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Comparative efficacy and complications of long-acting and intermediate-acting insulin regimens for adults with type 1 diabetes: an individual patient data network meta-analysis

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ABSTRACT

Objective To examine the comparative efficacy and complications of long-acting and intermediate-acting insulin for different patient characteristics for type 1 diabetes mellitus (T1DM).

Design Systematic review and individual patient data (IPD) network meta-analysis (NMA).

Data sources MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials were searched through June 2015.

Eligibility criteria Randomised controlled trials (RCTs) on adults with T1DM assessing glycosylated haemoglobin (A1c) and severe hypoglycaemia in long-acting and intermediate-acting insulin regimens.

Data extraction and synthesis We requested IPD from authors and funders. When IPD were not available, we used aggregate data. We conducted a random-effects model, and specifically a one-stage IPD-NMA for those studies providing IPD and a two-stage IPD-NMA to incorporate those studies not providing IPD.

Results We included 28 RCTs plus one companion report, after screening 6680 titles/abstracts and 205 full-text articles. Of the 28 RCTs, 27 studies provided data for the NMA with 7394 participants, of which 12 RCTs had IPD on 4943 participants. The IPD-NMA for A1c suggested that glargine once daily (mean difference [MD]=−0.31, 95% confidence interval [CI]: −0.48 to −0.14) and detemir once daily (MD=−0.25, 95% CI: −0.41 to −0.09) were superior to neutral protamine Hagedorn (NPH) once daily. NPH once/two times per day improved A1c compared with NPH once daily (MD=−0.30, 95% CI: −0.50 to −0.11). Results regarding complications in severe hypoglycaemia should be considered with great caution due to inconsistency in the evidence network. Accounting for missing data, there was no evidence of inconsistency and long-acting insulin regimens ranked higher regarding reducing severe hypoglycaemia compared with intermediate-acting insulin regimens (two-stage NMA: glargine two times per day SUCRA (Surface Under the Cumulative Ranking curve)=89%, detemir once daily SUCRA=77%; one-stage NMA: detemir once daily/two times per day SUCRA=85%). Using multiple imputations and IPD only, complications in severe hypoglycaemia increased with

diabetes-related comorbidities (regression coefficient: 1.03, 95% CI: 1.02 to 1.03).

Conclusions Long-acting insulin regimens reduced A1c compared with intermediate-acting insulin regimens and were associated with lower severe hypoglycaemia. Of the observed differences, only glargine once daily achieved a clinically significant reduction of 0.30%. Results should be interpreted with caution due to very low quality of evidence.

PROSPERO registration number CRD42015023511.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review with individual patient data network meta-analysis (IPD-NMA) followed the methods guidelines in the Cochrane Handbook, applied Confidence in NMA (CINeMA) to assess certainty of evidence, and reported findings using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extensions for NMA and IPD meta-analysis.

⇒ Compared with the findings of our previous systematic review that only included aggregate data, the inclusion of IPD allowed us to increase certainty in the treatment effects and include randomised controlled trials (RCTs) with non-reported published outcome data or participant characteristics.

⇒ Limitations of the NMA include the age of the included RCTs, high risk of within-study bias, small-study effects in severe hypoglycaemia, and intransitivity because of sex and participant age.

⇒ IPD were available for fewer than half of the eligible RCTs from a single funder, highlighting potential retrieval bias.

⇒ The literature search was conducted 7 years ago, but obtaining IPD in a timely manner was very challenging; further eligible studies may have been published since then.

INTRODUCTION

A previous systematic review and network meta-analysis (NMA) showed that long-acting

insulin (glargine, detemir) is superior to intermediate-acting insulin (neutral protamine Hagedorn (NPH), lente), providing better glycaemic control and reducing the occurrence of severe hypoglycaemia in patients with type 1 diabetes mellitus (T1DM).[1] Also, evidence base on multiple study designs and any type of insulin (ultra-long, long, intermediate-acting and human/animal insulin) in adults with T1DM showed that both ultra-long-acting and long-acting insulin were superior to intermediate-acting insulin in reducing glycosylated haemoglobin (A1c).[2] However, the relative efficacy and safety of these formulations for different patient subpopulations (eg, baseline A1c, diabetes-related comorbidities) are unknown.[3–6] Organisations including the American Diabetes Association, Diabetes Canada and the European Association for the Study of Diabetes recommend tailoring insulin regimens according to an individual's needs.[7–9] However, there is a lack of high-quality evidence to support tailoring of insulin regimens to these characteristics. For example, a recent Cochrane review found detemir reduced severe hypoglycaemia compared with NPH and that there were no clinical differences between children and adults, but evidence was of moderate certainty.[10]

Standard NMAs use aggregate data (AD), that is, intervention effects and associated CIs, usually obtained from primary study publications or authors. Alternatively, NMAs can use individual patient data (IPD) from each eligible study, specifically, data from each patient enrolled in the original study. There are multiple advantages with using IPD in NMA, such as adjusting and exploring treatment effect modifiers and including treatment-by-covariate interactions to allow for treatment effects to vary by patient-level characteristics. The use of IPD provides greater statistical power than AD to detect the effect of an interaction between treatment and covariate, particularly when patient-level covariates are of interest, avoids dichotomisation of continuous variables (eg, age) and decreases the chances of aggregation bias due to the use of group-level information in the analysis.[11 12] An IPD-NMA allows for estimating treatment effects conditional on patient characteristics and particular populations, and can reduce heterogeneity and inconsistency between different sources of evidence in a network of randomised controlled trials (RCTs). Therefore, an IPD-NMA can provide more precise, confident and informative results compared with an AD NMA.[13]

Our previous systematic review with NMA using AD[1] evaluated long-acting versus intermediate-acting insulin, but definitive conclusions could not be provided about whether the treatment effect changed for patients with different characteristics. To inform health professionals and clinical practice guidelines, we sought to examine the comparative efficacy and complications of different presentations of insulin regimens, that is, hypoglycaemic agents, for patients with T1DM with different characteristics. In this systematic review, we informed our NMA using IPD, which allows for tailoring of results to specific patient characteristics.

METHODS

Protocol

Our protocol was prospectively registered (PROSPERO; registration # CRD42015023511) and published.[14] Additional information is also provided in the online supplemental files 1 and 2. Below, we briefly summarise our methods.

We reported our findings using the Preferred Items for Systematic Reviews and Meta-analysis (PRISMA) statement for NMA of healthcare interventions, and the PRISMA extension to IPD.[15 16]

Eligibility criteria

We updated our previous systematic review[1] of RCTs comparing long-acting versus other long-acting or intermediate-acting insulin regimens. Eligible studies were RCTs including adults with T1DM assessing A1c change and/or severe hypoglycaemia. A severe hypoglycaemic event was defined as reported in the individual trials and generally included a medical emergency in which patients needed healthcare assistance to quickly ingest sugar or receive a glucose injection. We selected the A1c outcome, as it is a validated surrogate endpoint for reduction of cardiovascular complications.[17] We selected the severe hypoglycaemic event outcome, as it is associated with significant use of healthcare resources and higher risk of mortality.[18]

Search strategy and study selection

Experienced librarians designed and ran our literature searches (LP, BS).[1] The following databases were searched: MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials up to 16 June 2015. We scanned references of included studies and relevant reviews to identify additional relevant RCTs.

After conducting a pilot test on a random sample of RCTs, pairs of reviewers (FY, JDI, MG and PAK) screened titles, abstracts and full texts, independently. The same reviewers extracted data. Any conflicts were resolved through discussion. Overall, there was 90% agreement between reviewers during screening.

IPD collection process and data abstraction

Two individuals (a senior scientist ACT and a research assistant Susan Le) contacted authors to request IPD. Briefly, we followed the strategies outlined below. More details can be found in our RCT protocol.[19] We sent (a) an email requesting IPD, (b) email reminders to the authors (four in total) at 2-week, 6-week, 10-week and 14-week intervals after the initial email, (c) reminder letters in week 7 and (d) telephone reminders in week 15. We offered coauthorship on our updated systematic review provided that the authors shared their anonymised IPD and met the International Committee of Medical Journal Editors (ICMJE) authorship criteria.[20] Two individuals (AAV and Susan Le) also contacted funders of the eligible RCTs. If funding was not reported in an RCT, we confirmed funding with the original author (whom we

emailed during the RCT). We contacted industry funders after navigating the data sharing process through the relevant websites, online portals, email or phone inquiry. Two follow-up reminders were sent to the funders.

To retrieve IPD, we contacted the corresponding author for each trial and, if unsuccessful, followed with the next-in-order author, as described elsewhere.[21] We also contacted all industry funders of RCTs.

We requested the following IPD: (a) participant characteristics including participant age, sex, pregnancy status, baseline A1c level, presence of comorbid conditions, history of hypoglycaemia, other medications used, patient retention along with reasons for drop-out and number of participants; (b) interventions, including treatment allocated, and dosage; (c) outcomes, A1c values and severe hypoglycaemia, including time to development and measurement or event dates; and (d) study-level characteristics, such as year conducted and method of randomisation.

From each RCT, we extracted the following study characteristics: year of publication, country and continent as reported or according to the first author, and journal in which the study was published. We categorised each RCT according to funding source: (1) industry-funded, (2) publicly funded, (3) mixed and (4) non-funded studies. For trials where IPD were not available, we also extracted: (a) patient characteristics: study size and percentage of men; (b) outcome data: study data (eg, events or mean and SDs and sample size per arm) and (c) treatments compared.

Risk of bias and quality appraisal

We used the Cochrane risk of bias tool to assess within-study bias,[22] and checked consistency between the IPD and trial publications. We also checked baseline imbalance for important characteristics across the treatment groups.

When at least 10 studies were available, small-study effects were examined visually using the comparison-adjusted funnel plot under the fixed-effect model.[23] The NMA findings were assessed for each outcome using the CINeMA tool (Confidence in NMA; see online supplemental file 1 for more details).[20]

Synthesis

We described the characteristics of the included patients and treatments using frequencies and distributions. Since IPD were available through a single funder-specific platform, we conducted a one-stage analysis for the retrieved IPD (12 studies). To include all eligible RCTs in the meta-analysis, we conducted a two-stage analysis, whereby each patient was analysed separately in each RCT in the first stage and then the RCT aggregate estimates were synthesised in a random-effects standard meta-analysis or NMA in the second stage (main analysis). We graphically summarise the geometry of the included trials in a network plot.

One-stage analysis of trials providing IPD

We conducted a one-stage IPD-NMA based on data provided to us by trial funders and used a Bayesian approach adjusting for all of the available requested patient characteristics and including treatment-by-covariate interactions.[24] We considered two different assumptions regarding the treatment-by-covariate interactions: (a) independent regression coefficients per study and treatment comparison (ie, assuming that all treatment-by-covariate interactions are different for each treatment vs the control), and (b) identical regression coefficients across studies and comparisons (ie, assuming that all treatment-by-covariate interactions are common for each treatment vs the control). Assuming identical regression coefficients assumption is a strong assumption but is a less data-demanding approach compared with the independent regression coefficients assumption, where the number of parameters increases in the model per treatment comparison.[25 26] Our IPD analyses are based on the intention-to-treat principle including patients who had been previously excluded from a trial's analyses where data were available. We also used imputation techniques as described in online supplemental appendix 1.

Two-stage analysis

For those studies providing IPD, we fitted a logistic regression model for severe hypoglycaemia and a linear regression model for A1c within the funder's portal to get adjusted treatment effects. We conducted a two-stage analysis for IPD only, as well as combined adjusted IPD with AD treatment effects in a standard meta-analysis or NMA model (main analysis) using a frequentist approach. We included patient-level covariates with main terms in the model including all of the available requested patient characteristics. Unadjusted estimates from retrieved IPD and AD were also combined in a joint NMA model as a subsequent analysis.

A common-within network between-study variance was assumed across comparisons for all NMA models.[27] We estimated the between-study variance (τ^2) using the DerSimonian and Laird[28] method for the two-stage analyses and used a $\tau \sim U(0,2)$ prior to the one-stage analyses. We compared τ^2 with the relevant distributions provided by Turner $et\ al$[29] and Rhodes $et\ al$[30] to assess heterogeneity. We calculated I^2 on the combined IPD and AD NMA, to quantify overall heterogeneity and inconsistency.

We visually inspected similarity of the distribution of prespecified effect modifiers, such as age and sex, across treatment comparisons to assess for transitivity.[31–33] Consistency was assessed globally and locally with the design-by-treatment interaction model[34 35] and the loop-specific method,[36 37] respectively. We monitored changes in between-study heterogeneity and network inconsistency using subgroup NMA and network meta-regression analyses on the prespecified potential effect modifiers. More details are provided in online supplemental appendix 1.

We present the summary OR and mean difference (MD) along their corresponding 95% CIs and predictive
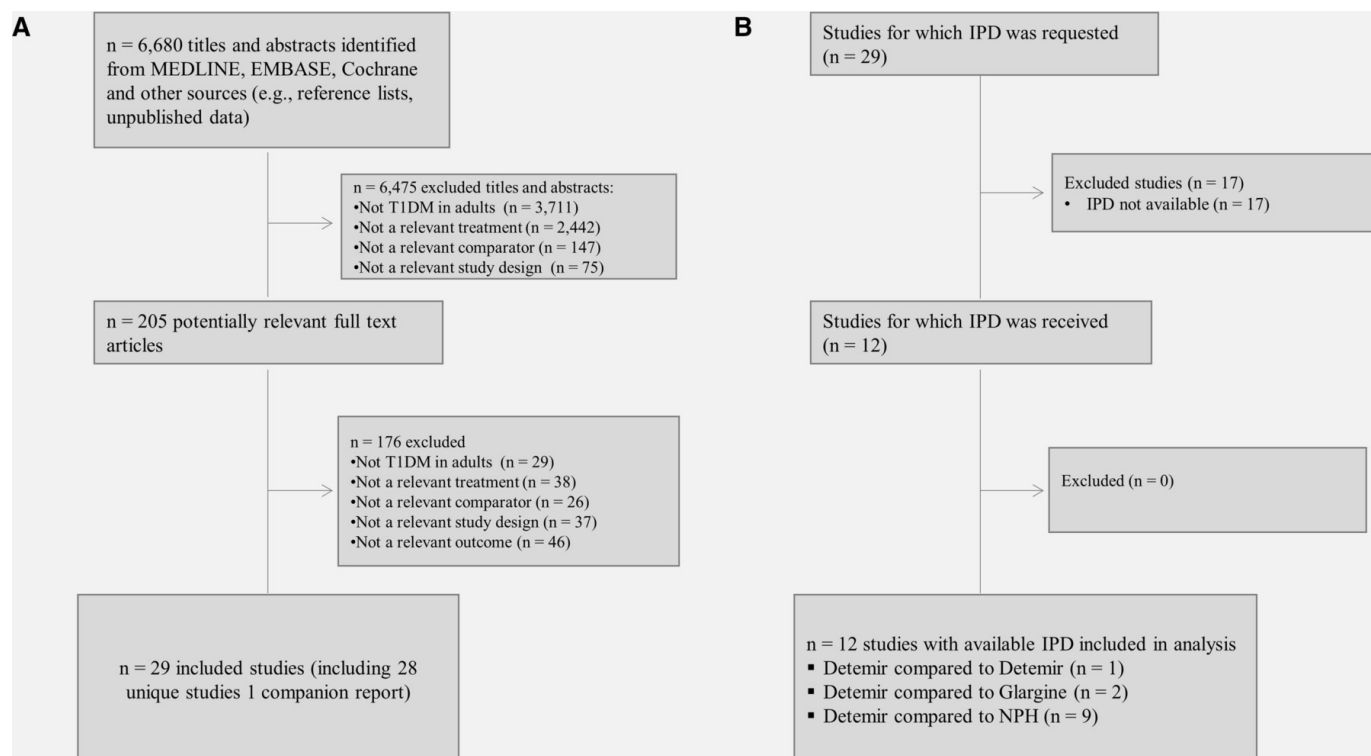
Figure 1 Flow diagram for study inclusion in the review (A) and studies retrieved with individual patient data (IPD) (B). NPH, neutral protamine Hagedorn; T1DM, type 1 diabetes mellitus.

intervals (PIs).[38] We assessed all MDs using the minimal clinically important difference (MCID), adopting a cut-off point greater than 0.30[39] percentage units (U.S. Food and Drug Administration [FDA] considered a clinically meaningful threshold of 0.30 or 0.40). We ranked the interventions under the consistency assumption using p-scores and the surface under the cumulative ranking curves (SUCRAs), and present them in a rank-heat plot.[40–42] The SUCRA is the numerical summary of the rank distribution for each treatment, with range 0%–100%, where 100% reflects the best treatment and 0% the worst treatment. A frequentist statistic equivalent to the SUCRA statistic is the p-score statistic. All analyses were conducted in the RStudio[43] using R V.3.6.2 and V.3.4.3 (available in funder's platform) and the *R2jags*,[44] *meta*[45] and *netmeta*[46] packages, respectively.

Patient and public involvement
Not applicable.

RESULTS
Literature search, study selection and IPD obtained
We screened 6680 titles and abstracts and 205 full-text articles. We included 29 trials (28 unique studies and 1 companion report; figure 1A and online supplemental appendix 2).

Of the 28 RCTs, 23 were industry funded, 22 were funded by one industry funder and 1 RCT jointly by two industry funders. Of the remaining studies, two were publicly funded and three did not report funding

information. None of the authors of the 28 RCTs (7428 participants) and the identified companion report[47] shared their study IPD.[21] We contacted two funders for these RCTs. We requested data for 15 RCTs (5052 participants) from Novo Nordisk and obtained IPD for 12 RCTs (4943 participants), shared data through a proprietary-specific platform after 1058 total waiting days for a response (up to 9 March 2020; online supplemental appendix 3). The supplied IPD included data for severe hypoglycaemia, which were not reported in a published RCT.[48] We contacted Sanofi-Aventis for nine studies, but none of the IPD were provided. Figure 1B shows the study flow for retrieving IPD.

Study and patient characteristics
The mean age of patients across the 28 trials ranged from 26 to 47 years. The majority of the RCTs were conducted in Europe or Oceania and included patients with A1c ranging from 6.85% to 9.70% (table 1 and online supplemental appendix 4). Study duration (defined from first patient recruited to last patient followed up) ranged between 10 and 19 years (online supplemental appendix 5). Across RCTs with available IPD, we observed no imbalance in participant characteristics in the intervention and comparison groups (online supplemental appendix 6). For studies that were industry funded, we found that smaller studies and studies of populations with lower baseline A1c were less likely to supply IPD (study size, studies with no supplied IPD: median 68 participants, IQR 47–147 participants, studies with supplied IPD:

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Table 1 Study and patient characteristics

	All unique studies in the systematic review (N=28)	Studies with available IPD (N=12)
Total # of participants	7428	4943
Sample size (range)	20–747	130–747
Year of publication (range)	2000–2015	2003–2013
Treatment period in weeks (range)	4–104.35	16–104.35
Mean % of female (range)	45.14 (0–100)	48.08 (21–100)
Mean age in years (range)	38 (26–47)	39 (30–42)
Mean A1c in % (range)	7.97 (6.93–9.45)	8.14 (7.02–8.85)
Mean duration of T1DM in years (range)	15.29 (10.00–18.55)	15.90 (12.25–17.25)
Study conducted in: frequency (%)*		
Africa	3 (10.71)	3 (25.00)
Asia	1 (3.57)	1 (8.33)
Oceania	21 (75.00)	11 (91.67)
Europe	6 (21.43)	5 (41.67)
North America	4 (14.29)	1 (8.33)
South America	1 (3.57)	1 (8.33)
Not reported	1 (3.57)	1 (8.33)
Interventions examined: frequency (%)*		
Detemir	16 (57.14)	12 (100.00)
Glargine	16 (57.14)	2 (16.67)
NPH	22 (78.57)	9 (75.00)
Outcomes reported: frequency (%)*		
A1c	28 (100.00)	12 (100.00)
Severe hypoglycaemia†	21 (78.57)	10 (83.33)
Funding (%)		
Industry funded	23 (82.14)	12 (100.00)
Publicly funded	2 (7.14)	–
Not reported	3 (10.71)	–

– means not applicable.
*Multiple countries, interventions and outcomes reported per study.
†Includes serious and major hypoglycaemia. Four studies included zero events in all arms and were excluded from the analysis.
A1c, glycosylated haemoglobinIPD, individual patient data; NPH, neutral protamine Hagedorn; T1DM, type 1 diabetes mellitus.

median 400 participants, IQR 288–468 participants; and A1c baseline, studies with no supplied IPD: median 7.68, IQR 7.11–7.93, studies with supplied IPD: median 8.14, IQR 7.92–8.35) (online supplemental appendix 7). Non-industry-funded studies did not supply IPD.

Risk of bias and IPD integrity
Based on the publication of the 28 RCTs, at a high risk of bias were 3 (11%) for allocation concealment and 21 (75%) for blinding of participants and personnel (online supplemental appendix 8). Ten (36%) RCTs had an unclear or high risk of incomplete outcome data bias and 16 (57%) RCTs had a high potential risk of 'other' bias. Overall risk of bias was comparable in studies with available and unavailable IPD (online supplemental appendix 8).

Overall, IPD were consistent with results from published RCTs (online supplemental appendix 9). The median dropout rate in IPD was 6% (IQR 3%–9%). No detection of publication bias was observed in the comparison-adjusted funnel plot for A1c, but small-study effects were detected in the finding of severe hypoglycaemia pointing towards NPH being better (online supplemental appendix 10).

Network meta-analysis
In total, 27 studies (7394 participants) provided eligible data for the NMA. No evidence for intransitivity was observed in A1c or severe hypoglycaemia outcomes regarding study duration and A1c baseline (online supplemental appendix 11). However, the distribution of sex differed between the comparison NPH once daily versus detemir once daily (mean per cent male: 73%) and the remaining network (mean per cent male: 52%) in A1c. Although the distribution of the year of publication was on average similar across all comparisons in the A1c network, an imbalance was evident in severe hypoglycaemia for the treatment comparison glargine once daily versus NPH once/two times per day that included studies published before 2005 compared with the remaining network. While no inconsistency was detected between direct and indirect evidence for A1c, evidence of inconsistency was found for severe hypoglycaemia (online supplemental appendix 12). Figure 2 shows the network plots for the two outcomes.

Glycosylated haemoglobin (A1c)
The NMA for A1c included 27 RCTs with 8 treatment nodes and 7394 participants, of which 12 RCTs (4943 participants) contributed IPD.

Network of studies with aggregate and fully adjusted treatment effect estimates from IPD
All available treatment options were included in this network. Glargine once daily reduced A1c compared with NPH once daily (MD=−0.31, 95% CI: −0.48 to −0.14) and NPH four times a day (MD=−0.40, 95% CI: −0.76 to −0.04). NPH once daily/two times per day improved A1c compared with NPH four times a day (MD=−0.40, 95% CI: −0.77 to −0.02). Detemir once daily (MD=−0.25, 95% CI: −0.41 to −0.09) and NPH once daily/two times per day (MD=−0.30, 95% CI: −0.50 to −0.11) were superior to NPH once daily (table 2 and online supplemental appendix 13). Glargine once daily and NPH once daily/two times per day achieved an MCID. However, results were imprecise according to PIs only for glargine once daily versus NPH once daily.
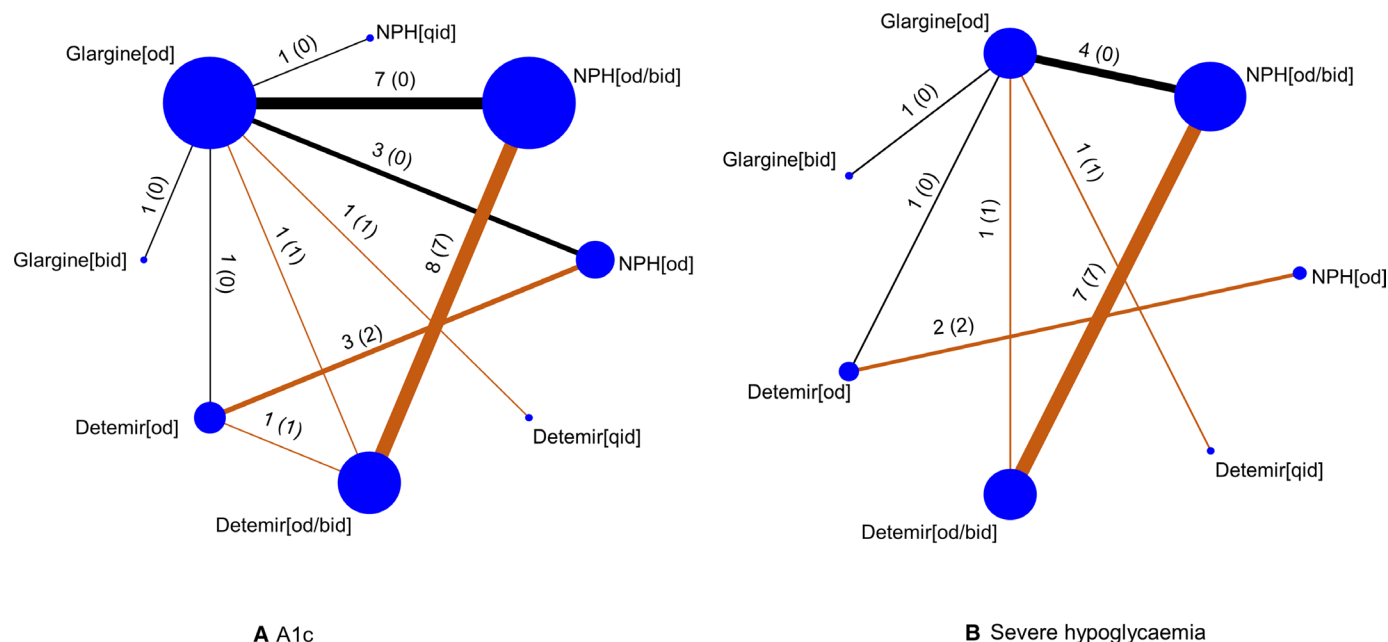
Figure 2 Network diagrams for (A) A1c and (B) severe hypoglycaemia outcomes. Each node and line are weighted according to the number of studies. Numerical values represent the number of studies per treatment comparison overall and with individual patient data (IPD). Orange-coloured edges include at least one study with available IPD, and black-coloured edges include aggregate data only. A1c, glycosylated haemoglobin; bid, two times per day; NPH, neutral protamine Hagedorn; od, once daily; qid, four times a day.

Long-acting analogues were likely superior to intermediate-acting insulin regimens with detemir four times a day (p-score=71%) having the greatest likelihood of being the most effective in improving A1c followed by glargine once daily and detemir once daily/two times per day (p-score=67%, figure 3A).

Network of studies with fully adjusted treatment effect estimates from IPD

Studies in this two-stage NMA compared detemir once daily, once daily/two times per day and four times a day, glargine once daily, and NPH once daily and once daily/two times per day. Detemir once daily ranked best (p-score=76%), followed by detemir once daily/two times per day (p-score=63%; online supplemental appendix 14). However, results were imprecise.

Network of studies with AD

Studies in this NMA compared all available treatments. NPH once daily/two times per day improved A1c compared with NPH once daily (MD=−0.30 95% CI: −0.48 to −0.12) and NPH four times a day (MD=−0.40, 95% CI: −0.76 to −0.04). Although results were associated with an MCID, they were imprecise according to PIs apart from the comparison NPH once daily/two times per day versus NPH once daily. The most effective treatments were most likely detemir once daily/two times per day (p-score=78%) and glargine once daily (p-score=68%).

Additional analyses: network of studies with AD and treatment effect estimates from IPD

The analyses using crude IPD and AD suggested that NPH once daily/two times per day improved A1c compared with NPH once daily (MD=−0.30 95% CI: −0.49 to −0.12) and NPH four times a day (MD=−0.40, 95% CI: −0.76 to −0.04) (online supplemental appendix 14). Results were also associated with an MCID. The most efficacious treatment was likely detemir once daily/two times per day (p-score=71%). Excluding the nodes with insulin regimen four times a day from the network, detemir once daily/two times per day (p-score=65%) and glargine once daily (p-score=65%) ranked best. In contrast to studies with serious overall risk of bias, studies without serious overall risk of bias suggested no difference between NPH once daily/two times per day and NPH four times a day (MD=−0.21 95% CI: −0.67 to 0.25). Adjusting for differences in baseline A1c, sex, RCT duration and age, NPH once daily and four times a day were the least effective treatments. However, the treatment effect for A1c did not significantly change with a unit increase in any of the aforementioned potential effect modifiers.

Additional analyses: network of studies with treatment effect estimates from IPD

Studies in the one-stage NMA of studies with IPD only compared detemir once daily, two times per day, once daily/two times per day and four times a day, glargine once daily, and NPH once daily, two times per day, once daily/two times per day (online supplemental appendix 15). Detemir two times per day ranked best (SUCRA=67%), followed by detemir once daily/two times per day (SUCRA=66%). However, results were imprecise (online supplemental appendix 15). Analyses using IPD only estimated detemir once daily and two times per day as two of the best insulin regimens. This agreed with sensitivity

Table 2 NMA results in A1c and severe hypoglycaemia

Treatment comparison	NMA model	A1c			Severe hypoglycaemia*		
		Mean difference (95% CI)	Heterogeneity (τ^2)	P-score	OR (95% CI)	Heterogeneity (τ^2)	P-score
Detemir (once daily/two times per day) vs NPH (once daily/two times per day)							
	AD+IPD adjusted	−0.01 (−0.11 to 0.10)	0.01	0.67	0.71 (0.49 to 1.04)	0.11	0.42
	AD+IPD crude	−0.01 (−0.12 to 0.10)	0.01	0.71	0.75 (0.53 to 1.05)	0.12	0.39
	AD	−0.03 (−0.13 to 0.07)	0.01	0.78	0.70 (0.47 to 1.05)	0.18	0.49
	IPD adjusted	−0.01 (−0.09 to 0.07)	0.00	0.63	0.77 (0.58 to 1.03)	0.00	0.97
	IPD crude	−0.02 (−0.10 to 0.07)	0.00	0.56	0.79 (0.60 to 1.03)	0.03	0.94
Detemir (once daily) vs NPH (once daily/two times per day)							
	AD+IPD adjusted	0.05 (−0.14 to 0.25)	0.01	0.50	0.30 (0.07 to 1.37)	0.11	0.79
	AD+IPD crude	0.10 (−0.08 to 0.28)	0.01	0.41	0.30 (0.07 to 1.37)	0.12	0.80
	AD	0.10 (−0.07 to 0.28)	0.01	0.40	0.32 (0.06 to 1.63)	0.18	0.78
	IPD adjusted	−0.05 (−0.24 to 0.13)	0.00	0.76	–	–	–
	IPD crude	−0.09 (−0.28 to 0.11)	0.00	0.78	–	–	–
Detemir (four times a day) vs NPH (once daily/two times per day)							
	AD+IPD adjusted	−0.03 (−0.33 to 0.26)	0.01	0.71	0.75 (0.27 to 2.06)	0.11	0.36
	AD+IPD crude	−0.02 (−0.34 to 0.30)	0.01	0.69	0.76 (0.28 to 2.07)	0.12	0.36
	AD	0.01 (−0.28 to 0.30)	0.01	0.64	1.18 (0.39 to 3.59)	0.18	0.18
	IPD adjusted	0.03 (−0.30 to 0.36)	0.00	0.52	2.45 (0.75 to 8.01)	0.00	0.15
	IPD crude	−0.01 (−0.37 to 0.34)	0.00	0.52	1.84 (0.59 to 5.76)	0.03	0.18
Glargine (two times per day) vs NPH (once daily/two times per day)							
	AD+IPD adjusted	0.00 (−0.38 to 0.37)	0.01	0.63	0.11 (0.00 to 2.50)	0.11	0.84
	AD+IPD crude	0.00 (−0.37 to 0.36)	0.01	0.65	0.11 (0.00 to 2.48)	0.12	0.85
	AD	0.00 (−0.37 to 0.36)	0.01	0.65	0.10 (0.00 to 2.32)	0.18	0.87
	IPD adjusted	–	–	–	–	–	–
	IPD crude	–	–	–	–	–	–
Glargine (once daily) vs NPH (once daily/two times per day)							
	AD+IPD adjusted	0.00 (−0.11 to 0.10)	0.01	0.67	0.67 (0.39 to 1.14)	0.11	0.45
	AD+IPD crude	0.00 (−0.11 to 0.10)	0.01	0.68	0.66 (0.39 to 1.12)	0.12	0.47
	AD	0.00 (−0.11 to 0.10)	0.01	0.68	0.70 (0.38 to 1.30)	0.18	0.48
	IPD adjusted	0.06 (−0.23 to 0.34)	0.00	0.41	2.19 (0.77 to 6.25)	0.00	0.25
	IPD crude	0.01 (−0.27 to 0.29)	0.00	0.45	1.60 (0.62 to 4.15)	0.03	0.30
NPH (once daily) vs NPH (once daily/two times per day)							
	AD+IPD adjusted	0.30 (0.11 to 0.50)	0.01	0.11	0.49 (0.10 to 2.50)	0.11	0.51
	AD+IPD crude	0.30 (0.12 to 0.49)	0.01	0.11	0.48 (0.10 to 2.46)	0.12	0.52
	AD	0.30 (0.12 to 0.48)	0.01	0.11	0.54 (0.09 to 3.16)	0.18	0.50
	IPD adjusted	0.18 (−0.07 to 0.42)	0.00	0.12	–	–	–
	IPD crude	0.08 (−0.17 to 0.32)	0.00	0.24	–	–	–
NPH (four times a day) vs NPH (once daily/two times per day)							
	AD+IPD adjusted	0.40 (0.02 to 0.77)	0.01	0.07	–	–	–
	AD+IPD crude	0.40 (0.04 to 0.76)	0.01	0.07	–	–	–
	AD	0.40 (0.04 to 0.76)	0.01	0.07	–	–	–
	IPD adjusted	–	–	–	–	–	–
	IPD crude	–	–	–	–	–	–
NPH (once daily/two times per day) (reference)							

Continued

Table 2 Continued

Treatment comparison	NMA model	A1c			Severe hypoglycaemia*		
		Mean difference (95% CI)	Heterogeneity (τ^2)	P-score	OR (95% CI)	Heterogeneity (τ^2)	P-score
	AD+IPD adjusted	–	0.01	0.64	–	0.11	0.12
	AD+IPD crude	–	0.01	0.67	–	0.12	0.12
	AD	–	0.01	0.66	–	0.18	0.20
	IPD adjusted	–	0.00	0.56	–	0.00	0.63
	IPD crude	–	0.00	0.45	–	0.03	0.58

Two-stage NMA analysis results are presented for (1) AD and fully adjusted results from studies with IPD, (2) AD and crude results from studies with IPD, (3) crude AD, (4) fully adjusted results from studies with IPD, (5) crude results from studies with IPD.
*The consistency assumption did not hold in any of the NMA analyses including AD alone or in combination with IPD.
A1c, glycosylated haemoglobin; AD, aggregate data; IPD, individual patient data; NMA, network meta-analysis; NPH, neutral protamine Hagedorn.

analyses on prior to between-study variance, imputation methods, and crude or fully adjusted IPD. Across all adjusted IPD analyses, A1c baseline was positively and clinically importantly associated with the treatment effect. The multiple imputation by chained equations suggested that detemir once daily/two times per day best improved A1c. However, results were imprecise due to the sparsity of the network.

Heterogeneity across all analyses was low according to the empirical distribution (median 0.03, 95% range: 0.00 to 4.95) by Rhodes *et al.*[30] On average, confidence in NMA results was moderate and ranged between low and high across treatment comparisons in the network (online supplemental appendix 15).

Severe hypoglycaemia

The NMA for severe hypoglycaemia included 17 RCTs with 8 treatment nodes and 6438 participants, of which 10 RCTs (4436 participants) contributed IPD. Four studies included zero events in all arms and were excluded from the analysis.[49–52] Study definitions on severe hypoglycaemia are provided in online supplemental appendix 16. The average time to at least one serious hypoglycaemic event across studies with available IPD ranged between 21 and 272 days (online supplemental appendix 17).
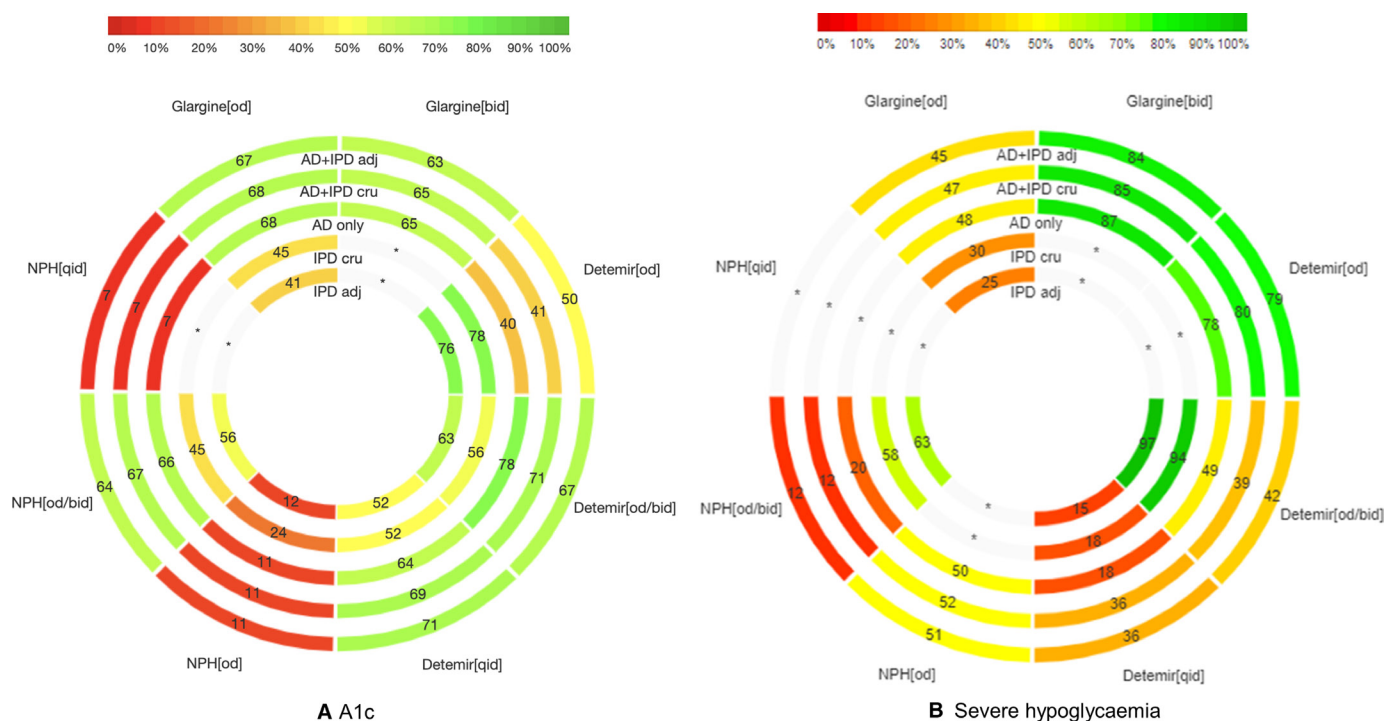

Figure 3 Rank-heat plot of p-scores for (A) A1c and (B) severe hypoglycaemia. Circles from inside out present results for two-stage network meta-analyses including: (1) fully adjusted results from studies with individual patient data (IPD), (2) crude results from studies with IPD, (3) crude aggregate data (AD), (4) AD and crude results from studies with IPD, (5) AD and fully adjusted results from studies with IPD. A1c, glycosylated haemoglobin; bid, two times per day; NPH, neutral protamine Hagedorn; od, once daily; qid, four times a day.

Network of studies with AD and fully adjusted treatment effect estimates from IPD

Studies in this NMA compared all available treatments. Although glargine two times per day (p-score=84%) and detemir once daily (p-score=78%) had the highest ranking score with the least complications regarding severe hypoglycaemia (table 2, figure 3B and online supplemental appendix 13), results were imprecise, and the network of evidence was inconsistent. Thus, these observations should be interpreted with great caution. Estimated ORs for direct and indirect evidence of the comparisons detemir once daily/two times per day versus glargine once daily, and glargine once daily versus NPH once daily/two times per day pointed to the opposite direction (online supplemental appendix 18). These results were explored further in additional analyses (see also online supplemental appendix 14 and 19).

Network of studies with fully adjusted treatment effect estimates from IPD

Studies in this two-stage NMA compared detemir two times per day, once daily/two times per day and four times per day, glargine once daily, and NPH two times per day and once daily/two times per day (online supplemental appendix 19). Detemir once daily/two times per day ranked best among all insulin regimens (SUCRA=97%, online supplemental appendix 14). Although heterogeneity decreased to I^2=0%, results were imprecise and firm conclusions could not be drawn. The network included no loops, and inconsistency could not be assessed.

Network of studies with AD

Studies in this NMA compared all available treatments. Similar to NMA of adjusted IPD and AD, despite glargine two times per day (p-score=87%) and detemir once daily (p-score=78%) had the highest likelihood of causing the least complications for severe hypoglycaemia (online supplemental appendix 14), direct and indirect evidence in the network were inconsistent. Hence, results should be considered with great caution.

Additional analyses: network of studies with AD and treatment effect estimates from IPD

The analyses using crude IPD and AD agreed with the main analysis (adjusted IPD and AD), but different sources of evidence in the network were still inconsistent. Subsequent analyses using adjusted IPD and AD did not explain inconsistency in the evidence network. Only sensitivity analysis accounting for missing data and using AD to apply the informative missingness OR showed no evidence of inconsistency in the network, which may suggest that missing data impact on consistency between direct and indirect evidence. Of the 17 studies with AD, 16 reported the number of dropouts with median dropout rate 3% (IQR 2%–10%) across groups. Heterogeneity was comparable with the main analysis (τ^2=0·14), and glargine two times per day (SUCRA=89%) and detemir once daily (SUCRA=77%) were most likely the insulin regimens with the least complications regarding severe hypoglycaemia. However, results were imprecise.

Additional analyses: network of studies with treatment effect estimates from IPD

Studies in the one-stage NMA of studies with IPD only (crude or fully adjusted) compared detemir two times per day, once daily/two times per day and four times a day, glargine once daily, and NPH two times per day and once daily/two times per day (online supplemental appendix 19). Analyses suggested that detemir once daily/two times per day was the insulin regimen with least complications in severe hypoglycaemia. The network included no loops, and inconsistency could not be assessed. Accounting for missing data and adjusting for potential effect modifiers in the one-stage NMA, we found that the likelihood of experiencing a severe hypoglycaemic event increased with diabetes-related comorbidities (regression coefficient in sensitivity analysis with multiple imputations: 1.03, 1.02–1.03; online supplemental appendix 19). The credibility of claimed effect modifications remains limited.

Heterogeneity across all analyses was moderate compared with the Turner *et al*[29] empirical distribution (median 0.04, 95% range: 0.00 to 1.58). Confidence in the NMA results was very low (online supplemental appendix 15).

DISCUSSION

In this review, we evaluated efficacy and complications from each type of long-acting versus intermediate-acting insulin regimens for patients with T1DM for the outcomes A1c and severe hypoglycaemia using studies with both AD and IPD. Our results showed that long-acting insulin regimens were more efficacious for reducing A1c than intermediate-acting insulins. Among the intermediate-acting insulin regimens, we found that NPH once daily/two times per day performed best. Despite the higher efficacy of the long-acting insulin regimens, of the observed differences only glargine once daily achieved an MCID. Overall, NMA results were imprecise with moderate confidence.

Long-acting insulin analogues were associated with lower severe hypoglycaemia. Patients receiving glargine two times per day were less likely to experience a hypoglycaemic event, followed by detemir once daily and detemir once daily/two times per day. Our results were imprecise, yet our findings showed that among all insulin regimens, the therapy with the most complications regarding severe hypoglycaemia was NPH once daily/two times per day. Adjusting for differences by study or patient characteristics, including sex, RCT duration and age, we found that severe hypoglycaemia occurred less often for patients receiving long-acting versus intermediate-acting insulin regimens. Also, our NMA accounting for missing data showed that the likelihood of severe hypoglycaemic events was associated with diabetes-related comorbidities. However, results on severe hypoglycaemia should

be interpreted with caution due to very low quality of evidence, including network inconsistency, imprecision and potential reporting bias.

To our knowledge, this is the first IPD-NMA of long-acting and intermediate-acting insulin regimens for patients with T1DM. We were able to obtain IPD for 43% of RCTs and 67% of known randomised participants from a single funder. Data sharing was indeed disappointing. We followed the methods guidelines in the Cochrane Handbook,[53] applied the CINeMA tool,[20] and reported in accordance with the PRISMA extensions for NMA and IPD meta-analysis.[15 16] Compared with the findings of our previous systematic review,[1] including IPD allowed us to: (a) increase certainty in the treatment effect estimates; for example, glargine once daily was superior to NPH once daily, and NPH once daily and four times a day were inferior to NPH once daily/two times per day, in regard to A1c; (b) include trials that we previously were unable to include since outcome data were not reported in their publication[54]; (c) explore for treatment-by-covariate interactions that were not reported in the original publications (eg, comorbidities, additional medications); and (d) observe minor differences between published results and reanalysis of IPD (most likely because we adopted the intention-to-treat principle, whereas RCTs excluded some patients from their published analyses). It should be noted that NPH or detemir four times a day is not a label recommendation and should be administered once daily or two times per day; however, in this systematic review, we only report the eligible studies and what they applied.

There are some limitations in this study. First, we were able to include IPD for fewer than half of the eligible RCTs, highlighting potential retrieval bias for IPD. Empirical evidence shows that it is inevitable to obtain only part of the requested IPD from the RCTs included in a systematic review.[21 55–57] Unavailable IPD can be in part of a study dataset (eg, missing information on a specific outcome or participant characteristics) or in a whole study. However, as shown in simulation studies,[58] the use of both IPD and AD in the same model has improved precision in treatment effects and power to detect a true treatment effect. A key advantage of using IPD (over AD alone) is the potential to improve completeness and validity of data in each RCT, and hence reduce bias due to reporting in publication. Second, the available IPD did not allow analyses that could have informed personalisation of medicine, tailoring insulin regimens to the individual's characteristics (ie, lifestyle, diet, general health, motivation, hypoglycaemia awareness status and ability for self-management), as planned in our protocol due to absence of these data.[3–6] To inform guideline recommendations, future RCTs should collect data that will enable tailor efficacy and complications of long-acting and intermediate-acting insulin regimens to these characteristics. Third, the comparison-adjusted funnel plot for severe hypoglycaemia suggested there is an indication for small-study effects pointing to NPH being better, and hence results should be interpreted with caution. Fourth,

the network of evidence for severe hypoglycaemia was inconsistent. The network was only consistent when we accounted for missing data in the analysis, suggesting that attrition bias may explain disagreement between direct and indirect evidence. Other potential reasons for inconsistency may include the presence of small-study effects, and the intransitivity due to the imbalance in the distribution of publication year across treatment comparisons. In particular, the treatment comparison glargine once daily versus NPH once daily/two times per day was informed by studies published before 2005. It should be noted that in 2005, the ICMJE made registration of clinical trials obligatory.[59] Hence, we expect that there are differences in the tactic and quality of studies published before and after 2005. Intransitivity was also observed in A1c regarding sex. Fifth, on average, confidence in NMA findings in A1c was moderate, which was due to the high risk of within-study bias, imprecision and heterogeneity across studies. Confidence in the network of severe hypoglycaemia was very low, because of high risk of within-study and reporting bias, imprecision and incoherence. Sixth, the literature search was conducted 7 years ago, and further eligible studies may have been published. However, obtaining IPD in a timely manner was very challenging (eg, 740 days were required to access IPD from initial inquiry). Seventh, in this review, we included the long-acting insulins glargine and detemir, but we did not identify studies assessing the (ultra)long-acting insulin degludec. However, it should be considered that degludec was only approved in September 2015 by the FDA and in August 2017 by Health Canada, and our literature search was conducted in June 2015. Eighth, we considered studies by De Leeuw et al[60] and Vague et al[61] as two independent studies, while these publications report on the same RCT. However, the contribution of the Vague et al[61] study to the network estimates was on average 1.81% to the A1c treatment effect estimates and 1.27% to the severe hypoglycaemia treatment effect estimates, suggesting that the findings of this study only minimally impacted the NMA findings.[20]

We expect that our findings will be of interest to patients, health professionals and other end-users, such as the American Diabetes Association and Diabetes Canada, the European Association for the Study of Diabetes and other national and international organisations. To optimise healthcare for patients with T1DM, high-quality and well-conducted RCTs measuring patient-important outcomes including glycaemic variability and time-in-range are of immediate need, particularly in low/middle-income countries.[62] Also, sharing of IPD from such future trials and those RCTs already completed is crucial to decrease the uncertainty surrounding our findings and facilitating tailored decision-making. Our study showed that industry-funded studies shared IPD for large RCTs (>200 patients) with patients of poor control of A1c baseline (>8%). IPD retrieval is not yet well established in the field of T1DM. We need to advocate to ensure that scientists have routine access to these data for reanalysis and meta-analysis.

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