Abstract

Objective

To assess the relative efficacy and safety of basal insulin regimens, in adults with type 1 diabetes mellitus (T1D).

Methods

A systematic review and Bayesian network meta-analysis (NMA) of randomised controlled trials (RCTs) comparing two or more basal insulin regimens were conducted. The following basal insulin regimens were included: neutral protamine hagedorn (iNPH) (once (od), twice (bid) and four-times daily (qid)), insulin detemir (iDet) (od) and (bid), insulin glargine 100 IU (iGlarg) (od) and insulin degludec (iDegl) (od). We searched the following databases: Medline-(OVID), Embase-(OVID) and the Cochrane Library (Wiley). Study quality was appraised using Cochrane risk-of-bias checklist for RCTs. Two outcomes (change in haemoglobin A_{1c} (HbA_{1c}) and rate of severe/major hypoglycaemia (SH)) were analysed. Network inconsistency was assessed using Bucher's and Chi-Squared tests.

Results

Thirty studies met the eligibility criteria. Twenty-five were included in the HbA_{1c} network and 16 in the SH network. All studies were of moderate quality. No network inconsistency was evident in the HbA_{1c} network. Of the seven regimens of interest, iDet (bid) had the highest probability of being best [mean change in HbA_{1c} -0.48 (95% Credible Interval (CrI): -0.69 to -0.29)]. In contrast, the SH network demonstrated both considerable uncertainty and significant network inconsistency (Chi-squared test, p=0.003).

Conclusions

Of the specified frequency regimens, iDet (bid) had the highest probability of being the best basal insulin regimen in terms of reduction in HbA_{1c}. Ranking of the regimens in terms of SH rate was highly uncertain and no clear conclusion could be made.

Introduction:

For people with type 1 diabetes mellitus (T1D), basal insulin replacement should provide glucose control between meals and overnight, with minimal risk of hypoglycaemia. Modern insulin replacement therapies aim to replace basal insulin independent of meal-related insulin requirements. (1;2) An insulin that has a long and peakless duration of action is expected to be optimal for basal replacement, with minimal numbers of injections required to provide basal cover that reliably lasts at least 24 hours.(1;2) Reducing the number of injections needed to provide basal cover is desirable, but issues around flexibility, to address situations such as the delayed risk of hypoglycaemia after increased physical exertion or increased alcohol consumption, and the normal diurnal variation in basal insulin requirement, should be accommodated. (1;2)

Current regimens for basal replacement for people with T1D in the UK include human intermediate acting insulins, such as the isophane or Neutral Protamine Hagedorn (iNPH) (human, porcine or bovine), which are still used for reasons of patient preference and because of their robust evidence base and relatively low cost; the insulin analogues detemir (iDet) and glargine (iGlarg), which have flatter 'peakless' insulin action profiles,(1;2) and more recently the very long-acting insulin degludec (iDegl).(3) Each new basal insulin analogue has data to suggest less day to day variability than earlier insulins and more prolonged duration of action,(4;5) with the newest and most expensive basal insulin replacement, iDegl, showing particularly low variation and long duration of action.(3) There is evidence that, at least in some people, neither iNPH nor iDet nor iGlarg provide 24-hour glucose control with a once-daily injection,(6;7) and because of stress laid on flexibility of basal dosing in structured education programmes such as DAFNE,(8) twice-daily basal regimens are increasingly used in clinical practice.

A systematic review (SR) and network meta-analysis (NMA) were undertaken to assess the safety and efficacy of basal insulin regimens.(9) The aim was to inform the National Institute for Health and Care Excellence (NICE) recommendation regarding basal insulin regimen choice for adults with T1D to update the recommendations made in NICE guideline for adults with T1D published in 2004 (CG15) and the technology appraisal (TA) for iGlarg 100 IU (TA53).(10;11)

The latest published SR and NMA of basal insulin regimens did not include trials of iDegl, and included studies in children and pregnant women whose basal insulin requirements can be very

different from non-pregnant adults. (12) For this reason, we have undertaken this SR and NMA, to identify and synthesise all published RCT evidence, in adults only. We focus on two main outcomes: change in HbA_{1c} and rate of severe/major hypoglycaemia (SH). These were considered to be the most critical for people with T1D; where the aim of therapy is to achieve the right balance between tight glycaemic control (by lowering HbA_{1c} to a target level associated with minimal risk of long term complications), whilst avoiding SH events which can be life-threatening. These were also the outcomes that were required for subsequent analysis of cost-effectiveness, reported elsewhere.(13)

Methods

The protocol for the NMA and the associated systematic review was developed and approved by the NICE guideline development group (GDG), a team of experts consisting of diabetologists, nurse and dietitian diabetes educators; patient representatives; a general practitioner; a chemical pathologist and a pharmacist as well as the research technical team. It followed the standard PICO format (specifying **P**opulations, **I**nterventions, **C**omparators and **O**utcomes). The protocol, PICO characteristics, and outcomes of the complete systematic review are reported in detail in the full guideline, and its Appendix M, and summarised below. (9;14) No ethics approval was required for this work.

Search strategy

The search strategy was designed to combine population, intervention and comparator terms using the Boolean operator "AND" then applying a filter to identify randomised controlled trials (RCTs). Terms used for the population included: "diabetes mellitus", "insulin dependent diabetes mellitus"," sudden onset or juvenile or childhood" and insulin depend* or insulin deficien*. Terms used for the interventions and comparator included:" insulin, long-acting"," insulin, isophane", "detemir* or degludec* or glargine*". Details of the search strategy are presented in the supplementary material.

Information sources

JC ran the searches in Medline (OVID), Embase (OVID) and the Cochrane Library (Wiley) using population search terms. For Medline and Embase, an RCT filter was also added (See supplementary material, part I for all search terms and filters). Searches were run up to 28 August 2014 and were

limited to retrieve material published in English. Reference lists of the included studies were searched for additional trials.

Eligibility and exclusion criteria:

To be eligible for inclusion, a study had to satisfy the pre-specified protocol PICO elements. We included RCTs that compared any two or more of the following interventions to each other in a population of adults (defined as ≥18 years) with T1D: insulin NPH once daily (iNPH-od), twice daily (iNPH-bid), four times daily (iNPH-qid), insulin detemir once daily (iDet-od) and twice daily (iDet-bid), insulin glargine (100 IU) once daily (iGlarg-od) and insulin degludec once daily (iDegl-od). These regimens were chosen as they were the regimens used in current clinical practice in the UK at the time of the review. Only UK licensed doses were included. Studies of more than one frequency of administration of the same insulin within the same treatment arm (e.g. iDet-od/bid and iNPH-od/bid) were included to increase the analysis power, though these regimens were not of interest to our research question which aims to identify the optimal insulin in a specified frequency of administration.

Exclusion criteria included studies of pre-mixed insulins, those with follow-up times of less than 4 weeks; as the GDG considered that HbA_{1c} and the occurrence of SH would not be changed in this time; and studies in children or pregnant women. Cross-over trials were also excluded as well as studies with mixed populations (both type 1 and type 2 diabetes),unless data had been reported for the subgroup of T1D patients. Studies comparing only different dosages of the same insulin were excluded, as were studies which used different short-acting insulins in the arms compared within the trials. Literature reviews, posters, letters, editorials, comment articles, unpublished studies, conference abstracts and studies not in English were excluded.

The two outcomes that were considered most critical to people with T1D: glycaemic control (as measured by change in HbA_{1c} (%) from baseline), and SH (as measured by the rate of SH events measured in number of events per person year of follow-up) were included in the analysis. SH was defined as any hypoglycaemic event requiring the assistance of a third party. (14)

Study selection

The titles and abstracts of records retrieved by the searches were sifted for relevance by the second author (ROM), with potentially significant publications obtained in full text. These were assessed

against the inclusion criteria. Studies that met the inclusion criteria were read in full and relevant data were extracted as described below. Owing to practical limitations, study selection and critical appraisal were undertaken by one reviewer only (ROM). Evidence was, however, considered carefully by the GDG for accuracy and completeness.

Data extraction and risk of bias assessment

The following data were extracted from the included studies: study characteristics, sample size, follow-up, interventions and outcomes including number of SH events and change in HbA1c from baseline. The data extracted for the NMA were double-checked for accuracy by DD. Risk of bias was appraised using the Cochrane risk of bias checklist for RCTs (see supplementary data, part II).(15) Outcomes were calculated using the numbers reported by the authors, which was, where possible, on an available case basis. The number of person-years was calculated, if not reported, for each trial arm by dividing the number of SH events by the rate per person year or else approximated by the mean follow-up time multiplied by the sample size. Studies reporting 0 events for the SH outcome in both of the treatment arms were excluded from the analysis, as they do not contribute information to the network.

Data synthesis and analysis

Direct meta-analyses were conducted in Review Manager software (RevMan) version 5.3 (*available at http://tech.cochrane.org/revman).* A random effects (RE) model was applied to all comparisons and for both outcomes, since this was the model that had a better fit in the NMA (see explanation below). Additionally, it took account of unexplained heterogeneity between trials. A Bayesian NMA was conducted to simultaneously compare these multiple treatments while preserving randomisation. NMAs allow for comparisons between interventions that have not been compared head-to-head in RCTs, and offer additional precision by 'borrowing strength' from indirect evidence. (16) The analysis was performed using the software WinBUGS version 1.4.3. iNPH (bid) was used as the network comparator, as it is still commonly used and was in line with the original NICE guideline recommendation.

The methodology recommended by NICE Decision Support Unit (DSU) in its technical support document TSD2 was used. (16) A generalised linear model with a normal likelihood and identity link

function was used for the HbA_{1c} network, with parameters estimated by Markov-chain Monte-Carlo (MCMC) simulation. For each parameter, the evidence distribution is weighted by a distribution of prior beliefs. A non-informative prior distribution was used to maximise the weighting given to the data. The priors for the differences in HbA_{1c} were normally distributed with a mean of zero and standard deviation of 100. A mean change in HbA_{1c} of -0.32% (95% CI: -0.49%, -0.15%), for iNPH (bid) was used as the baseline treatment effect. This was calculated from a single-arm, meta-analysis of the seven studies that included this regimen(17-23) using RE model (see supplementary material, part III).

To account for the different follow-up times when modelling SH rate, an underlying Poisson process with a constant event rate was assumed, and a log-link function used to model the event rate. A baseline SH event rate of 0.35 events per person-year (95% CrI: 0.11 to 0.95) was used. This was calculated from a single-arm Bayesian meta-analysis of the iNPH (bid) trials,(17-20;22-24) using a RE model.

For both analyses, a series of 100,000 burn-in simulations were run to allow convergence and then a further 100,000 simulations were run to produce the outputs. Convergence was assessed by examining the history, kernel density plots, and Brooks-Gelman Rubin plots. Goodness of fit of the model was tested by calculating the residual deviance. Analyses were attempted both as fixed effect (FE) and random effects (RE) models and the Deviance Information Criterion (DIC) compared. A lower DIC indicated better model fit, with a difference of 3 to 5 considered important.

Bucher's test and Chi square test for inconsistency (an extension of the Bucher's method to networks with multiple loops),(25) were used to assess whether inconsistency existed between direct and indirect evidence in the HbA_{1c} and SH networks; respectively.

Results were presented as the effect estimates (expressed as the median of the posterior distribution for the mean change) and 95% credible intervals (CrIs). Interventions were ranked according to their effect sizes in each simulation. For each intervention, we report the median rank and the 95% CrIs for the rank.

The following sensitivity analyses were also attempted: i-excluding studies with performance and detection bias due to inadequate blinding, ii- excluding studies with selection bias (due to inadequate

allocation concealment) and those with attrition bias, iii- using half-normal prior distribution for between-study heterogeneity (σ ~ Half-Normal(0,0.322), instead of vague priors, and (iv) testing the impact of the treatment effect estimate from the largest study on the pooled treatment effect.

Results

The search retrieved 1109 records. Additionally, we included 4 studies from the NICE technology appraisal 53 (TA53) that were conducted in people with T1D (See Supplementary material, part I). (26-29)

Twenty-nine studies, published in 31 papers,(5;7;17-24;26-45;45;46) met the inclusion criteria. All except one, (44) which did not report change in HbA_{1c} and reported no SH in either arm, were considered suitable for inclusion in the NMA. The characteristics of these studies are summarised in Table 1. The network diagrams and the extracted data for the two outcomes (change in HbA_{1c}, and SH events) are included in the supplementary material, parts III and IV.

For the HbA_{1c} network, 25 studies, published in 27 papers, (5;7;17-23;26-43) were included (see Table 1). . The risk of bias assessment for these studies ranged from low to high risk of bias. Three, (24;45;45;46) were excluded because they did not report the change in HbA_{1c}, or its standard deviation, for the relevant comparison or it was not possible to calculate these from the data.

From the 25 studies included in the HbA_{1c} network, 27 different comparisons were generated (these are outlined in Table 1 and described in detail in the full guideline (13)), as two studies had multiple comparisons. One study [published in two papers (BIRKELAND 2011(31) and HOME 2012(32))] was a 3-arm trial assessing two different doses of iDeg (od) versus iGlarg (od); the second study, Heller 2009,(43) conducted a subgroup analysis of different administration frequencies of insulin treatments.

Insert table 1 here

For the SH network, 16 studies,(17-20;22-24;28;29;31;33-35;40;42;43;45;45;46) of eight interventions, were included. Twelve of the original 29 studies retrieved were excluded because they either did not report SH as an outcome, did not report the number of SH events or its rate, or reported zero SH events in both arms of the trial. The 16 studies, with serious to very serious risk of bias, generated 16 comparisons (outlined in Table 1 and described in detail in the full guideline (13)). iNPH (qid) could not be included as an intervention in this network, since both of the studies relating to this regimen reported no SH events in both arms.

All of the studies were considered as being at moderate or high risk of bias (see Supplementary material, part II: Cochrane risk of bias summary table for details). The main contributing factors were allocation concealment and lack of blinding, which was often not possible for studies involving iNPH since the formulation is cloudy in appearance.

Change in HbA_{1c}

Both the NMA and the direct meta-analysis results are presented in Figure 1. The direct meta-analysis results (presented in the unshaded area in Figure 1) showed that efficacy as assessed by reduction in HbA_{1c} favoured iDet (bid) over the reference treatment, iNPH (bid) (-0.16; 95% CI:-0.27 to -0.05). The comparison of the other treatments with iNPH (bid) crossed the line of no effect and no firm conclusion could be made. iNPH (qid) had significantly lower efficacy compared to iGlarg (od) (0.40; 95% CI: 0.36-0.44). No other statistically significant differences were identified. The forest plots for these pairwise comparisons are presented in the Supplementary material, part III.

The RE model had a better fit, (DIC of -91.75 compared with -83.77 for the FE model) and a total residual deviance of 49.62, which corresponded well to the total number of trial arms, 52. The between study heterogeneity in the RE analysis was 0.09 (95% CrI: 0.03 to 0.17). Table 2 summarises the results of this analysis.

Insert table 2 here

The results show that iDet (bid) was significantly more effective than iNPH (bid) in reducing HbA_{1c} (see Table 2 and the grey area in Figure 1). It had a tight 95% CrI around the mean, indicating a precise estimate of effect. iNPH (qid) was also significantly worse compared to all other insulin

regimens. This difference was clinically significant. No other statistically significant or clinically important differences were evident in this network.

iDet (od/bid) was ranked first, with a tight CrI around the mean, followed by iDet (bid), iGlarg (od), iDet (od), iNPH (od/bid), iDeg (od), iNPH (bid), iNPH (od) and iNPH (qid) in that order (see supplementary material, part V for the diagram showing the relative ranking for all regimens). CrI around the median rank were wide for all regimens, except for iNPH (qid) which was significantly less effective when compared with iNPH (bid) and all other insulin regimens in the network. Significant inconsistency was not identified between the direct and NMA results for any comparison. All the differences from the NMA lie within the 95% CIs from the direct comparison of the same treatments (Figure 1). Bucher's test did not show significant inconsistency in the network (p=0.64).

Insert Figure 1 here

Severe/major hypoglycaemia (SH)

The direct meta-analysis results (shaded area in Figure 2) did not show any statistically significant or clinically important differences in SH among the insulin regimens compared in head-to-head clinical trials. The forest plots for these pairwise comparisons are presented in the supplementary material, part VI.

The RE model had a better fit, with a DIC of 225.9, compared to 257.32 for the FE model, and a total residual deviance of 31.4 which corresponds well to the total number of trial arms, 32. The between study heterogeneity was 0.56 (95% CrI: 0.31 to 1.1), which was considered to indicate a moderate degree of heterogeneity.

Table 3 presents the SH event rate and the hazard ratio (HR) for each regimen compared to iNPH (bid) from the NMA. HRs for every possible pair-wise comparison are presented in Figure 2 alongside the rate ratios (RRs) obtained from the direct, pairwise MA.

Insert Table 3 here

The NMA results (grey area in Figure 2) showed no statistically significant or clinically important differences in SH rate between the regimens. All the comparisons to iNPH (bid) (except insulin iDet

[bid]) have a large uncertainty, because the one study connecting iNPH (bid) to the other treatments in the network had very few events

Insert Figure 2 here

On the basis of the median rank, none of the regimens ranked first. iDet (od/bid) intervention is ranked second. iDet (bid), iGlarg (od), iNPH (bid) and iDeg (od) all have median rank of four followed by iNPH (od) and iDet (od) both in rank five, followed by iNPH (od/bid) in rank six. All interventions had very wide CrIs around their rank (see supplementary material, part VI, for the ranking diagram).

The Chi-squared test for network inconsistency was significant (p=0.003). This was explored through a sensitivity analysis excluding studies of iNPH (od/bid) and insulin detemir (once or twice daily) from the analysis (Bartley 2008,(34) Hermansen 2001,(45) Heller 2009,(43) Ratner 2000,(29) and Raskin 2000(28)), as these two regimens have mixed frequencies of administration and so were heterogeneous by definition.

This sensitivity analysis was run both as FE and RE models. The RE model had a better fit, with a DIC of 225.73 compared to 257.81 for the FE model. The RE model had a total residual deviance of 31.3. This corresponded well to the total number of trial arms, 32. The between-study heterogeneity was 0.6 (95% CrI: 0.31 to 1.3), indicating moderate heterogeneity. It was not possible to test for inconsistency in the resultant network as it did not include any closed loops. Table 4 presents the main results from this sensitivity analysis, showing SH event rates for each insulin regimen and HRs when compared to iNPH (bid).

Insert Table 4 here

All the differences in the network remained non-significant with very wide CrIs around the mean effect estimates and mean rank. The network diagram, ranking and results of the sensitivity analysis are included in the Supplementary material, part VII.

It was not possible to perform sensitivity analysis (i) as all studies had performance and detection bias. For sensitivity analysis (ii), we excluded two of the three studies that had inadequate allocation concealment, as the Chatterjee 2007(24) study was the only study connecting iNPH (bid) to the severe/major hypo network. The results of this sensitivity analysis of the SH network were consistent

with the base case analysis in terms of the best and worst interventions, however, iNPH (od) and iNPH (bid) switched ranks. The CrIs around the median rank, however; remained very wide and completely overlapping suggesting no clear differences between the insulin regimens in relation to this outcome. For the HbA_{1c} network, none of the sensitivity analyses resulted in any change of ranking.

In sensitivity analysis (iii), we tested the impact of changing the priors used for the between-study heterogeneity. The results showed a change in the ranking of the insulin regimens in the SH glycaemia network, where iGlarg (od) became second followed by iDet (bid). iDegl (od), iNPH (bid), iNPH (od). In the HbA_{1c} network, the rank of iDet (bid) changed from third to first [mean change in HbA_{1c} : -0.47 (-0.77 to -0.16)], which further supported its superiority in terms of glycaemic control. Sensitivity analysis (iv) was not possible to undertake in the SH network; as the largest study (Russell Jones 2004(35)) was the only one connecting iDet (od) to the network. In the HbA_{1c} network, this analysis resulted in switching of ranks between iNPH (od) and iNPH (bid).

Discussion

This review and NMA included a total of 28 studies, of seven different basal insulin regimens directly relevant to clinical practice. The studies formed two networks of evidence each for a different outcome (change in HbA_{1c} and number of SH events). The first outcome network (change in HbA_{1c}) included 25 trials in 8542 patients. The analysis showed that only iDet (bid) and iNPH (qid) were significantly different from iNPH (bid), our reference treatment, and only iDet (bid) showed superiority. The second network, for SH events, included 16 trials in 6266 patients. Although none of the comparisons in this network showed a statistically significant difference in the rate of SH and there were no significant differences in the rank of iDet (bid), iGlarg (od), iNPH (bid) and iDegl (od). iDet (bid) came directly after iDet (od/bid) in terms of median event rate. Excluding the five studies of the mixed-frequency regimens (leaving 11 studies in 4062 patients) to address inconsistency in the network; iDet (bid) and iNPH (od) had similar median rank, followed by all other regimens. Combining the results of the two NMAs, we were therefore able to conclude that the evidence supported iDet (bid) as the best option among the basal insulin regimens of interest in this analysis.

Compared to earlier systematic reviews on the topic, (47-49) our review includes the most comprehensive set of RCTs of basal insulin regimens, published up to and including August 2014. It

is the only review to include trials of iDegl [od]. It took into account both the type of insulin and its frequency of administration, one of only two reviews to do so (the other being Tricco et al. 2014(12)). Our results are in line with previous systematic reviews with regards to the superiority of the long-acting insulins, detemir and glargine, compared to intermediate acting insulin NPH. They are also in line with that of Tricco's review in relation to the SH outcome, where iDet (od/bid) is ranked first, (12) but is different in relation to the HbA_{1c} outcome, where our analysis shows that only iDet (bid) achieves a reduction in HbA_{1c} superior to that achieved by our network comparator, iNPH (bid).

In contrast to Tricco's review, we did not include trials in children and pregnant women or observational studies and we included trials of iDegl (od). Our model for the analysis of SH events takes into account the fact that these are repeated events that can occur more than once for the same patient, using Poisson likelihood. This was not the case with the model used by Tricco et al;(12) which utilised a binomial likelihood. Additionally, we discovered an error in the reporting of the number of SH events in the iNPH arm of one of the RCTs. (28) This error will have affected the results of Tricco's analysis and all previous meta-analyses that used the proportion of patients with one or more SH events as their outcome measure and reported treatment effect in terms of odds ratios (OR), as it leads to an erroneous conclusion regarding the effect size of iGlarg (od) relative iNPH (od/bid). The corresponding author of this RCT has been contacted and informed about this error. This error would not affect our analysis, hence, our analysis is more accurate in relation to the SH outcome than previously published meta-analyses of basal insulin regimens' effect on SH in T1D. (47-49)

The results of the NMA show a trend towards better glycaemic control and better ranking for iDet (bid) compared to the once-daily regimen, iDet (od). This is in line with current evidence that shows that, at least in some people, neither iNPH nor iDet nor iGlarg provides 24-hour glucose control with a once-daily injection.(6;7) It is possible that periods of basal insulin deficiency, masked clinically by cover from meal-related insulin replacement, contributes to a lesser efficacy of glucose lowering with the once-daily basal regimens. While this disadvantage may be reduced with iDegl and the recently released iGlarg U300, modern insulin replacement regimens also lay stress on flexibility of basal dosing so that users can adjust basal insulin doses acutely to accommodate lifestyle issues such as intermittent exercise or alcohol consumption. Such dose adjustment is taught in structured education programmes for teaching adults with T1D flexible intensified insulin therapy such as the German

STTP programme and the English language equivalent, DAFNE, or Dose Adjustment for Normal Eating. (8;50) In the UK's national DAFNE programme, only twice-daily basal insulin regimens are associated with improvement in HbA_{1c}.(51)

A perceived disadvantage of a twice daily basal insulin regimen is the additional injection. However, users, perhaps particularly users with T1D, may consider this less important than their health care professionals and anecdotally, many find the advantages of stable 24-hour cover and flexibility outweigh the disadvantage. This was confirmed by the two patient members in the committee.

A limitation of this NMA is the small number of studies per comparison, leading to a sparse network. This meant that the analysis had low statistical power to detect the differences between the included treatments. This was particularly true in the SH network. Additionally, the high risk of bias in many of the included studies, especially those using iNPH as a comparator was another limitation. iNPH has a different appearance from analogue basal insulins and so blinding is not possible. Despite our efforts to ensure homogeneity in the included trial characteristics in terms of mean body weight, duration of diabetes and baseline HbA_{1c} (which are known to be important effect modifiers), there was still residual heterogeneity. The wide CrIs around the mean effect estimates and mean rank for some of the HbA_{1c} data and all the SH data also indicate high levels of uncertainty regarding the ranking of the insulin regimens in relation to their impact on SH. Additionally, the fact that iDet (od/bid) ranked higher than either of its component regimens (bid and od) despite iDet (bid) being superior to iDet (od), when the expected ranking of such mixed regimen would be somewhere in between the two, might also indicate residual confounding or imprecision in the analysis.

However, the range of sensitivity analyses conducted showed that the results of the HbA_{1c} NMA were robust to changes in included studies and the prior distributions used. On the contrary, some of the sensitivity analyses resulted in changes in the results of the SH NMA; particularly the relative ranking on iNPH (od) and iNPH (bid).

The NMA provides a hierarchy of the included regimens in terms of their effectiveness and safety separately. Given the difference in the ranking of the included regimens in relation to the main outcomes, it would not be possible to draw a conclusion regarding the optimal basal insulin regimen based solely the results of this review. It is also important to consider their cost effectiveness.

Future research should focus on assessing the relative efficacy of the different basal insulin regimens in large multicentre clinical trial with long follow-up to allow for direct, head-to-head comparison. Analysis of the cost-effectiveness of these regimens from other countries' and health systems' perspectives are also warranted to ensure that decisions made regarding reimbursement of these insulin regimens is based on thorough assessment of both effectiveness and cost-effectiveness.

Conclusion

This SR and NMA of RCTs of existing basal insulin regimens in the UK provides a, coherent set of relative treatment effects which could be used to inform cost-effectiveness analyses. The results show the likely superiority of insulin detemir in relation to glycaemic control, with the twice daily regimen achieving better results compared to the once daily regimen.

Author contributions

DD, ROM, DW, JC, BH and SAA designed the study. JC conducted the database searches. ROM sifted the studies, undertook the initial inclusion/exclusion and extracted the data. DD undertook quality assurance of data extraction. DD and DW and ROM analysed the data. DD drafted the first draft of the manuscript. All authors contributed to the interpretation of the results, commented on the paper drafts and approved the final manuscript.

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