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REVIEW ARTICLE

The Evidence Base for Diabetes Technology: Appropriate and Inappropriate Meta-Analysis

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Abstract

When we are interested in making decisions about best use, comparative therapeutic efficacy, or cost-effectiveness of diabetes technologies such as insulin pump therapy [continuous subcutaneous insulin infusion (CSII)] or continuous glucose monitoring, meta-analysis for the purpose of literature summary is inappropriate and may be misleading. Instead, "decision-making meta-analysis" is more appropriate and should involve either preselection of trials based on intended use [e.g., elevated baseline hemoglobin A1c or hypoglycemia rate for trials of multiple daily injections (MDI) versus CSII] or metaregression of summary effect sizes in different trials against potential effect-modifying covariates such as baseline risk, or models of the covariates that determine effect size using individual patient data. Appropriate meta-analysis should also only include trials that are of sufficient duration to accurately measure outcomes such as severe hypoglycemia, and they should not use obsolete technology that is of proven inferiority to current technology. The use of appropriate decision-making meta-analysis is illustrated by the change in the rate ratio for severe hypoglycemia in randomized controlled trials of MDI versus CSII in type 1 diabetes from 1.56 (95% confidence interval 0.96–2.55; $p = .074$) for literature-summary meta-analysis to 2.0 (1.08–3.69; $p = .027$) for decision-making meta-analysis of all patients and 3.91 (1.35–11.36; $p = .01$) for trials in children.

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Introduction

Appropriate use of medical technology involves an assessment of affordability, safety, patient acceptability, ethical implications, and clinical effectiveness in comparison with an established treatment. When considering the evidence base for therapeutic effectiveness, meta-analysis has been the most influential methodology in recent years, with data from randomized controlled trials (RCTs) usually preferred over observational studies.[1] Two of the most important and relatively new technologies in diabetes management that deserve thorough assessment of clinical and cost effectiveness are insulin pump therapy [continuous subcutaneous insulin infusion (CSII)] and continuous glucose monitoring (CGM); both are relatively costly and may, perhaps, be better used in some patients than others.

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Abbreviations: (CGM) continuous glucose monitoring, (CSII) continuous subcutaneous insulin infusion, (HbA1c) hemoglobin A1c, (MDI) multiple daily injections, (NICE) National Institute for Health and Care Excellence, (RCT) randomized controlled trial, (RR) rate ratio, (SMBG) self-monitoring of blood glucose

Keywords: continuous glucose monitoring, continuous subcutaneous insulin infusion, decision making, diabetes mellitus, diabetes technology, insulin pump therapy, meta-analysis

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Several meta-analyses have been reported for CSII[2–10] and CGM,[10–15] which, particularly in the case of CSII, have been used in cost-effectiveness studies and as a major part of the evidence base for some national guidelines. For example, the U.K. National Institute for Health and Care Excellence (NICE) considered, on the basis of evidence up to 2008, that CSII in type 1 diabetes is associated with a reduction in severe hypoglycemia and hemoglobin A1c (HbA1c) compared with multiple daily injections (MDI) and that insulin pump therapy should be an appropriate treatment option for adults and children ≥12 years of age with type 1 diabetes when attempts to achieve target HbA1c levels with MDI have resulted in disabling hypoglycemia or when HbA1c levels have remained ≥8.5% (69 mmol/mol) on MDI despite a high level of diabetes care; NICE recommends insulin pump therapy for children <12 years when (in addition to the adult criteria) MDI is considered impractical or inappropriate.[16]

However, some recent meta-analyses of RCTs comparing glycemic outcomes during MDI versus insulin pump therapy have reached conclusions that might lead practitioners now to question the value of insulin pump therapy and guidelines such as those of NICE. For example, Fatourechi and coauthors,[4] in a meta-analysis of 15 RCTs in type 1 diabetes, found no significant difference in severe hypoglycemia rates on MDI versus CSII. Yeh and coauthors,[10] in a synthesis of data from 33 studies, concluded that "MDI and CSII showed similar effects on HbA1c levels and severe hypoglycemia in adults and children." What are the likely causes of this discrepancy in evidence interpretation from meta-analyses, and are some meta-analyses more appropriate than others for making decisions about clinical and cost effectiveness?

The purpose of this article is to argue the case that meta-analysis using mainly summary data from all or nearly all published RCTs to provide a synthesis of the literature on the effectiveness of diabetes technologies such as CSII or CGM can be misleading when deciding on the best and most cost-effective use of these technologies.

The Problems with Meta-Analysis

In conventional meta-analysis, summary outcome measures [e.g., the mean difference in HbA1c or a rate ratio (RR) for severe hypoglycemia for MDI versus CSII or for self-monitoring of blood glucose (SMBG) versus CGM] are extracted from each of a number of independent trials (usually from the published article) and then combined using statistical procedures involving a weighted average, where large trials have more influence. This enables a calculation of an overall effect size representing all the studies.

The general problems and misunderstandings with meta-analysis have been discussed.[17,18] However, a particular caution that is underemphasized is that meta-analysis can be used for two main purposes that differ in methodology and interpretation: one purpose is to summarize the literature on a subject (e.g., How many RCTs have compared MDI versus CSII, and what is the average HbA1c difference found in these trials?), and the other is to make therapeutic and economic decisions (e.g., Which, if any, diabetes patients are most likely to benefit from CSII or CGM, and are these therapies a cost-effective use of resources?).[19] Literature-summary meta-analysis rarely accomplishes the second aim.[19]

In a technical support document,[20] the NICE Decision Support Unit advises that when evidence synthesis is intended for decision making (e.g. decisions on cost effectiveness or comparative treatment efficacy), rather than for summary of the literature, the trial inclusion criteria for meta-analysis should be restricted to a specific target population with relatively narrow definitions associated with the intended use of the treatment, such as a point in disease progression, a level of disease severity, the fact of previous treatment failure, and so on. Alternatively, meta-regression or individual patient data meta-analysis should be used to relate treatment effects to patient characteristics that might be potential effect-size modifiers, such as age, disease duration, or baseline risk.

There are several excellent guides available to the best conduct of meta-analysis and systematic reviews,[21,22] which include advice on trial selection and exploring between-study heterogeneity. However, in spite of this guidance, most meta-analyses of diabetes technologies have been a summary of the literature and have often focused on trials and patient populations that I argue are inappropriate for clinical and economic decision making.

The Problem of Meta-Analysis of Diabetes Technologies

Many people with type 1 diabetes can achieve satisfactory control on MDI; insulin pump therapy used on clinical grounds, as opposed to patient preference, is intended for those who do not.[16,23] However, RCTs of insulin pump therapy versus MDI have usually been conducted in volunteers with type 1 diabetes without specific clinical problems and not in those with persistent poor control on MDI. It is known from individual patient data[24,25] and from summary data from RCTs[14] and observational studies[14] that the greatest effect of insulin pump therapy in improving HbA1c or reducing severe hypoglycemia is in those patients with the highest baseline HbA1c or hypoglycemia frequency. People with type 1 diabetes already well controlled on MDI may not improve further by switching to insulin pump therapy.[23]

Thus, in the context of diabetes and CSII, trials need to be preselected for meta-analysis where the study patient characteristics are approximate to those who are intended for CSII—type 1 diabetes patients with an elevated HbA1c or frequent and disabling episodes of severe hypoglycemia during MDI (not trials that may include subjects with all or any degree of hyperglycemia or hypoglycemia). Alternatively, regression should be performed of glycemic outcomes on MDI versus CSII against baseline HbA1c or baseline severe hypoglycemia frequency using Bayesian or other statistical methods to avoid regression to the mean.[3,19] This would involve metaregression of summary data[3] or deriving regression models of the determinants of effect size using individual patient data. It is also important only to include studies of sufficient duration, as neither hypoglycemia rate nor HbA1c can be accurately assessed in short-duration trials—for severe hypoglycemia, trials with ≥6 months' duration (or possibly ≥4 months when the baseline rate is high) are recommended.

In meta-analyses of CSII versus MDI,[4,9,10] many of the studies selected had variously a baseline HbA1c less than the NICE cutoff of 8.5% (69 mmol/mol; e.g., References 26–29) or even the substantially lower baseline of <8% (64 mmol/mol; e.g., References 30–34), where little change in HbA1c would be expected on switching to CSII. Several selected studies specifically excluded patients with severe hypoglycemia at entry (e.g., References 31, 33, and 34) or excluded those with hypoglycemia unawareness who were therefore unlikely to have frequent hypoglycemia (e.g., References 29 and 35). Many studies selected were of <6 months' duration (e.g., References 29, 30, 32, 33, and 35), where an accurate assessment of hypoglycemia frequency was unlikely.

To illustrate the difference between meta-analysis for literature summary rather than decision making, consider the meta-analysis forest plot in **Figure 1**. Here I have performed a conventional random-effects meta-analysis of the summary data for the severe hypoglycemia RR (severe hypoglycemia rate measured as episodes/100 patient-years on MDI ÷ rate on CSII) for the 12 RCTs of adequate trial duration[26,27,29,31,36–43] cited in several published meta-analyses of MDI versus CSII[3–5,10] (details of sample size, trial duration, patient characteristics, and so on can be found in the original studies and in the published meta-analyses). The RR for the severe hypoglycemia frequency on MDI versus CSII does not reach statistical significance for these 12 studies [RR 1.56 (95% confidence interval 0.96–2.55); $p = .074$].

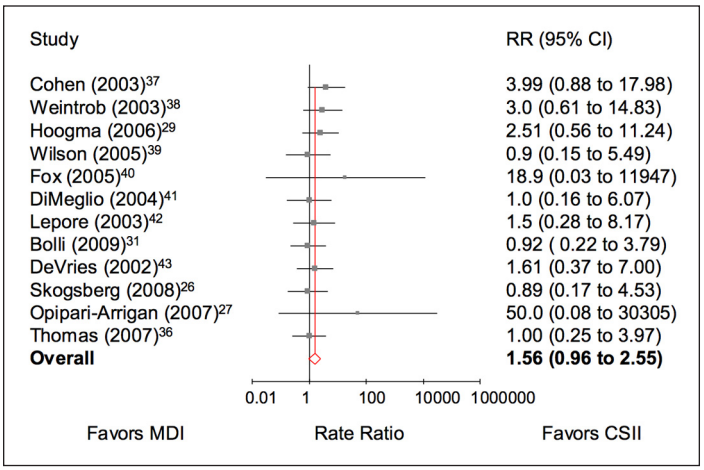

Figure 1. Conventional literature-summary random-effects meta-analysis of severe hypoglycemia RRs on MDI versus CSII. Data were extracted from summary hypoglycemia rates in 12 published RCTs where trial duration was ≥4 months. CI, confidence interval.

Now consider **Figure 2**, where I present a L'Abbé plot of severe hypoglycemia rates on CSII versus severe hypoglycemia rates on MDI for these 12 RCTs. This is a graphic procedure for examining heterogeneity between trials;[44] if there is no difference between two treatments for a given trial, the points will lie on the line of equivalence (RR = 1). Note that for these 12 RCTs, 7 of 12 points are below the line of equivalence, indicating less hypoglycemia on CSII than MDI, with a general tendency for studies with a larger baseline risk (high frequency of hypoglycemia

on MDI) to have the greatest treatment effect. Those studies with a baseline severe hypoglycemia rate of less than approximately 18–20 episodes/100 patient-years show no or minimal change with CSII versus MDI. Trial selection for meta-analysis according the groups likely to benefit should, of course, be predetermined and based on clinical guidelines or other evidence and not based on a *post hoc* analysis of heterogeneity.[45] Though NICE does not give an exact definition of disabling hypoglycemia,[16] the severe hypoglycemia frequency in trials of MDI-treated patients (e.g. glargine) with type 1 diabetes selected for not having disabling hypoglycemia is approximately 16–20 episodes/100 patient-years,[46] so excluding trials for decision-making meta-analysis where the severe hypoglycemia rate is less than approximately 16–18 episodes/100 patient-years is justifiable.

In **Figure 3**, a forest plot is shown where I have performed a repeat meta-analysis using the RCTs from **Figure 1**, but where trials with a low frequency of severe hypoglycemia (<18 episodes/100 patient-years) at baseline are excluded (i.e., including only patients with disabling hypoglycemia who would be eligible for CSII under NICE guidelines). Here, the RR is increased to 2.00 (1.08–3.69; p = .027).

It is important to note that the point here is not to calculate a definitive effect size for hypoglycemia RR on MDI versus CSII, if only because standard errors extracted from trial data can often only be estimated, but that *using the same meta-analysis methodology*, the RR can vary enormously according to trial selection.

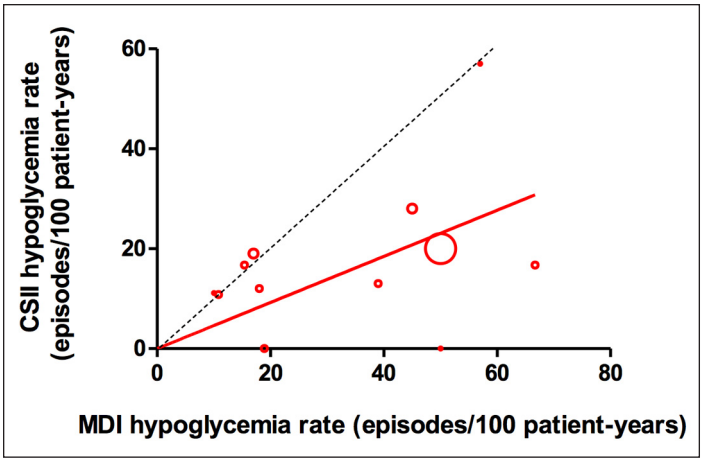

Figure 2. L'Abbé plot of severe hypoglycemia rates on MDI versus CSII. Data were extracted from the RCTs used in **Figure 1**. Circle diameters are proportional to study number. The dotted line is line of equivalence where RR = 1.

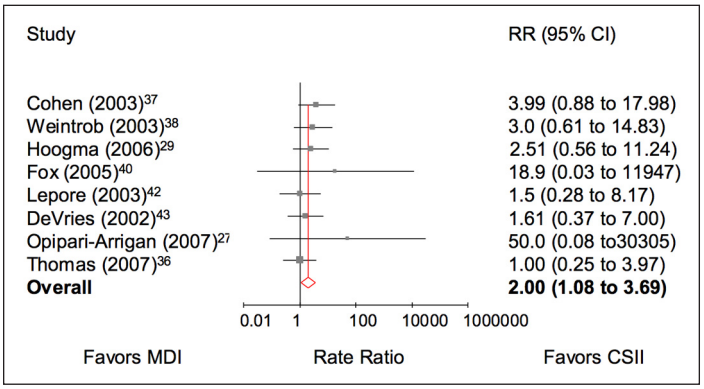

Figure 3. Decision-making random-effects meta-analysis of severe hypoglycemia RRs on MDI versus CSII. Only RCTs where the baseline population (MDI) rate of severe hypoglycemia was elevated (>18 episodes/100 patient-years) were included. CI, confidence interval.

Randomized Controlled Trials versus Observational Studies

Although observational studies are at greater risk of bias, valuable supplementary information on effectiveness not available from RCTs can be obtained from these groups because they are often larger, studied over a longer time, and more representative of those for whom insulin pump therapy is intended.[3,16] Meta-analysis that does not include observational trials as well as RCTs may capture only part of the information available on effectiveness in target groups. In a meta-analysis that combined RCTs and observational studies comparing HbA1c and severe hypoglycemia frequency, which was restricted to trials with high baseline hypoglycemia frequency, with ≥6 months of trial duration that were reported after 1996 and using only analog short-acting insulin, we performed a meta-regression of effect size against baseline risk.[3] This showed that, whereas the mean difference in HbA1c was approximately zero at a baseline HbA1c of 7% (53 mmol/mol), it was 1.5% (16 mmol/mol) at an HbA1c baseline of 9.5–10% (80–86 mmol/mol). Equally, the mean severe hypoglycemia RR approaches 1 at population rates of approximately 10 episodes/100 patient-years but is 10–20 when the baseline rate is >100 episodes/100 patient-years.

Whereas the median (interquartile range) of the severe hypoglycemia frequency of the 12 RCTs in **Figure 1** is 29 (16–50) episodes/100 patient-years, the median hypoglycemia frequency of the observational studies was 97 (76–251) episodes/100 patient-years.[3] Though the latter trials were, of course, selected for having an MDI hypoglycemia rate ≥10 episodes/100 patient-years at baseline, this comparison highlights the low frequency of hypoglycemia in

published RCTs and underlines the fact that observational studies arguably give more information for the purpose of decision making about the response to treatment in the type of patient that would be considered for CSII in routine clinical practice (high HbA1c and/or disabling hypoglycemia on MDI).

Meta-Analysis of Multiple Daily Injections versus Continuous Subcutaneous Insulin Infusion in Children

One should note that children generally have a shorter duration of diabetes than adults and therefore a lower baseline level of severe hypoglycemia (hypoglycemia rates increase with diabetes duration[47]); the mean hypoglycemia-reducing effect of insulin pump versus MDI might therefore be somewhat less in children than adults if trials of short diabetes duration are included.[3] One must be careful not to conclude from this that children cannot achieve a substantial improvement in hypoglycemia frequency and quality of life by changing to insulin pump therapy, as was reported to the NICE Appraisal.[16] For the RCTs mentioned earlier and in **Figure 1**, four are in children who have a baseline severe hypoglycemia rate ≥18 episodes/100 patient-years.[27,37,38,40] Here random-effects meta-analysis gives an RR of 3.91 (1.35–11.36; $p = .01$), indicating substantial benefit of CSII in children (forest plot available on request).

The Problem of Meta-Analysis of Obsolete Technologies

For therapeutic decision making for today's clinical practice, meta-analysis should be based on the most appropriate comparator treatment. While it cannot be assumed that the latest technology and insulin is necessarily more effective than previous generations, there is good evidence that early generation insulin pumps from the 1980s have suboptimal performance, including limited capacity to alter basal rates or bolus profiles, and monomeric insulin is currently considered the insulin of choice for CSII.[23] Notwithstanding this, several published meta-analyses[2,7,9] have included some trials with early insulin pumps and nonmonomeric insulin. For this reason, it is probably best to limit trials for meta-analysis of MDI versus CSII to those published after approximately 1996.[3]

Appropriate Meta-Analysis of Self-Monitoring of Blood Glucose versus Continuous Glucose Monitoring

These caveats about inappropriate meta-analysis also apply to CGM. Here, the important effect modifiers for the change in HbA1c between SMBG and real-time CGM are frequency of sensor usage and baseline HbA1c.[14] Thus, although the mean difference in HbA1c between SMBG and CGM is a comparatively modest 0.20–0.27% (2.2–2.9 mmol/mol) as reported from summary meta-analysis of RCTs,[12–15] Bayesian metaregression models of the determinants of HbA1c difference derived from individual patient data from six RCTs comparing SMBG and real-time CGM show that for frequent sensor usage (7 days per week) and a high baseline HbA1c of, say, 10% (86 mmol/mol), CGM is predicted to lower HbA1c by approximately 0.9% (9 mmol/mol) compared with SMBG.[14] Literature-summary meta-analysis therefore underestimates the clinical efficacy of real-time CGM versus SMBG, which is revealed by decision-making meta-analysis.

One should also note that although several meta-analyses have reported that there is no difference in the frequency of severe hypoglycemia between SMBG and real-time CGM,[12–15] that is probably because RCTs that have been published to date have not been designed or powered to test the effect of CGM on severe hypoglycemia or had a very low frequency of severe hypoglycemia at baseline or did not specifically study those with disabling hypoglycemia or those at high risk of this (with hypoglycemia unawareness). Appropriate meta-analysis of changes in severe hypoglycemia with CGM cannot therefore be performed at the moment.

Arguments against and Limitations of Decision-Making Meta-Analysis

Selecting and excluding trials clearly reduces the number of studies available for meta-analysis and may weaken conclusions about the overall effect size. The exclusion of trials with certain characteristics might be done with arbitrary cutoff values and rules and is thus subject to bias, unless the selection criteria are justified and predetermined.

Although the best way of exploring the effect of patient-level covariates such as age, diabetes duration, and baseline HbA1c or hypoglycemia frequency is probably by meta-analysis of individual patient data, this is a more complicated and lengthy procedure and presents considerable problems in acquiring the data from original authors and/or trial sponsors.

Conclusions

I argue the case here that decision-making meta-analysis should be appropriate in terms of trial selection and methodology, and my recommendations are summarized in **Table 1**.

Table 1.
Recommendations for Appropriate Decision-Making Meta-Analysis

- **Either**
  preselect trials where average patient characteristics match those of the intended use of the treatment (e.g., for CSII versus MDI, elevated HbA1c or disabling hypoglycemia on MDI)
- **Or**
  perform a metaregression of summary effect size against possible effect-modifying covariate (e.g., for CSII versus MDI, regress difference in mean HbA1c against baseline HbA1c)
- **Or**
  perform individual patient data meta-analysis and construct models of determinants of effect size (e.g., for SMBG versus CGM, sensor usage and baseline HbA1c as determinants of difference in HbA1c)
- Select only trials of adequate duration where outcome can be accurately measured (e.g., for severe hypoglycemia, generally ≥6 months or ≥4 months when baseline risk is very high)
- Do not select trials where the intended patient population has been excluded (e.g., for CSII versus MDI, those with severe hypoglycemia or with hypoglycemia unawareness at baseline)
- Do not select trials using obsolete technology of proven inferiority to usual current treatment with the technology (e.g., early generation insulin pumps)
- Consider additional information offered by meta-analysis of observational studies

There is still much to debate about diabetes technologies such as insulin pump therapy and CGM, such as the extent to which improvements in wellbeing, lifestyle flexibility, energy, and working ability indicate that patient preferences should be also a selection criterion (when funding is available) in addition to clinical benefit. There is limited trial information at the moment that would enable a decision-making meta-analysis of, for example, quality-of-life changes with MDI versus CSII or, especially, SMBG versus CGM. Most quality-of-life data for CGM versus SMBG are from trials where subjects already have a high baseline quality of life because they are mostly well-educated CSII users or have low hypoglycemia frequency or a have a near-normal HbA1c at baseline.

For the time being, health care practitioners should be cautioned that evidence of clinical effectiveness from meta-analysis should be interpreted with regard to trial selection and patient characteristics. When meta-analysis is performed appropriately and for the purpose of decision-making, there is good evidence that insulin pump therapy is effective at improving hyperglycemia and hypoglycemia in those who have failed to achieve target levels of control on MDI. Similarly, the study of the clinical use of CGM is still at its beginning, but decision-making meta-analysis to date has revealed strong evidence for a substantial reduction in HbA1c and mild-to-moderate hypoglycemia compared with SMBG.[14] Appropriate trials for effects on severe hypoglycemia have yet to be performed and therefore to be included in meta-analyses.

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