life data on absolute number of hypoglycaemic events in order to evaluate risk of SHE among patients with DM using various treatment regimens. These estimates can then be used e.g. in cost studies or to populate economic models on DM and its complications.

In order to make the estimates as close to real-life settings as possible, we decided to use observational studies only and not randomized controlled trials (RCTs). Importantly our goal was to assess the absolute risk of SHE in an observational, rather than interventional, context, i.e. we want to assess what the risk of hypoglycaemia is when we observe a patient to use a given therapy, and not when we prescribe a given therapy to patient. In real-life clinical practice many factors influence the treatment selection in DM, baseline risk of SHE being probably one of them. That is why a problem of confounding would appear when trying to interpret our results (obtained from observational studies) in interventional manner. Thus, for our purpose observational studies are more relevant than RCTs. It is also important to stress that our results ought not to be used to compare treatments between each other to see what the results of replacing one treatment by another would be. Therefore we did not present relative rates.

As there are numerous drugs that can be used in DM, some grouping is necessary, as otherwise the body of evidence for each individual treatment would be too small to make credible inferences, and random errors would drive the results. That is why we decided to group all possible treatment regimens in a dozen of categories (4 in T1, 8 in T2) based on clinical guidelines and consultation with clinical experts.

The paper is structured as follows. In the next section we present the methodology of our systematic review. We present the search strategy and criteria used, as well as assumptions made in meta-analysis of the data. We then present results in section 3. These encompass the results of our systematic review of observational studies and of a review of secondary studies that was used to fill in the gap when primary studies were unavailable for some regimens. We also present the resulting estimates of SHE rates for analysed regimens. We discuss the findings and limitations in section 4 and briefly conclude in the last section.

METHODS

We analysed SHEs in type 1 and type 2 (T1&T2) DM patients. We used SHE definition proposed by Jönsson et al.[7] i.e. an event of low plasma glucose level when a patient requires help from another person to manage, as this definition directly relates to resource usage.

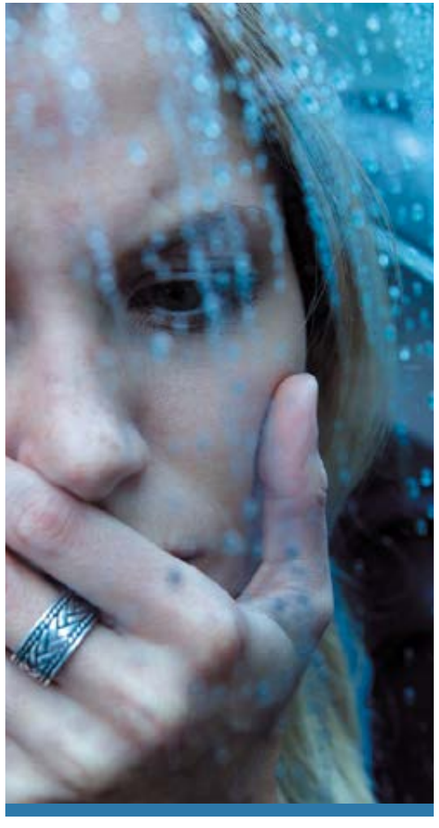
Based on the anticipated different drug related SHEs risk we defined the following treatment groups. In T1 DM: insulin pumps, basal-bolus insulin therapy with long-acting insulin analogue as the basal component (BBA), basal-bolus insulin therapy with human insulin as the basal component (BBH), biphasic insulin analogue, biphasic human insulin. In T2 DM: sulfonylurea (SU) with or without other oral drugs but excluding insulin, other antidiabetic medications especially oral antidiabetic medications different than SU (OADs excl. SU), basal long-acting insulin analogue (BOTA), basal human insulin (BOTH), basal-bolus with long-acting insulin analogue as the basal component (BBA), basal-bolus with human insulin as the basal component (BBH), biphasic insulin analogue, biphasic human insulin (all insulin regimens could be in combination with OADs). We defined basal bolus insulin therapy as long acting insulin analogue once or twice daily and short/ultrashort insulin at mealtime (BBA).

Although SR did not have a registered protocol, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[13]. As we wanted to assess SHEs rates in real-life rather than in experimental settings we looked for observational studies in: MEDLINE, Embase and The Cochrane Library databases (search strategies are given in Online Resource ESM_1). To account for changes in clinical practice in recent years and possible impact on treatment related risks, only recent studies were included (newer than 10 years).

We limited our search strategies to insulins or SU (i.e. we used no specific keywords for other-than-SU oral antidiabetic medications). We took this approach as NICE, IDF, ADA and EASD guidelines[7,14-17] firmly indicate that among oral antidiabetic medications used for treatment of T2 diabetes sulfonylureas are associated with an increased risk of hypoglycaemia as compared to other drug groups. The risk of hypoglycaemia associated with GLP-1 agonists and DPP-4 inhibitors is similar and very low[18,19]. Hence we treated GLP-1 agonists and OADs other than SU as one group, associated with a similar and most likely negligible SHEs risk. We assumed that the estimate of the risk of hypoglycaemia will use the best data found for one of these drugs. We decided to narrow the primary search then and to asses SHE rate in this group by applying a relative rate found in the literature as compared to SU, as described in more details below.

Precisely, specific inclusion criteria for observational studies encompassed: i) population of children and adults with T1 or T2 diabetes; ii) study design, i.e. observational, retrospective or prospective; iii) at least 100 participants (in total in a study, possibly split into smaller subgroups); iv) assessment of SHEs defined as an episode when the patient required an assistance from another person; v) publication date from 1st January 2002 until the search date, i.e. 1st October 2012.

Two authors independently conducted the selection process of relevant trials. Protocol assumed that in case of discrepancies between the authors discussion would be held until consensus was reached.



To estimate SHEs rates various types of data had to be extracted: time horizon in which hypoglycaemia was assessed, number of patients in a study group, number of hypoglycaemic episodes (absolute or mean per patient in a specified period of time, if available), number of patients experiencing at least one SHE (if available). If one study was described in many manuscripts, then the ones with the most appropriate and complete results were selected for extraction (e.g. data for a total study cohort instead of subpopulation, results presented separately for patients with T1 and T2 diabetes or results split by insulin regimens of interest). Data from included studies were extracted by one of the reviewer and checked by the other one.

As mentioned above, we planned to assess the risk related to other antidiabetic medications – GLP-1 or OADs (excluding SU) for T2 DM, calculating the relative rates as compared to SU based on secondary studies and then imposing them on the background SU-related SHE rate. We looked for the relative rates in secondary studies (SRs, meta-analyses) searched in a systematic way (see Online Resource ESM_1 for a search strategy) in MEDLINE, Embase, The Cochrane Library and Centre for Reviews and Dissemination (CRD). Inclusion criteria for this additional search encompassed: i) search performed at least in two databases (including at least one of the above databases), ii) at least two authors, iii) description of search strategy, iv) inclusion of randomized controlled trials (RCTs) conducted on T2 DM with at least one of the following: dipeptidyl peptidase-4 inhibitor, glucagon-like peptide-1 agonist, other oral antidiabetic drugs i.e. metformin, TZD, v) with hypoglycaemia defined as an episode when a patient required help form another person. We decided to use RCTs as they are more common to provide data on relative rates (than observational studies).

Our systematic review of primary studies yielded no studies in T1 DM patients treated with biphasic insulins. We thus had to update our methods and we conducted a supplementary literature search for secondary studies. We applied a similar methodology as with OADs, i.e. we looked for systematic reviews of RCTs in T1 DM patients treated with premixed insulins. We then applied relative rates to assess absolute rates.

We wanted eventually to asses annual SHEs rates per one person, i.e. average number of SHEs per one patient-year of staying on therapy. We assumed a random effects model, i.e. assumed that mean rates per treatment regimen in individual studies are drawn from some distribution, whose average we aim to estimate. We assumed that number of SHEs in individual patient follows a Poisson distribution, which allowed to use the information on both the average number of SHEs in a study and the fraction of patients with at least one SHE in a given horizon. Our model was expressed in Bayesian framework and implemented in WinBugs (see Online Resource ESM_2). Random effects model and non-informative priors were used. Median from a posterior distribution was used as a point estimator, and 2.5% and 97.5% percentile defined a 95% Bayesian confidence interval.

Risks related with other ADs were assessed in a two-step procedure. First a relative rate between other ADs and SU was assessed based on RCTs using fixed effect model in WinBugs. It was then applied to the baseline rate estimated for SU from observational studies.

We assessed the quality of included studies using the Newcastle-Ottawa Scale[20] – for case-control and cohort studies. According to systematic review by Deeks et al.[21], this scale is one of the two best identified for evaluating non-randomised interventional studies and is suitable for use in a systematic review (either as a scale or a checklist). Moreover, this tool is mentioned in the Cochrane Handbook as a tool for assessing methodological quality or risk of bias in non-randomized studies[22]. Non-interventional studies of other types were assessed by focusing in methods of patients selection, methods of outcome recording, study size and study representativeness.

RESULTS

Systematic review of observational studies

Literature search (for primary studies) yielded 6214 records, from which 994 duplicates were removed. The remaining 5220 articles were screened by title and abstract, and then 526 full texts were reviewed. Finally, 101 manuscripts [23-123] describing 55 individual trials were assessed as eligible for the analysis. Fig. 1. shows the studies selection process. Characteristics of included studies and references to the excluded studies with justifications are given in Online Resources ESM_3 and ESM_4, respectively.

For T2 DM 76 articles describing 35 studies were included: 11 (11 278.88 patient-years in total) provided data on BOT with insulin analogue; 7 (2142.13 patient-years in total) – BOT with basal human insulin; 6 (3022.27 patient-years in total) – BB with basal insulin analogue; 3 (227.46 patient-years in total) – BB with basal human insulin; 12 (63 776.85 patient-years in total)

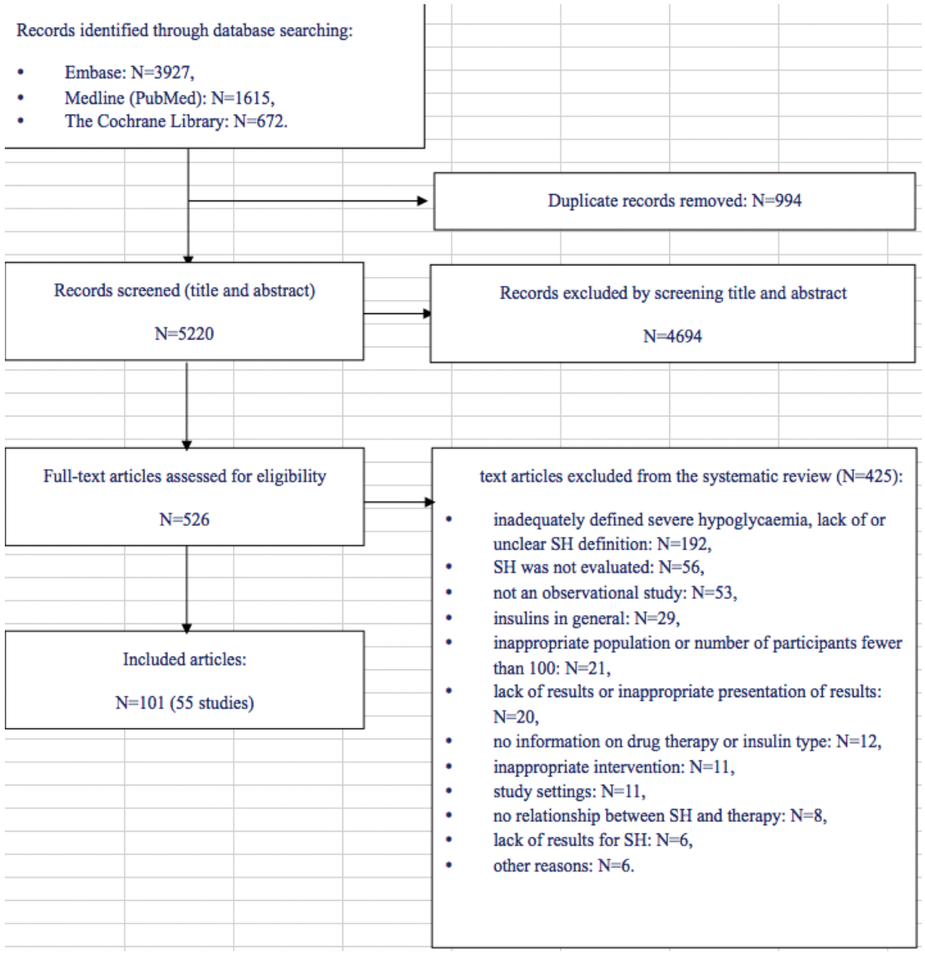


Figure 1. Systematic review of observational studies selection process

THE REIMBURSEMENT ACT INTRODUCED THE RESTRICTION ON THE NHF EXPENDITURES ON DRUGS TO 17% OF THE TOTAL RESOURCES DIRECTED TO THE FINANCING OF GUARANTEED SERVICES IN THE NHF FINANCIAL PLAN.

– pre-mixed insulin analogues; 6 (2265.87 patient-years in total) – pre-mixed human insulin ; 6 (1776.00 patient-years in total) – sulfonylureas.For T1 DM 33 articles describing 21 studies were included: 14 (6714.61 patient-years in total) provided data on SHEs in patients on insulin pumps, 7 (9656.18 patient-years in total) – BB with insulin analogue as the basal component, and 6 (2881.57 patient-years in total) – BB with human insulin as the basal component. As mentioned above, no studies on the treatment with biphasic insulins in T1 diabetes were found. A supplementary search for studies on pre-mixed insulins in T1 was carried out using the following key words: "biphasic", "pre-mix", "insulin", "type 1" and "diabetes" and resulted in six systematic reviews[124-129] describing five relevant RCTs[130-135] (as no observational studies were found by our SR, we decided to use RCTs). These were then used to assess relative risk in this group of drugs relative to risks estimated based on primary, observational studies.

We used New Castle Ottawa Scale[20] for case-control and cohort studies to assess the quality of included studies. Observational studies of other types were assessed with focusing in methods of patients selection, methods of outcome recording (regarding only severe hypoglycaemia), study size and study representativeness. Overall studies' quality varied. Among 9 case-control studies three scored 2 out of 9 possible points, three – 3 points, two – 4 points, and one – 5 points. Among 13 cohort studies one study scored 5 out of 9 possible points, six – 6 points, and six – 7 points. The residual studies, assessed by description with no scoring, were of medium quality. Details on quality of included studies is given in Online Resources ESM_5.

Systematic review of secondary studies

Literature search for other antidiabetic drugs yielded 12 systematic reviews (see fig. 2 in ESM_6), from which a study conducted by Karagiannis et al.[136] was assessed to provide the most appropriate data on severe hypoglycaemia associated with various antidiabetic medications in type 2 diabetes (for reference list of included studies and excluded studies with justification see ESM_7).

Data from the RCTs included in the study Karagiannis[136] indicated that in insulin-naïve patients with T2 DM treatment with sulfonylureas resulted in higher SHEs rate than treatment with other OADs (0.009 vs 0.0008 events per person-year, respectively, in patients treated with SU and patients treated with OADs other than SU – the estimated relative rate was 14.14, 95% CI: 5.53; 47.18, for the comparison of SU to DPP-4, while there was no statistical proof to differentiate the risk rate between these other OADs. The fact that SUs are related with greatest risk among all the OADs supports the approach to concentrate on SU risk in the systematic review of primary studies.

SHEs rates for various treatments

Systematic review carried out for SHEs risk in assumed drug groups provided data on absolute annual number of SHEs per one treated patient with diabetes. Results available in each of the studies split by diabetes type are presented in Tables 1 and 2. The quantitative analysis of these data resulted in the following mean annual SHEs rates per person are presented in Table 3.

Our results show that SHEs rates differ among drug regimens. In T1 DM basal-bolus insulin therapy with human insulin as the basal component was associated with the highest risk of SHEs (1.1 events per person-year) while the insulin pumps led to the lowest risk of SHEs (0.18 events per person-year). In type 2 diabetes basal-bolus insulin therapy with basal human insulin was also associated with the highest risk of SHEs (0.56 events per person-year) and patients may be at the lowest rate of SHEs when treated with OADs other than SU (0.006 events per patient-year). This pattern in type 2 diabetes may reflect the disease progression, from oral antidiabetic medications to insulin in monotherapy or combined with OADs.

Table 1. Diabetes type I results of the included studies

Study	Time horizon (years)	Number of participants	Patients with ≥1 SHE	Number of events	Mean events no per patient-year	SD
Insulin pump therapy						
Bruttomesso 2002	7.4	138		92	0.09	0.02
de Bock 2012	3	75		11	5	
Garg 2004c	0.97	216	45	84	0.4	Not clear
Jakisch 2008	1	412/300/199		74/60/34	17.87/20.04/17.33	2.85/3.91/4.47
Kapellen 2007	1/1/2.75/2.75	248/544/76/177			0.25/0.14/0.27/0.27	
Katz 2012	1.69	93		50	31.8	
Leinung 2010	1	117	37	68	58.9	
Muller-Godeffroy 2009	0.5	88	6			
Nimri 2006	1/1/1	127/129/23			11.1/23.3/0	
Reda 2007	2.6	105		15	0.05	
Rudolph 2002	3.01	107			19.2	
Scaramuzza 2011	1.7/1.4	493/493			6.6/3.9	
Scheidegger 2007	0.46	19	1	1		
Wood 2006	1	132			7.4	
Basal bolus with long-acting insulin analogue						
DAFNE, Keen 2012	1/1	124/124	15/6	37/22		
Garg 2004 a	1.09	292 (98, 299)	81 (28, 81)	167 (n.a., n.a.)	0.57 (0.5, 0.6)	
Herwig 2007	1.68	74		11	0.14	0.4
Kapellen 2009	1	6558			32.2/100	3
Katz 2012	1.8	50		31	34.4	
Kristensen 2012	1	1052			1.47	SE=0.18
PREDICTIVE, Marre 2009	1	647		11	0.02	
PREDICTIVE, Preumont 2009	0.5	232			0.1	0.7
PREDICTIVE, Sreenan 2008	0.23	1500			0.52	
PREDICTIVE, Yenigun 2009	0.08/0.23	506/506		94/28		
Basal bolus with human basal insulin						
Garg 2004b	1.06	98	30		1.2	SEM=0.40
Hartemann--Heurtier 2003	1/1	110/110	14/26		0.2/0.83	0.62/3/34
Herwig 2007	1.68	68		62	0.73	1.68
Kristensen 2012	1	2085			1.09	SE=0.11
Leckie 2005	1	243	83		0.98	
PREDICTIVE, Sreenan 2008	0.077	1500			3.51	

Table 2. Diabetes type II results of the included studies

Study	Time horizon (years)	Number of participants	Patients with ≥1 SHE	No of events – absolute or mean per patient-year
Basal long-acting insulin analogue ± OADs				
A1chieve, Home 2011	0.46	12 078 and 3467		0 and 0.01
EARLY, Hanefeld 2012	0.46	1389	1	1
FINE, Tsai 2011	0.50	2016 and 16		0.003 and 0
IMPROVE, Gumprecht 2009	0.25	245		0.197
Kawamori 2008	0.46	97	0	0
LIGHT, Verges 2012	0.25	1863	18	0.12
PREDICTIVE, Dornhorst 2008 b	0.08	118		0.26
PREDICTIVE, Meneghini 2009	0.23	1652		0.00
PRESENT, Jang 2008	0.23	348		1.1
Sudhakaran 2010	0.46	54	0	0
Sudhakaran 2011	0.46	2743	0	0
Yang 2012	0.31	297	2	2
Basal human insulin ± OADs				
FINE, Tsai 2011	0.50	589		0.031
Furlong 2002	2.42 (median)	133 and 67	6 and 1	
Honkasalo 2010, Honkasalo 2011	1	431	53 (12.3%)	116
IMPROVE, Gumprecht 2009	0.25	497		0.153
PREDICTIVE, Dornhorst 2008 b	0.08	175		0.78
PRESENT, Jang 2008	0.23	3414		0.39
Sudhakaran 2010	0.46	23	0	0
Basal bolus with long-acting insulin analogue ± OADs				
A1chieve, Home 2011	0.46	1593 and 2512		0 and 0.001
JDDM23, Oishi 2012	0.50	126	1	1
PREDICTIVE, Sreenan 2008	0.23	2137		0
SAFIR, Zick 2007	0.15	455	0.7% of patients	0.05
Suzuki 2012	1	400	1	1
Zjačić-Rotkvić 2012	0.5	203	0	0
Basal bolus with human insulin ± OADs				
Biesenbach 2006	1	34		0.05
JDDM23, Oishi 2012	0.23	126	1	1
PREDICTIVE, Sreenan 2008	0.23	126		0.78 per patient year
Pre-mix insulin analogues				
A1chieve, Home 2011	0.46	27 591 and 13 318		0 and 0.20 per patient-year
BIAsp Start, Berntorp 2011	0.52	1154	2	2
Danish BIAsp Study Group, Breum 2008	0.5	392	4	
IMPROVE, Khader 2010	0.5	1613		0.05
IMPROVE, Valensi 2009	0.5	52 419		0.008
INITIATE plus, Oyer 2011	0.46	4812	87	127
Levit 2011	2.9	115	0	0
Ligthelm 2009	1.5	149	0	0
Makela 2012	0.5	496		19
Nobels 2012	0.5	498	6	
PRESENT, Gao 2009	0.23	3697; 4754; 2392; 817		0.04; 0.13; 0.3; NA
PRESENT, Khutsoane 2008	0.50	21 977		0.1
Temizel 2010	1	71		0.06 per patient- month
The 1-2-3 study, Garber 2006	0.31	100 and 68 and 25	3 and 3 and 1	
Pre-mix human insulin				
Gu 2012	0.31 and 0.31	409 and 235		2 and 0
IMPROVE, Shah 2009 a	0.25	3856		0.355
Nobels 2012	0.08	592	4	
PRESENT, Shestakova 2007	0.23	3241	162	0.7
Progens-first-step, Strojek 2008	0.25 and 0.25	482 and 483	1 and 2 patients during first 13-week observation and during second 13 weeks, respectively	2 and 2 episodes, respectively
Temizel 2010	1	69		0.04 per patient-month
SU				
Andayani 2010	0.5	49	1	1
Aung 2012	1	10.43	24	
Exhype, Pettersson 2011	0.5	430	5 (1.2%)	
Iványi 2012	2.54	86	2	2
UK Hypoglycaemia Study Group	0.73	103		0.1
Vexiau 2008	0.5	400	16	

Table 3. Annual mean (95% CI) number of SHEs in patients with type 1 and type 2 DM

Therapy	Average number of SHEs per patient per year	95% CI	Remarks
Type 1 DM			
basal-bolus (basal insulin analogue)	0.53	0.29–1.18	
basal-bolus (basal human insulin)	1.10	0.57–2.71	
insulin pump	0.18	0.13–0.25	
pre-mix insulin analogue and pre-mix human insulin	1.10		due to lack of statistically significant differences between pre-mix human insulin and pre-mix insulin analogues, the same SHEs rate as for pre-mixed insulin analogues (so BBH)
Type 2 DM			
BOT analogue	0.13	0.04–1.17	
BOT human	0.21	0.08–0.88	
basal-bolus (basal insulin analogue)	0.01	0.003–0.25	
basal-bolus (basal human insulin)	0.56	0.16–9.65	
pre-mix insulin analogue	0.10	0.05–0.26	
pre-mix human insulin	0.20	0.07–0.93	
sulfonylureas	0.05	0.02–0.14	
OADs (excl. SU)	0.006	0.001–0.008 S	

DISCUSSION

We conducted a systematic review and meta-analysis in order to estimate average annual rates of severe hypoglycaemia events associated with various insulin regimens and other antidiabetic medications. For insulin therapy and sulphonylureas we included observational studies that met the predefined criteria to directly assess rates of SHEs. For residual antidiabetic medications in type 2 diabetes we used data from another systematic review to assess the relative SHE frequency and apply it to a baseline rate estimated for SU. Due to lack of observational data for premix therapies for type 1 we had to refer to secondary studies as well in order to assess the relative risks in comparison to other therapies and indirectly calculate associated SHEs rates. That is why this part of results should be treated with greater caution.

The inclusion criteria for observational studies were defined so as to obtain as high quality of identified studies as possible. Thus, we decided to use newer publications only to account in possible changes of diabetes management over time (only studies published from 2002 on were used). Further we took into account only studies with at least 100 participants (we did not want to include small studies of a poor quality as the number of participants is also assessed in The Newcastle-Ottawa Scale). Most importantly the definition of SHE used in the identified studies was carefully checked so as to guarantee consistency among them, but at the same time we had to reject numerous studies due to lack of information in the definition used therein. That reduces the body of evidence but provides greater consistency of results. The overall quality of the studies, as measured by the New Castle Ottawa scale, is nonetheless rather medium. The most frequent shortcomings of the included case control studies were no definition of controls and using self reports or medical records only for the ascertainment of exposure. Major shortcoming of the included cohort studies was that it was not demonstrated that the outcome of interest was not presented at the start of the study. The heterogeneity of the studies is quite substantial, that is why a random effects model was used, and the resulting confidence intervals for mean rates are rather wide. We still have to notice that best available evidence was used, and so these limitations simply suggest the direction for further research when more observational studies have been published. With more data a better assessment of overall means should be possible, and perhaps a meta-regression approach could explain some sources of heterogeneity.

The applied methodology allowed to use two types of results reported in the studies, either number of SHEs or fraction of patients with at least one episode. As can be seen in tables 1 and 2, various reporting was used in identified observational studies. Focusing on number of SHEs only would substantially reduce the amount of data available, and that is why we decided to assume the Poisson distribution. Obviously, this assumption comes at a price, as potential biases may emerge. Poisson distribution forces the mean being equal to the variance, while hypoglycaemia events may concentrate in single patients more than this distribution would suggest (e.g. patient lifestyle either diminishes or augments chances of an event), but may also spread out more evenly (e.g. a patient having experience SHE will adapt her lifestyle to reduce future risk). We considered using another distribution (e.g. negative binomial) to allow for difference between mean and variance, but additional parameters made the estimation process and results very unstable. Secondly, it was mostly in T2 that substantial amount of data came in the form of number of patients with at least one SHE, where the overall risk was quite small and so the discrepancy between Poisson and some other distribution would be much smaller.

Eventually, annual rates varied from 0.18 for insulin pump up to 1.1 for basal-bolus with human basal insulin and from 0.006 for oral antidiabetic drugs up to 0.21 for basal human insulin with oral antidiabetic medications for type 1 and type 2 DM, respectively. Spread of results between individual studies is large, which means that several other factors may affect the outcome (e.g. life style). More data would probably make it possible to identify these factors, e.g. by meta-regression. However, the mean value may be still estimated and our calculations are based on the best (available at the time of the review) data.

It is worth to mention that our analysis of observational studies yielded results different from those based on RCTs. And so the risk of SHE associated with sulfonylureas estimated from observational studies amounted to 0.05 event per patient per year, and was higher than 0.01 coming from RCTs included in the systematic review by Karagiannis et al.136. This can lead to the conclusion that a real SHEs risks are higher than those in RCTs due to factors other than therapy associated with hypoglycaemia occurrence, however obviously both numbers are estimated with an error, and both are actually small in absolute terms.

It's important to notice that our purpose was not to compare given drugs between themselves – that is we defined our approach so as to get the best possible estimate of SHE rate for each treatment separately, rather than the best possible estimate of relative SHE rate between pairs of treatment regimes. The latter would require e.g. looking for studies with several arms encompassing more than one treatment regimen, so as to get relative effects and then meta-analyse them (while we meta-analysed individual treatment rates for each regimen separately). Another important decision would then also be whether to use interventional or observational studies, and that depends largely on a question we are asking. If we wanted to know – "what is the risk if I give this treatment to my patient?" – we should rather go for interventional studies. In our case our question rather is – "what is the risk if I observe this patient using this treatment" – and then observational studies seem to be more appropriate, as they account for the fact that some patients may be using drugs that address their life-style and moderates their baseline SHE risk. Additionally, observational studies do not impose very strict protocol that may bias complication rates downwards in RCTs when compared to real-life situations. Thus, our results should not be used to quantify consequences of switching patients between drug regimens, but rather to assess the actual overall burden of SHE when drug usage patterns are known.

We did not find other systematic review or meta-analysis that evaluate real-life risk of severe hypoglycaemia among diabetic patients (type 1 and type 2) for various therapies. A review closest to ours was the one conducted by Bolen et al.[137] that summarized the English-language literature on the benefits and harms of oral agents in adult patients with T2 DM. In their review, Bolen et al. included 216 controlled trials and cohort studies and 2 systematic reviews in total of which 169 articles evaluated adverse events. In comparison to our review they estimated weighted absolute risk differences between individual drugs, drug groups or therapies, while our aim was to estimate average annual rates of SHEs associated with various insulin regimens and other antidiabetic medications. Moreover, they presented combined results for minor and major hypoglycaemia and did not provide the definition of major hypoglycaemia. Results of their meta-analysis indicated that in patients receiving second generation sulfonylureas hypoglycaemic episodes (minor and major) were more frequent than in patients receiving metformin or TZD. They obtained concordant conclusion as can be seen in NICE, IDF, ADA and EASD guidelines[14-17] in the treatment of type 2 DM which indicate that sulfonylureas are associated with higher risk of hypoglycaemia than other antidiabetic oral drugs.

Other meta-analysis of observational studies conducted in patients with T2 DM by Goto et al. [138] evaluated association between severe hypoglycaemia and risk of cardiovascular disease. Cohort studies and randomised controlled trials were included as long as an observational analysis of the analysed association was available. Goto et al. included six studies in their meta-analysis (two were secondary analyses of RCT and four were based on administrative databases) of which none fulfilled inclusion criteria of our systematic review due to inappropriate definition of severe hypoglycaemia. The association between SHE and cardiovascular disease was estimated with the use of relative risk as a measure of effect. Results suggest that severe hypoglycaemia is associated with approximately twice the risk of cardiovascular disease. These results indicate the need for evaluation and quantification of the risk of severe hypoglycaemia.

CONCLUSIONS

Various drug regimens differ in terms of severe hypoglycaemia risk, as also pointed out in published guidelines. Our results indicate that basal-bolus therapy with basal human insulin is associated with the highest average number of SHEs per patient per year, both in type 1 and type 2 DM, while insulin pump and OADs (excl. SU) seems to be the safest therapies in T1 and T2 diabetes, respectively. These differences can be quantified based on results of published observational studies. Results of the current analysis can be used to provide parameters for cost-of-illness studies estimating the overall burden of hypoglycaemia.

LIST OF ABBREVIATIONS

- AD – antidiabetic medication
- BB – basal-bolus
- BBA – basal-bolus insulin therapy with long-acting insulin analogue as the basal component
- BBH – basal-bolus insulin therapy with human insulin as the basal component,
- BOTA – basal supported oral therapy with long-acting insulin analogue as the basal component
- BOTH – basal supported oral therapy with human insulin as the basal component
- CI – confidence interval
- DM – diabetes mellitus
- OAD – oral antidiabetic medication
- RCT – randomized controlled trial
- SHE – severe hypoglycaemia event
- SU – sulfonylurea
- T1, T2 DM – type 1, type 2 diabetes mellitus
- TZD – thiazolidinediones

COMPETING INTERESTS

The project was funded by Novo Nordisk. The author(s) declare that they have no competing interests. There is no specific organization that may in any way gain or lose financially from the publication of this manuscript.

AUTHORS' CONTRIBUTIONS

MJ, JP, MN and MC are the authors of general analytic framework. MJ, JP, ER and MN have participated in the systematic review. All authors participated in preparing, read and approved the final manuscript.

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