input
INsulin PUmp Therapy
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Review of NICE Technology Appraisal No. 57 Insulin Pump Therapy
Joint submission from INPUT and Insulin Pumpers UK

Background

Continuous subcutaneous insulin infusion (CSII), or insulin pump therapy, may appear complicated to healthcare professionals and patients alike. Perceptions grounded on the state of the art as it was 20 years ago have contributed to opinions that it is an overpriced, risky therapy of last resort that is appropriate for only up to 2% of British type 1 diabetes patients (National Institute for Clinical Excellence guidance No. 57, 2003). Meanwhile, 10-20% of type 1 diabetes patients in other EU member states and around 25% of type 1 diabetes patients in the US currently use insulin pumps. The Diabetes Control and Complications Trial (DCCT) results showed in 1994 that tight control of blood glucose levels in type 1 diabetes can reduce the incidence of microvascular complications such as retinopathy and nephropathy by up to 76%. The DCCT follow-up study, Epidemiology of Diabetes Intervention and Complications (EDIC) has shown that even at similar HbA1C level as patients on conventional (twice-daily) insulin therapy, patients on intensified diabetes management regimens including pump therapy will develop fewer long-term complications of diabetes. Today, 10% of the NHS budget goes to diabetes treatment (type 1 and type 2 combined) – with an unknown percentage of that to treating complications of type 1 diabetes. Given the reduced diabetes-related mortality and morbidity, and thus increased length and quality of life that can be achieved with intensive management of diabetes, it is absurd and irrational both financially and ethically that insulin pump therapy remains out of reach for all but a handful of British diabetics.

INPUT is a patient led support group for diabetics using insulin pumps run by pump users and their families. Our sister group, Insulin Pumpers UK is a web based discussion group with the same objectives. We are independent organisations that offer no allegiance to any manufacturer. Our prime objectives are to increase the awareness and understanding of insulin pump therapy, and to help, support and educate insulin pump users and their families in their use.

INPUT, serves as a clearinghouse for information on insulin pump therapy and an advocacy group for consistent funding for insulin pumps across the UK. NHS Primary Care Trusts must comply with NICE guidance's, but inadequate governmental supervision of their implementation and little support from the Department of Health to establish best practices have made the NICE guidance on insulin pump therapy very difficult to enforce. INPUT works with Diabetes UK, the JDRF, the Department of Health, members of Parliament, the diabetes care industry, consultant diabetologists, diabetes specialist nurses, general practitioners, and Pump Management for Professionals (PUMP) to bring about full adoption of the NICE guidance on insulin pump therapy.

In addition to tighter control of blood glucose levels and improved long-term outcomes, tight glucose control achieved via insulin pump therapy can improve quality of life to people with diabetes. These may include the freedom to eat only when one is hungry, the opportunity to sleep without fear of severe nocturnal hypoglycaemia, the chance to undertake sports and exercise without harming oneself or others, and the self-confidence to attend university or pursue a dynamic career – activities taken for granted by people without diabetes. Diabetic men may avert erectile dysfunction; diabetic women can live free of thrush and have healthy pregnancies resulting in normal-weight, full-term babies. These improvements in diabetic patients' quality of life serve to reduce the burden of diabetes on the healthcare system and society as a whole. If people with diabetes can maintain normal weight and physical activity, their risks of developing cardiovascular disease and insulin resistance are reduced. If people with diabetes have educational qualifications and a longer life expectancy, they may make greater contributions to the economy without taking early retirement.

The financial costs of insulin pump therapy are often mentioned as a barrier to its wider application across the diabetic population. A pump, covered by the manufacturer's warranty for four years, costs on average £2550, plus £1250 p.a. for consumables (infusion sets, insulin cartridges, batteries, etc.). If a pump is replaced every four years, the average yearly cost of the therapy is £1600. One overnight stay in hospital following admission to A&E for a diabetic emergency costs £350. One procedure of dialysis treatment for diabetic kidney disease costs £504. One course of laser treatment for diabetic retinopathy costs £847, plus incalculable weeks off work. In light of these costs for treating poorly controlled diabetes, insulin pump therapy as preventative medicine seems a bargain!

Problems with current NICE guidance

Insulin pumps were first introduced in the late 1970's and were relatively crude by modern standards and because the insulin in use at the time was not as stable as today's insulin's, they also had reliability problems. This, together with some poor patient selection, caused a certain amount of distrust within the UK medical profession and this meant that there were only a few consultants and hospitals prepared to recommend and support pump therapy.

In 1998 there were approximately 180 pump users in the UK, now in 2007, there are around 5000.

Following the publication of NICE guidance on 26th February 2003, it was hoped that this number would grow and that many leading hospitals would now prescribe this treatment for diabetes. However, that has not proven to be the case.

The NICE guidance issued as a Health Technology Appraisal in February 2003 (ref: TA057) was generally considered to be confusing both for those involved in providing pumps and those who might or might not be entitled to use them. The NICE guidance is open to interpretation. Primary Care Trusts (PCTs) are not providing pump services in a uniform manner and are able to do this partly as a result of the confusion around the interpretation of the guidance.

Commissioners at PCT level are confused by the guidance and concerned by the potential costs. This has resulted in a variety of different reactions: full support; capping of patient numbers (often on the basis of the 1 to 2% of the population with Type 1 diabetes suggested by the NICE guidance as being eligible for pumps); capping of finance; approval on an individual patient basis; no support at all.

The current NICE guidance is now based on out of date information; changes in pump technology and the usage of analogue insulin renders much of the evidence base quoted in the NICE technology appraisal redundant. NICE guidelines take no account of the practical problems of dealing with children and adolescents.

The NICE assumptions of 1 to 2% pump uptake are not in line with other countries' uptake of this therapy; in the US pump use is around 25%, in Europe it is between 12-20%, in Israel it is 20% with a proportionately higher use in children as it is in Sweden where pump use in paediatric clinics is running around 20%.

One of the issues affecting pump availability appears to be the diabetologists' position on pump therapy. One diabetologist concluded (when considering his adult Type 1 patients) that depending upon whether you are a pump evangelist or a pump sceptic, the number of patients who could be considered suitable for pumps could vary by a factor of 10.

This is reflected on the ground, where pump evangelists have set up services, often using soft money, while other areas remain totally without provision (particularly for paediatrics).

There is concern about the opportunity cost of providing pump services. Some diabetes networks and Public Health Specialists are concerned that the cost of providing insulin pump services could wipe out their ability to secure funding for other diabetes related developments. Another concern is that increases in the number of pump users would only result in marginal health gains for a small number of people with diabetes. There are still major gaps in the provision of diabetes services and potentially much greater health gains could be achieved from the early identification of people with diabetes, providing structured education care etc. These issues need to be considered in the light of research on the cost and quality of life benefits of pump use.

There is a need for a well developed paediatric service. Two thirds of people with Type 1 diabetes will present as children or adolescents. The benefit of good control to avoid the early onset of complications in adult life is crucial. The incidence of Type 1 diabetes in childhood has been rising and is currently 6.3% per annum, with onset at earlier age over the last two decades.

In the UK there is both a post code and a professional lottery determining whether people are offered the chance of pump therapy. There is inconsistency from one PCT to the next in their interpretation of NICE guidance and there is reluctance on the part of many clinicians to contemplate and offer pump therapy. The financial situation of individual PCTs is often used to justify whether or not a full pump service is provided.

Highly specialised service? The idea put forward by NICE that a pumps service can only be offered by highly specialised centres may explain some of the reluctance to provide services. However, in principle and in practice when you come to institute pump therapy this does not add up. NICE are quite happy for individual units or consultants to use 'basal/bolus' regimens yet these are just as demanding if not more so in specialised dietetic and nurse time as pumps (views on this point differ, the consensus is that both require a significant level of support especially at initiation). Both therapies need the patients to relate bolus insulin to carbohydrate intake and make corrections between meals. The difference is that on a pump it's easier to control not only the boluses (pumps can deliver to higher accuracy with bolus spread over time) but importantly the background, particularly overnight.

There is a need for single cohesive service. There needs to be a clearer understanding of where pumps fit into the overall care of people with Type 1 diabetes. Is it right to develop a pump service within a Type 1 service that has inadequate specialist nursing support, little access to dietetic advice, and is unable to support 24 hour advice? The key issue is not the insulin pump, but a single cohesive service whether the patients are on pumps or not. It is important to consider that people with other types of diabetes could also benefit greatly from access to pump therapy. It would be useful to develop an algorithm which would help to identify whether patients would or would not be suitable for CSII.

There is a need for continuity from paediatric to adult service. Most patients with type 1 diabetes will present in childhood or adolescence. Their management should be a smooth continuum not a sudden disjunction at age 18. There should be an understanding that someone who is well supported on a pump at age 17 will continue to be equally well supported at age 18 with funding in place to allow this support to continue.

There needs to be a clear understanding that if the managing physician has decided to treat a patient with a pump consistent with local practice and interpretation of the guidelines that the PCT of residence accepts responsibility for funding and that this should also be norm if the patient migrates to another area. Networks can help with this on a local level, by developing consistent arrangements within the network, and between neighbouring networks. Arrangements need to include continued provision of support and consumables. Provision must also be made for EU individuals who have come to stay in the UK who are already established pump users in their parent country.

Unless a cure for diabetes finally comes along, or a totally different insulin delivery system is developed, it seems likely that demand for pumps will continue to increase. This will be driven by the patient choice agenda. Also, if paediatric services continue to develop, it is likely that a significant proportion of people with Type 1 diabetes will spend much of their lives with an insulin pump, so the total population of pump users will continue to climb each year for the foreseeable future.

Insulin pump therapy should be considered for all people with type 1 diabetes as an option for intensified insulin therapy.

NICE guidance should be clear about the way forward with insulin pump therapy. It must not remain just a paper exercise; a paradigm shift must take place in order for NICE guidance to be part of diabetes service delivery.

Patient/carer group: INPUT

Submission regarding children and adolescents

3.3 1. 1). Effects of technology: course of the disease

- For babies or children on small doses of insulin, a pump is a far more accurate tool than injections. Not only the very young, a 12 year old who is very insulin sensitive, requiring only 3-4 units per day, cannot achieve anything like satisfactory glycaemic control, HbA1c or quality of life as the insulin pen is just too crude, hence frequently swings between hyper and hypo, even unconsciousness.

- Reduced HbA1c is achievable compared to conventional injection therapy and MDI, with loss of fewer body sites over a period. Important when child is young, has a small body and fewer sites available.

- Reduced extremes of blood glucose swings/excursions, using a pump means children are better able to maintain the "middle ground", may achieve similar Hba1c to injection therapy but it can reflect better average glycaemic control and is therefore causing less microvascular damage, less glucose and ketone excretion.

- Reduced number of hypos

- Reduced night-time hypos

- When starting to go low, blood glucose goes "lower slower" so can catch and deal with hypo effects before child/adolescent is unconscious or fitting. This is important for young children as repeated severe hypos thought to effect cognitive function, and studies have shown people diagnosed when very young have poorer academic achievement than those diagnosed older or non-diabetic peers. It is important for adolescents for social reasons, a major cause of hyperglycaemia in adolescents is due to their 'running high' in fear of being seen to loose control and hypo in public or in front of their peers.

- Quality of life for child and their family. Includes things such as being able to eat out, acting spontaneously, teenagers going out and eating late with peers, eating pizza (hard to keep control eating pizza on injections), laying in late, not eating when not hungry, for dealing with sports and exercise, for dealing with concurrent illness and avoiding hospital admissions, for going on school trips and holidays abroad.

- School routine can be easier to get pump support than injection support, especially for young children who cannot self-inject. Schools vary but support in school for injections is a growing problem area, and it has been known that children have not been able to transfer to MDI, although recommended by their consultant to achieve better control (and we all know over 80% of audited children under 16 in the UK are still failing to achieve anything like reasonable HbA1c targets), because there is no-one to give their lunch-time injection. In turn, this will affect their overall HbA1c, energy levels and ability to concentrate at school (in a recent survey it was found children could be at school, no-one give the lunch-time injection, that child then running high BGs until collected from school at the end of the school day). For older children, pump bolusing is less intrusive and embarrassing than having to go to the medical room to be overseen injecting. On a pump, children and adolescents do not need to go into lunch first on their own, but can join their peers and bolus at the table, thus reducing social exclusion and feeling "different".

- Achieving educational potential; diabetes can put students at a disadvantage to non-diabetic peers due to glycaemic swings and the effects of highs and lows, stress, growth spurts, exercise etc. as well as having poorer hearing, and some being excluded from school trips simply for 'being diabetic', put in lower GCSE groups so unable to sit for higher level GCSE, which can affect future access to higher education, educational course/options and job prospects. Failure to achieve academic potential has effects long-term for that student, on whether able to fulfil educational goal, and to access career of choice and well-paid employment. The educational achievement of the student with diabetes has the knock on effect of being linked to that person's eventual socio-economic position, which in turn is linked to how they will fare health-wise, there still being major health inequalities for those with chronic conditions and low economic status, especially for males.

- Being independent; having a pump helps a child's independence and confidence, ownership of their diabetes, it's not always something someone is doing to them, they are involved and able to bolus themselves. Additionally, when that child becomes a young person, at 18 around years of age, having a pump can be seen as less of a risk by parents if that student is going to move away from home into student accommodation for university of college.

- **2). <u>Impact of effects on patients HRQoL</u>**

- On child/adolescent – feeling better, more energy, feeling 'normal', being able to join in with peers, go to birthday parties with less feeling of being different, people outside the immediate family happier to have that child in their home as they will not be injecting, less sharps to dispose of, less fungal infections due to reduced hyperglycaemia, more confidence not going to hypo in public, pump can be 'dressed-up' as a fashion accessory in patterned and colourful 'skins', injection devices cannot. Pump gives a feeling of ownership, being in control, held in hand and is child's 'pancreas computer'; a syringe or insulin pen is not seen lovingly or 'owned', it is merely a painful tool and a reminder that child is never more than a set number of hours from the next injection, a reduction in that child's freedom and spontaneity, sometimes remembered from their previous non-diabetic life. Given a choice, most children, but not all, we have dealt with prefer pumps. Better glycaemic control, especially during illness, also leads to less hospital admissions for the child.

- On family and siblings – siblings get a chance for attention from parents once the pump routine is learnt, not as onerous in some respects as MDI, but as more training is needed to start pump therapy, often get this, leading to better understanding of diabetes and more able to adapt and deal as problems arise, whereas there is a lack of training for some of those on injections. If the child is happy, this reflects on the family and their stresses and coping abilities.

- Improves psychological well-being in some cases.

- Reduces need for number of night-time BG checks in some cases, and if have the sensor pump, enables child/adolescent and parents to have full nights sleep confident that if child starts to hypo, pump will alarm, be heard and hypo can be corrected and child/adolescent kept safe. Additionally, for those without hypo awareness and impaired glucagon and glycogen response, where child/adolescent would not come round from unconsciousness without IV dextrose, the sensor pump is literally a life-saver.

- **3). <u>Valuation of impacts reflecting preference of general population</u>**

- 2007 survey, all parents' surveyed felt pumping was beneficial to both their child and their family. It should be the child and family's preference that is listened to here, not that of 'anti-pump' healthcare professionals, of whom there are still some employed in paediatric areas. Input and UKCWDAG have come across examples, both of DSNs, CCN's and consultants, but here is not the place to 'name names', just be assured they are still out there and certainly affect children's access to CSII.

- Allows children/adolescents to have a childhood lifestyle, invaluable!

- **3.3. 2. <u>Acceptable and appropriate compared with alternatives</u>.**

- 1). Literature reviews - copy enclosed Glycaemic control in children: can we turn failure into success? Journal of Diabetes Nursing 10(2) p48-54. Also article currently awaiting publication in Journal of Diabetes Nursing (appendix A)
- 2). Patient surveys - INPUT and Children with Diabetes Advocacy Group 2007 report, copy enclosed.
- 3). Summarised testimonials……..XX

- **3.3. 3. <u>Feasibility and impact</u>.**

- Organisational issues – availability of specialist services

- Diabetes UK recommends 70 patients per DSN, which is not yet achieved nationally, in fact, there are still many children completely without any PDSN dedicated service, despite there being diabetes-trained nurses out there unable to be employed in diabetes related jobs, and others having their diabetes work cut to work on a hospital ward part of the time. Due to current financial pressures and lack of pressure to provide paediatric services as recommended by NICE and DUK, there is bound to be an even greater lack of personnel for specialist pump services.

- The centres of excellence model as is being practised in Leeds and Yorkshire should be used as a basis for adaptation nationwide. Centres of excellence should not however, become omnipotent and fail to pass on experience and teaching, and helping to set up local services. For some families, travelling may be an issue, and out of pocket travelling expenses should be provided by PCT/referring hospital to enable families to travel to non-local centre.

- **<u>Equity</u>**

- There are different benefits across the population, for babies, young pre-school children, school aged children and adolescents pertaining to particular stages of development.

- Babies and under 5's, need only small exact amounts of insulin, pumps can do this, injections cannot. Parents using syringes for tiny amounts have to dilute the insulin with water for injection to get something like a quarter of a unit of Levemir; they are parents, not medics. Young children have less body, less skin, therefore fewer injection sites, and loss of sites is a big deal when you do not have many at that age, and little sub cut fat. Possibility of cognitive damage of young child/baby going hypo, we don't know for sure what damage severe hypos cause, but its been shown that the younger the child at diagnosis, the poorer the educational achievement, is it connected to hypos and brain development?

- Young children – pumps give better ownership of diabetes, more control, better able to be like peers and join in with school events, family find it easier to manage, beneficial for child and family, but only if child wants pump and family willing to learn to use it, carb count etc.Good during illness, prevents hospital admissions for intercurrent illness, easier to be home and deal with high/low BGs caused by illness than on injections, can use temporary basal rates, can alter by the half hour and varying percentages, more responsive and exact than using injections.

- Adolescents – far easier to manage the ups and downs of this age group, growth spurts, hormonal changes, menstruation cycles, stress, sitting exams, eating out spontaneously, having a lay-in late mornings, going to bed late night/early morning, school trips, holidays abroad, eating difficult foods that affect BG levels (pizza etc), during sport, for pregnancy. Additionally, pumps have memories and can check what adolescent insulin intake etc has been, download pumps at clinic, easier to manage change, difficulties occur when presenting hand written record books, authenticity of figures is unknown and cannot be checked from pen/syringe, no audit possible.

- **What is life like without the technology?**
- Poorer control, poorer HbA1c sometimes, headaches from lows, thirsty and pee a lot from highs, when high at night cannot relax, runs around the house until levels down and exhausted, then hard to get up for school following morning, cannot concentrate at school, diarrhoea after hypos night before so late for school in morning and embarrassing if it happens at school, seizures as go low so fast on injections, no warning whatsoever. Effects siblings, their quality of life, feel left out, jealous of the child with diabetes and the attention they get, fed up with child being ‘naughty’ and getting away with it, noisy when high, older siblings may have homework to do, younger ones may lack parents attention. Being different, having a totally clockwork routine lifestyle, not living with any quality, imagination or hope of being the same as peers or ‘normal’.

- Life without the pump was really grey, surviving, not enjoying living. The pump gave hope and changed the awful 4-hourly-for-ever routine, colour came back into our lives.

- **Equity of access**
- Still not happening everywhere for everyone. NICE is only of use if it can be consistently implemented, and it is still not being done. Our report recommends that:

- NICE guidelines and recommendations are only of benefit if implemented: a national, robust, non-optional continuous audit, perhaps by NICE, is required to ensure national NICE compliance, and enforcement powers to remedy situations where the guidelines are being contravened.

- Patients to have direct referral access to the NICE compliance service if their local service does not comply with NICE guidelines.

PATIENT PROFILES
INPUT & CWD

Profile – Aled age 3

Aled started pumping Dec 04, 12 months to the day after he was diagnosed (dx 20 months).

His HbA1c wasn't considered a problem 'for his age', usually in the high 8's. However, his control was poor - normally with huge swings from high to low, with little in the 'acceptable' range and this affected his moods and behaviour a great deal. Since being diagnosed, he had lost his 'sparkle', and now was often very restless and unsettled, grumpy and even verging on aggressive. He was such a cheekly little toddler before, that this was very sad to see, and was affecting him so much; it also stopped us doing things we / he wouldn't be able to cope with. We also had to stop many activities because of the Diabetes, even silly little things like going to Church - he would always fall asleep in the car on the way home, thus missing his lunch and dropping too low. Being a typical toddler, meal times could be great fun - you'd give him his usual morning / evening injection, place his meal in front of him, and he wouldn't want to eat. We were luckier than most in that Aled was generally a good eater, but it was still a problem.

After we started pumping, his levels improved dramatically, and in a very short space of time, which we weren't expecting. Yes, we still have plenty of highs and lows, but not as often, and we don't get the drastic swings used to be the norm. Consequently, Aled returned to being a 'normal' toddler. His temperament returned to normal, and he lost that awful aggression and shouting when his control was not good. Meal times are far easier to deal with, as are activities and nursery. The pump has given Aled back the quality of life which he lost when he became ill.

We have had a great deal of support from all of his team, and his consultant, who knew very little about the pump initially is very encouraged, and encouraging. At our first clinic visit afterwards, he asked if it wasn't a lot of work just so Aled didn't have to have injections. I explained to him that not having injections is just a (albeit huge) bonus - I wouldn't recommend it just for that. the real selling point for our family is that it has given Aled a far better quality of life than he was getting with the Mixtard twice daily, especially in such a young child when good control is nigh on impossible. So many people have commented since we started that Aled seems so much happier all the time.

Aled is now 3 1/2, and attends nursery for 2 hours a day. He has been pumping for nearly 11 months. We use the Medtronic paradigm 512 pump.

Helen, mum to Aled 3 1/2, dx 12/03 pumping 12/04; Jenny 6

Carmel [redacted]

I have had Type 1 diabetes for 46 yrs since the age of 3. As a consequence of this, have suffered many complications, cataracts, neuropathy hypertension obesity and stroke. I am a registered nurse and midwife which obviously means changing and unpredictable work patterns.

I love my work as a midwife and have to be on top form to be able to work with and for my mothers. I cannot allow my condition to interfere with my work, having a pump has helped me continue to work, despite slight disability, in a career I love. Through using the pump my HBa1c has reduced,

I still have some episodes of hyperglycaemia but I can bring my blood sugars back to acceptable results without enduring days of untreatable insulin resistance.

I no longer live in fear of hypos as I no longer have unpredictable long acting insulins on board and the odd hypo is easily treated without having to eat lots of unhealthy high carbohydrate foods which led to increased weight gain over the years. I am due to undergo surgery soon for my health which will mean drastically reducing food intake but will help me lose weight. Before the pump I know I could not have contemplated this but now with the pump I will be able to control my basal insulin requirements with drastically reduced food intake.

Carmel [redacted]

Caroline [redacted]

What can I say about the pump? I didn't want one! I was one of those rare breeds… a diabetic who kept refusing to try a pump!

Each time I visited my consultant he tentatively suggested one and I adamantly stated' it's not for me!' It wasn't that I hadn't considered it seriously. I had even asked my nearest and dearest; partner Mike, Dad, Sister, best friends…expecting each to unreservedly think it a good idea, anything to improve my health, but every one of them said it was not for me! Their reasoning was that I'm too bothered about how I look! I agreed whole heartedly! [The best bit about diabetes was that with injections no one need know I am diabetic unless I choose to tell them!]

This makes me sound like a bimbo, I know, but I'm actually far from that [I have a Masters degree!]. However, I am fashion obsessed…not particularly a keen follower [as I make a lot myself] but mad keen on appearance generally and femininity. What you'd call a girlie girl, I suppose!

As I increasingly began to suffer with complications, after 26 years of struggling to get good control using injections, my diabetes began impacting negatively on my life. My ulcerated feet meant I could only work 3 hours at a time 3 days a week in my M&S shop job [and I couldn't wear the shoes I wanted to!]. My eyesight was getting worse necessitating the use of magnifying glasses as well as my usual contact lenses [my embroidery had become difficult to see!]. High blood pressure meant more tablet taking but worst of all was the complete loss of hypo warning signals resulting in comas several times a week witnessed by my sister and friends who had never seen me like this in 26 years! Their shock and the fact I felt frightened to leave the house meant I finally relented and agreed to give the pump a go, with the proviso that I could revert back if I hated it!

After the initial tears, when the pump was placed in my hand, heavy and huge and the reality of it being attached to me at all times hit home, nothing could have prepared me for the transformation that was about to happen!

I am the sort of person who likes to give 100% and I decided I wanted it to work for me and what a difference after only a week! So much more energy! Blood sugars down to the levels I'd only ever dreamed of being! Within a month I had made moves to change my whole life because I felt so much better! I suddenly felt like the 'me' I always wished I felt well enough to be!

I applied to do a taster course at York college for qualified teachers who want to train to teach adults [I'd been out of teaching for 10 years as I felt teaching requires commitment to the students which I couldn't give as I was not sure how I'd be on a daily basis!]. I passed this course and was accepted on a City & Guild Adult Literacy Specialist course which required me to have some teaching practice set up. So, I hot footed it down to my local college and came away employed as both a Key Skills/ Basic Skills tutor and a Learning Support Assistant!

What a turn around! From part time shop assistant selling men's underwear! to 2 college jobs and there's more! This is me now with not enough minutes in the day! I also have a [fortnightly] Saturday job in' Fine Fabrics' , to feed my addiction and fuel my passion for dressmaking! I continue to work one day a week as a volunteer for my local hospice in one of their charity shops [as my mum died of cancer 7 years ago], and I am a volunteer usher at my local theatre whenever I can! On top of all this, I am starting my own business! But more of that later…
It hasn't been all plain sailing…I had 2 main problems with the pump. The biggest one was 'carrying' it. I was first presented with coloured cases to attach to a belt. I chose bright yellow!

But then the problem occurred. I have a large collection of belts, none for function all for fantasy! Broad waspie belts, thin diamante strings, glitzy chains, delicate embroidered, floral, appliqué, suede, jewel encrusted! …none could possibly be adorned with a sun yellow cover, masking as a mobile phone! Ughh! These belts were meant to draw attention. I wanted my pump to be discreet!

I was then shown a bra clip pump cover which appealed much more .but it was large plain black , an elastic loop to balance the pump on and Velcro to seal I took it but hated it. The plastic clip dug into my flesh, the Velcro stuck to my lacy lingerie causing it to bobble and tear! or it stuck to my mohair jumpers and became useless as a seal! The elastic 'strap' didn't hold the pump safely and it fell out embarrassingly in public and I had taken to walking round with a hand on my tummy to prevent this but my partner complained I looked pregnant in that pose!

I was also told there was a garter available and suddenly I felt relief That sounds more like it I thought as I am a huge stockings and suspenders fan …that was until I saw it! Not a bow or scrap of lace in sight! Huge plain white, clinical ungainly ..No thanks!

In despair I turned to the net only to be bombarded by hundreds of American sites where people were selling covers the size of handbags!, worn on ample bosoms over sweatshirts with tubing dangling everywhere! No! That wasn't for me! So I went to my sewing machine and started playing with scraps of gorgeous lace and fashioned my own covers made comfortable and safe by using an elastic loop which I thread the bra through so that it hangs centrally and then is pushed up to sit held in place by my bra [most of which are under wired though it works with others too!] Perfect! Pretty ! easy to access, very discrete and not a bit of Velcro or any danger of it falling! It took no time to get used to it and meant I could wear almost everything I wanted to! Plunging necklines could still be problematic until I devised my own garters with a small bag to hold the pump attached! Sexy! I still could feel feminine and people ask me on a daily basis where my pump is! How discreet!

On my first evening out with my partner Mike at our local [a typical 'lads' type of pub!] , I wore the smallest , tightest black bustier and slim pencil skirt with a split, stockings and killer heels with my pump safely secured to my inner thigh in a black and red lace garter complete with a bow! I felt fabulous and the guys kept saying I thought you were getting a pump .where is it! My response was ' that's for me to know and you to keep guessing!'

My second main problem with the pump was actually solved by these covers and garters too! I had naturally been worried how Mike, my partner of 14 years, would react to it .If it altered how I felt as a feminine woman it would undoubtedly affect him too. Initially it was hard. I became 'precious'. He was wary of the pump, frightened to go near me in case he dislodged something.

I was aware that he saw me physically as 'medical'. It was a constant reminder which didn't relate to sexy or attractive! This was until I made my girlie covers and garters which meant my pump blended in to my lingerie. So it was forgotten. If anything you feel more feminine than before as I often wear a garter in the day and in bed!

The pump has greatly improved the quality of life as it has freed me to be the person I always could have been if I had felt 'well'. The problems were all surmountable with a little enterprise! Now I have discreet 'secrets' that are life enhancers! And a new business to boot so hopefully other women with the same dilemma will be able to feel as feminine and confident as me!

Our son, Edward is three years old. He was diagnosed with type1 in July 2004 aged 27months. We were lucky, he started pump therapy just four months later and has a Paradigm 512. his Hba1c was 10.4 on injections and downloads from the CGMS were terrible, showing him to be either in a prolonged hyper or prolonged hypo and rarely anywhere in between. It was extremely stressful feeling helpless to do anything to correct this. Now that he uses a pump his Hba1c has come down to 6 so obviously we are immediately reassured that if we can keep around that level his long term complications are greatly reduced.

With a child being diagnosed at such a young age this is very important to us. He is like a changed child, gone are the mood swings that we experienced whilst on injections with bouncing levels and he is a happy and otherwise healthy child. With the pump we feel as though we are in control and able to take immediate action when Edward's sugar levels go out of range. His control is far from perfect, but now we have a tool which we can use to help to keep him stable and we, ourselves are happier parents because of this. It is very difficult to manage a toddler with diabetes, they can be faddy with their food, erratic with their activity levels, moody, excitable, prone to childhood infections etc. With a pump you can manage these situations more easily.

When Edward had chicken pox and didn't feel like eating it didn't matter we just didn't give the insulin for that particular meal. What a difference from when he was on injections and us knowing that once he had had his insulin he must eat something. There are so many benefits to having the pump, changing a canula every third day is much less stressful than multiple injections, we are able to adjust the basals for periods of increased activity or if levels are lower than we would like. (a particularly reassuring feature during the night) and as we have a child who loves pasta and other long acting carbohydrates we also get good results from using the dual and square wave bolus features. We would fight anybody who tried to take the pump away!

Neil and Jane [redacted]

Eleanor [redacted] Age 11

Our daughter was diagnosed with Type 1 Diabetes just after her eighth birthday. She started on 2 injections a day and went through various insulin regimes. Her HbA1c initaily dropped from 9+ to 8-8.5 but her daily blood sugar range was 2-26mmols. She started on MDI aged 8 3/4years, and always did her own lunchtime injection at school. She tried Insulatard and Novorapid, then Lantus (single doses first evening then switched to morning) and Novorapid. Eventually we were testing her once or twice every night, correcting highs with an extra injection of Novorapid and she was averaging 5-6 injections and 12 blood tests a day but her HbA1c was climbing slowly towards 9. She had to eat to time even with MDI and blood sugar range was still 3-20mmols on almost a daily basis. She had lost hypo awareness until blood sugars were under 2mmols, and had no hypo awareness at all at night. She started using a Minimed Paradigm 512 insulin pump with Novorapid and 6mm Quicksets 13 months ago just before her tenth birthday. Her HbA1c has been 7.4 - 7.9 since she started pumping. More importantly her blood sugar range has narrowed considerably, she has regained some hypo awareness, and is now able to detect high blood sugars at around 14mmols instead of 20+mmols. Within 2 weeks she told us that she could not remember feeling so well. She had always been an excellent student but her progress in maths had slowed prepump: maths was always mid morning when she had a huge post breakfast spike around 20mmols most days usually dropping to hypo before lunch. Her progress in maths is now on a par with her other subjects and she is making excellent progress at school. She manages her pump very well with supervision, carbohydrate counts and and is learning to adjust her boluses to reflect activity planned and bolus on board. She now does around 9 blood tests a day and changes her site twice a week. She has had 2 minor site infections in 13 months, but has had no other problems with pumping. She is very active and has had fewer post exercise hypos since starting pumping. We still test her blood sugars at night as her overnight blood sugars are not predictable: however she now sleeps through the correction bolus, and the highs are easier to correct with the pump. She loves the improved control, flexibility and sense of well being her pump has given her. It has made a tremendous difference to her health and her long term health prospects are therefore also likely to be improved.

Liz and Julian [redacted]

Profile – Fiona [redacted]

A review of my experience. Chop it if it is too long.

After 35 years of injecting insulin I converted to using a pump in 2003. I had only ever heard about pumps by looking at insulin pump relevant websites and user groups and through these recognised a tool which sounded ideal to help me manage diabetes alongside a hectic life. Life involved work in a hospital intensive care environment with irregular shifts, taxi to three teenagers, involvement in their sporting activities, travel etc. etc. I always had difficulties with the basal component of multiple injection regimes even with glargine and before that and had to cart a rucksack of food with me wherever I went, eating when I would rather not. I was also finding to my alarm that my hypo awareness was not there and I was reliant on very frequent blood glucose testing and corrections one way or the other which kept my HBA1c at a supposedly acceptable level below 6.5%, but at a cost. I also had an unrelated kidney tubular disorder and therefore couldn't risk the potential of diabetic nephropathy as well so needed normoglycaemia as much as possible.

I was fortunate that with significant pushing, information giving and letter writing I was approved for pump therapy. It has been fantastic, quite a learning curve for someone who thought she knew everything about managing diabetes. I know it can seem like a lot of work but I don't miss injections and the hypoglycaemia that accompanied them and I find food freedom liberating even though I was carbohydrate counting from a young age, now I can really manipulate and get it right most of the time.

What it has meant to me

Variable basal rates:

- Mean better nights without drops in blood glucose in the early hours.
- Significantly increased basal rates in the morning have eliminated the mid morning high blood sugars and the ability to eat much more at breakfast if I wish.
- Exercise without hypos, at any time I want as long as I adjust basals and take into account what insulin is on board and act accordingly.
- The experience of major surgery post op recovery recently was facilitated well by my pump management and adjusting both basal boluses very frequently according to blood glucose trends
- Travel through time zones no problem with easy changes with temporary basal rates according to needs.
- Variable basal rates mean that on night duty I can have a tiny dose midday and vastly increased dose on getting up in the evening and prevent blood glucose rising . It used to mean I couldn't eat even if hungry at times until I got blood glucose lower.

Bolus Insulin:

- Precise and ability to bolus points of a unit helps so much when having small doses and very insulin sensitive.
- Ability to vary the length of a bolus enables much better cover for certain meals.
- Socially so much easier to bolus in public situations, particularly with buffet type food etc.
- Easy to do a correction bolus wherever you are.

The most amazing thing for me was a return of hypo awareness at 4mmol and a definite recognition of hyperglycaemia at around 8mmol. Previously I obviously spent a long time above and below these levels.
Hypos are insignificant and at around 4mmol needing little more than one or two glucose sweets.

Of course we'd all rather not have diabetes, but having coped with it for nearly four decades, I can honestly say that using an insulin pump has been the best tool and educator for living with and understanding diabetes and quality of life issues around food and socialisation..

Fiona

Profile – Helen [redacted]

INSULIIN PUMPS - FANTASTIC. I am a Type 1 diabetic for 37 years, diagnosed at the age of 3. I have been using a MM 512 since April, this year, and am astonished at how much better controlled I am in such a short space of time.

Pre-Pump - Blood sugars varied between 2 and 30 mmols, on a daily basis, on a regime of Humalog in a pen, and Lantus overnight. Despite numerous dose changes, control was never much improved and remained erractic for 12 months or more. I suffered disabling hypos constantly, resulting in assistance from a husband who grew fed up of being awoken in the middle of the night to help with administering glucose, and, who eventually left me for being a "nuisance". I also found having to eat with the pen injections a real problem as I tend not to have regular meals. Having a lie in was also out of the question at a weekend. I suffer with retinopathy also, and have endured lots of laser sessions, which I find excruciatingly painful, and have always had a session of laser at my six monthly check up with ophthalmology dept. I also suffer with kidney damage, for which I take Lisinopril daily. HBA1c's always between 10.2-14

Post-Pump -- What a difference to my life!. I could never imagine that a tiny machine could make such a huge difference to my life. First HBA1c done since starting pump only in April, was 8. Never had such a low HBA1c for 10 years or more. The way I feel has changed so much also. My constant tiredness and lethargy have improved no end. The few hypos I do get, the symptoms are much less severe and can be corrected with less glucose. I went for my ophthalmology appt last week and for the first time ever, did not need any laser treatment. My blood sugars have improved greatly, they are still a little high, and some tweaking is needed with my basal rates, but now on a daily basis I range from 4.8 to 7.5 on average, a far cry from 2-30 mmols pre pump.

Additionally, of course, it is a relief to be free of 5 daily injections, extremely sore legs and abdomen. I find the insertion device I use with my Quickset inserts the canula almost pain free. I have suffered no problems with my insertion sites since starting the pump, and the majority of time, I find wearing the pump 24 hours a day is no problem whatsoever. You tend to forget about it after a while.

I can’t emphasise enough how much a pump has changed my life for the better. I think every diabetic should be given the chance to try one, without the funding issues etc that some people face. I must admit it did take some strong words from myself to my consultant to beg almost to try a pump, I think he got so fed up of me bombarding him and his secretary on a weekly basis, that in the end he agreed. However, it just proves in the 6 months I have been using a pump how much better my control is, and how I feel is no comparison to MDI. I would like to see pumps better advertised, perhaps on the TV, through radio etc to educate people about them, and inform people about them. I had thought of contacting my local paper to do a piece on the pump, but did wonder if I was allowed to advertise the pump, bearing in mind the brick walls some face in trying to get one etc.

To this end, I would never go back to MDI treatment. I can only hope and pray my pump stays with me for as long as I'm here. I do tend to worry that some time in the future some bright NHS spark may decide funding is to be stopped, or any other scenario, and I have to give it back. It takes hard work initially when starting the pump, and you have to be prepared to alter your basal rates around quite a lot, extra blood testing for some, but I always tested my blood sugars up to 7 or 8 times a day anyway, but IT IS WORTH IT. LONG LIVE THE INSULIN PUMP.

Thanks John,
Helen [redacted] from [redacted]

Jake [redacted] Age 9

Jake is 9 years old and has had diabetes for 6 years, he started on an insulin pump in January of this year (minimed 512). It has dramatically change our lives, he is doing much better at school (ie not missing parts of classes due to hypos). He is able to eat when he is hungry and we don't have to force food into to him to keep is blood sugars up. His HbA1c has now come down to acceptable levels from between 8-9 to 6.5.

The pump has not hindered him in anyway, he went to camp with the scouts this year for the first time on his own, we did have to go out and change a set for him, but is was really great that he didn't have to take mum along with him.

I hope this helps john

Michelle
Mum to Jake(9) dx99, Thomas(6) and James(4)

Profile – James [redacted] Age 12

My son was diagnosed with diabetes just before his 4th birthday. The effect on our whole family was obviously enormous and traumatic. Anxiety attended every part of life, however small. Even a short trip to the shops had to be thought about and things planned, and visits to friends' houses or parties were fraught times. Things that other children take for granted like staying with grandparents or sleep-overs with friends mostly just couldn't happen.

I became a clock - every two hours I would chase him with snacks or testing kits or injections. He always hated injections. Even as he got older they never just became routine, as everyone told me they would.

We bought a pump when he was 10 years old. We funded it ourselves (and still are) but we were lucky that our consultant and diabetic nurse at our local hospital were willing to support us through our training. He was the first child on a pump at our hospital.

Our lives changed from that moment. He is obviously still has diabetes but it has freed him (and us) so much. After the initial learning period of a couple of months to establish good basal rates and ratios our life could become spontaneous again. And his blood sugars are predicable and much, *much*, more stable.

I look back with horror at the things we found ourselves doing trying to keep his blood sugars reasonable before the pump - trying to distract him to stop him eating because his blood sugars were high, trying to fill him up with low carbohydrate food, or insisting he eat something when he didn't want it. These may not be what the diabetic 'experts' advise, but I can assure you, it's what happens to every family with young diabetic. The reality is a lot harsher and horrible than the theory.

Within a couple of months on the pump he was able to go on a day long hike with his scout group (four boys lead by a 13 year old, with a mobile phone, going through check points manned by adults). Just not possible before the pump.

This summer he achieved his ambition of going camping with the scouts - for 2 weeks. The camped in a field by a lake, sailed, canoed or swam every day, cooked by camp fires. Huge credit goes to the fantastic adults who reminded him to do blood test etc., but again, this sort of thing was just not possible before the pump. The benefit of being able to temporarily reduce basal rates to allow for activity and to be able to bolus for *whatever food* is produced, *and when it is produced*, meant that he could take part in this sort of activity.

Before the pump, so much of his behaviour could be put down to either high or low blood sugars, that there were distortions in the way he was treated. This was especially true when he was younger. How can you tell whether your child is behaving badly because his blood sugars are very high, very low, fed up being asked to test, or just being naughty? Teachers at school were also uncertain whether lack of concentration/fidgeting etc was due to blood sugar levels or not, and how best to treat such behaviour. His school work improved with pumping. He is a much happier, and self confident boy now, with a zest for life.

The last time he caught a "24-hour sick bug" that was doing the rounds at school he ended up in hospital on a drip for 3 days, pre-pump. The next time he got a similar bug whilst he was on the pump, we just altered his basal rates and he fine the next day. What is the cost of 3 days in the children's ward?

With an insulin pump we have finally been given a treatment which actually works removing the randomness and unpredictability of the injection regimes. His HbA1c since pumping has never been higher than 5.8%.

Diabetes is such a cruel disease that anything that makes it easier for young people should not be withheld by a humane and generally wealthy society.

Judith [redacted]

I started on my first insulin pump in August 2000, at that time I had virtually no hypo awareness, being able to walk about with a blood sugar of 1.6mmols - I also had very poor control during the night as I have now found out I need much larger amounts of basal insulin just before I wake up in the morning - no insulin injection regime could assist this.

Since starting on the pump my life has been revolutionised - there are even days when I almost forget I am diabetic! My hypo awareness is now brilliant I start getting symptoms in the low 3's which is wonderful, although at no time since diagnosis have I ever become unconscious with a hypo. Michael, my husband used to say I think you are going off check your sugars!

My HBA1c has been 5.8-6.0% with no hypos since going on the pump which I do not believe would be possible with an injection regime and happily I have no eye problems.

I would never want to give up my pump as my control is FAR better than on injections and my hypo awareness is now far better than it was on injections. It has been a really wonderful tool in my attempts at good control.

PS my husband is blind (not through diabetes) so it has always been of prime importance to try and keep my control and eyes as good as possible - the pump has allowed me to do just that.
good luck with your campaign

Judith xx

Oliver [redacted] Age 5

Our son Oliver is 4 and was diagnosed with Type 1 diabetes aged 17 months. Until he started pumping 3 months ago he was on mixed insulin am, Novorapid pm with extra fast acting insulin when needed to correct any highs. His HbA1c has always been quite good with an average of 7.1 . You would think based on this HbA1c that Oliver had good control but unfortunately this 'good' HbA1c was due to massive swings between highs and lows. He has always needed very little insulin during the night and the slightest bit of exercise could send his blood sugars crashing during the night leading to a lot of night time hypos. We had to be very strict with his diet, the timing of his meals, exercise, bedtime and wake-up time. He couldn't spend a lot of time away from us as no-one else except my mam would give an injection. This limited his social skills in a way and completely destroyed our social life! His meals had to contain a rigid amount of carbohydrate in order to get any control. With young children a tiny bit more carbohydrate can lead to very high blood sugars or even just 1/2 unit insulin too much can lead to hypos. It was really hard on him in a number of ways:
- to have to eat a certain amount especially if he wasn't hungry, resulting in force feeding sometimes
- to not be able to eat what and when other children ate, or even when he was just hungry
- to feel dreadful a lot of the time due to high / low blood sugars. Sometimes some highs were impossible to correct as 1/2 unit would be too much
- to be hospitalised with every illness.

Oliver has only been pumping for 3 months but he is a different boy already. Within 3 days he had so much more energy, he was jumping out of bed every morning instead of having to be dragged out. He became more confident in himself and was generally so much happier. Within a month he had grown 3 cm. He can miss a snack if he feels like it, he can have a second helping at mealtimes if he wants too, I could go on and on. The pump is easy to use which allows him to spend time with family and friends, and allow us a bit of 'time off'. He started school in reception class just after he started pumping. The teacher can bolus for a snack if he wants one or correct if his blood sugar is high which makes him feel a lot better and able to concentrate in class. We have had a couple of sick days whilst pumping and they were so much easier to manage. When he was vomiting and unable to keep anything down we were able to turn the pump rate down and keep him stable. On injections he would have ended up being admitted to hospital but we managed easily at home. We can also increase basals if necessary which is better than lots of extra injections when ill.

I could say so many more positive things about the pump but the most important is that we all, especially Oliver, have a life back. He feels just like any other child for the first time he can remember.

With the right tool this dreadful illness can be managed so much better, its disgraceful that most people have to put up such a fight to get access to a therapy that can literally change their lives. With the improved control possible, it can also reduce the 'timebomb' of diabetic complications and the cost associated with this.

I hope I haven’t gone on too much - I could say so much more in favour of pump therapy!

Andrea mam to Oliver 4 dxd Jun02, partner to Simon

LIFE ON AN INSULIN INFUSION PUMP

By

Paul [redacted]

For a number of years I had wildly fluctuating Blood Glucose readings. My Hba1C level was at around 7.4%. The scary bit for my wife and I was the nighttime hypos. I searched around for solutions to these problems and I considered that an insulin infusion pump would be a good solution. It got around the problem that a single basal injection of long acting insulin by tailoring the basal delivery to the body's need at different times of the day, mimicking the pancreas delivery of background insulin. An insulin infusion pump can deal with the "dawn phenomena".

After an eventful year struggling to obtain funding for an Insulin Infusion Pump, in late March 2004 I got my hands on a pump and the initial 3 months supply of consumables.

With the aid of an excellent book "Pumping Insulin" and 2 days of training at the Royal Bournemouth Hospital under the tutelage of Joan Everett. I am afraid to say that my local Diabetes Clinic is not providing support to me.

Travelling long distances has become easier because of the pump. I used to be concerned about travelling by air, particularly to the USA. On the pump time zones changes do not affect me as much as they used to, as I can eat as I wish.

To say that my life has been changed since using the pump is an understatement. I am now firmly in control of my diabetes, I rule, not the other way around. I am fitter and my hypo awareness seems to be slowly returning. I have lost some weight, and hope to lose some more. I am using less insulin using a pump than when I was injecting. I use between 30 and 40 percent less insulin. My HbA1c is now lower and my widely varying BGs are now less so. For the first time in more than 30 years I feel "normal", I can eat when I like and what I like within reason. If I decide not to eat that is quite all right too.

During the time I have been using a pump I have undergone minor surgery with absolutely no problems. The pump is now firmly part of me and is only detached to enable battery (every 8 weeks), insulin cartridge and infusion set changes (every $3^1/_2$ days). I even wear the pump in the bath.

In other countries, such as the USA, Germany and Sweden, the use of insulin infusion pumps for treatment of insulin dependent diabetes is generally the primary method, whilst in England and Wales, all other means of treatment have to be exhausted before getting to what is undoubtedly the best method of treatment in the vast majority of cases. In the UK, every improvement in treatment of diabetes has had to be fought for by patients e.g. blood glucose testing by patients, and I suppose whilst there is still a health service driven solely by short term cost it will ever be so. What should be evident to all sensible people is the simple fact that a superior method such as Insulin Infusion will in the end save money by reducing the cases of kidney failure, blindness, heart attacks and like consequences of poor diabetes control,

I live in hope that diabetes treatment will be the same wherever one lives and that the clinicians involved, spend time listening to the experts in day to day diabetes management, the patients.

Profile – Rob [redacted] Age 12

Rob is aged 12 years. He has been pumping for 21 months.

it has changed his life incredibly. He can now be free of me (his mum) for whole days without having to constantly refer back. He carb counts and gives the dose accordingly.

He can go to friends' houses, have tea, supper, snacks, midnight feasts and feel "normal" - he just works out the carbs and gives the doses. Obviously a real must in the life of a 12 year old boy. Imagine having to constantly say - no I cannot have that, I have diabetes. He loves feeling like one of the boys.

Also instead of the obvious 4 to 5 injections a day - he has 2-3 injections a week - and this is a fantastic difference for him.

If ever we think we are having a problem with the pump, I panic like mad at the thought of going back to those nasty injections.

His HBA1c has come down - although not as much as we would have liked or as much as we were hoping, but slowly and surely it is coming down - to just over 8% at the moment.

Long live the pump!!!!

Jane [redacted]

Rosemary [redacted]
Benefits of Insulin Pumping

I have had Type 1 diabetes since the age of 12 (now 37 years). Over the years I dealt with my diabetes as well as could, but found it harder and harder to control my blood sugars. In recent years the lack of control was starting t seriously affect my quality of life. I would have a 'good day' – ie no blood sugar problems requiring correction and feeling well the whole day – only about once every 3 months.

I finally found out about pumping through the Insulin Pumpers website. It was never mentioned to me by any GP consultant. Pumping has changed my life and allowed me to regain my quality of life. Inevitably, since my blood sugars are now so much better, it will have helped me to avoid complications which invariably set in after such a long period of time with Type 1 diabetes.

The reasons why it has helped me are as follows:

1. I need varying amounts of background insulin during the day and overnight. A long-acting insulin – even one of the newer ones which has a more predictable absorption pattern – cannot possibly cope with this. F example, in the middle of the night I need only around 0.3iu per hour, whereas upon waking this has risen 0.9iu or even more. My requirements continue at a high level through most of the morning, then gradually reduce at lunchtime and through the afternoon, stabilising and rising slightly through the evening. With a pump I can deliver only the background insulin that is needed and vary it according to the time of day. I c also vary pre-meal insulin according to the time the meal is taken, as this also varies.

2. My insulin requirements vary considerably according to the stage of my menstrual cycle. I can expect to have a couple of weeks with relatively stable requirements, at the start of my cycle, then my insulin requirements rise in stages through the rest of the cycle. This is most noticeable in the amount of background insulin needed in the morning, which can double between the beginning and end of the cycle

   With injections, it is simply not possible to cope with these variations, as the timing of them is very difficult to predict. With a pump I can make adjustments as I consider necessary and because the pump uses only short term insulin, these are effective quickly. With injections of long-acting insulin it would be very difficult to cope with these swings. Interestingly, when I was on injections I didn't even notice this sensitivity to hormone fluctuations, since my control was so poor. When I started pumping and had better control, I was able to see the pattern almost immediately, and had the correct tool to deal with it.

3. Overall, I have found that the pump is a very efficient tool for dealing with the many different factors which influence my blood sugars – people don't normally realise just how many of these there are!

I remain mystified about why the medical profession has not embraced pumping more wholeheartedly. For many people, injections alone cannot possibly allow them to control their diabetes properly. What does this cost the individual in terms of their health and quality of life and what does it cost the nation in terms of healthcare costs when they develop complications??

Sasha [redacted] Age 12: A little background

[redacted]

Medical Conditions

Insulin dependant Diabetes Mellitus
Year of diagnosis 1999

Coeliac Disease
Year of Diagnosis 2001

Mild Asthma

Diabetes Mellitus

Our daughter, Sasha [redacted] was diagnosed with type 1 diabetes in April 1999. We have actively managed her condition since diagnosis and consistently achieved good HBA1c levels. However these good HBA1c results conceal widely fluctuating blood glucose levels during many days in a typical month and she regularly has episodes of both hypo and hyper glycaemia.

We had tried a number of different insulin regimes since she was diagnosed, but none of them had solved the problems.

The good HBA1c results we have obtained had only been possible as a result of significant cost to our family's overall quality of life, and despite this, the occurrences of hypo and hyper glycaemic episodes remained at a worrying high level.

Prior to pump therapy Sasha was on MDI using a split dose of Insulatard plus Novorapid with meals. We also had a trial on Glargine which was not successful. More about this later.

HbA1c

Sasha's HbA1c had ranged from 6.9% to 7.3% over the last few years. However, this, seemingly good HbA1c concealed generally unstable blood glucose control with widely fluctuating blood glucose (BG) test results. A summary of a typical recent period pre pump showed that Sasha's blood sugars ranged between 2.0 and 27.2 mmol with twenty-one hypoglycaemic events occurring during the thirty-three day period. Three of these occurred from the hours of 11:00pm – 2:00am and 7 of them occurred during the hours from 2-7am.

Nocturnal Hypoglycaemia and Variable Basal Rate Needs

Sasha has a lack of hypo awareness when asleep during the night and in the first two to three years after developing diabetes she had more than 7 severe hypos, which resulted in convulsions that need to be treated with an injection of glucagon and/or the administration of Hypo Stop. As a result of Sasha's unpredictable levels and with her not waking when she had low blood sugar, we felt compelled to test during the night, every night, usually between 2.00am and 4.00am. If we did not test and intervene at these times we felt sure that Sasha would be having many more frequent severe hypos leading to fits. We also had to give the smallest dose of intermediate insulin (NPH) as possible to keep the night time levels from falling too low. This sometimes meant that the blood sugars during the night increased to an unacceptable level and if we did not intervene and correct the high levels on these occasions, she would on some days wake with high blood sugar levels, which would stay raised and be difficult to reverse for many hours of the next day. This caused her to feel tired, unwell and unable to concentrate at school.

Note: we did try Lantus but actually had worse results that with NPH. One of the most difficult problems for Sasha when using Glargine was once given you could not do anything to reduce the amount of long acting insulin on board. Therefore, if Sasha decided to go out and play football or ride a bike and play games with her friends outside during the afternoon and evening you could do nothing to stop the action of the already administered insulin. With Glargine, once it is injected it's" IN and ON" until it's gone! Extra snacks of food could be eaten but still didn't always stop the blood sugars from dropping at unexpected times during the night. We had to check BG levels even more often than previously! We had three episode of totally unexpected hypoglycaemia at night time which were only picked up on because we were carrying out night time checks.

Low insulin requirements overnight

Despite keeping the overnight insulin to a very low dose to avoid nocturnal hypos and administering the over night NPH insulin at 7.30 pm, so that the peak of the action happens before 11.30 pm, we often find readings of below 4mmols with some below 3.0 mmols. All these events require the assistance of a third party. We have to help Sasha to drink Lucozade or eat something as she does not wake up by herself and keeps falling back to sleep as we help her eat or drink. On some occasions we have to set the alarm clock to recheck the blood sugar again an hour or two hours later.

Effects on quality of life

Because of the fluctuations and unpredictability of Sasha's blood sugar she was unable to stay overnight at friend's houses and was seldom invited to play at other children's houses, as the parents are worried about Sasha having a hypo. This is made all the more upsetting as Sasha has an identical twin sister who does not have diabetes and was able to go to friend's houses for tea and to stay over night. Sasha finds this very upsetting and this has a significant effect on the quality of Sasha's life.

Looking towards Sasha's future

Sasha was diagnosed with diabetes at the relatively young age of four years. By the time that Sasha reaches the age of 25 she will have had diabetes for 20 years; by that time she may have developed complications caused by poor control. Any steps taken now will reduce the possibility of complications developing and diminish the effects of any that do. Treating complications can be a potentially expensive business. Effective treatment now will not only improve Sasha's quality of life now and in the future, it is likely to save the NHS money in the long run.

Diabetes is a chronic disease that is almost entirely managed by the patient and/or parents. One can muddle through for years with a mediocre or poor quality of life and poor health status for umpteen years before things get critical. We wanted Sasha to have a better quality of life now and a better outlook for the future and we believe that a pump has given Sasha this option.

Now Sasha has Insulin Pump.

After a three year fight to get a pump and finding a suitable hospital close enough Sasha started pump therapy at Gloucestershire Royal Hospital Gloucester, under the care of [redacted].

Sasha's quality of life had improved enormously. She now has a lot fewer hypos. She had more energy. She wakes up in the morning feeling much better. She started secondary school this September and has taken this completely in her stride. Having the pump has made it possible for her to have more independence she can now walk to and from school which was difficult before due to activity having such an effect on the blood sugar levels. She doesn't have to leave her group of friends to go off to administer an injection.

She takes part in competitive gymnastics. She trains for 3 hours on Sundays and checks her blood glucose levels removes the pump, tests and reconnect half way through and reconnects at the end of the session. During this time her blood sugar levels are usually still in range (over 4 mmols and under 8 mmols) we were unable to get this sort of control whilst using NPH or Glargine and in fact

after one gym session prior to pumping she had a severe hypo which involved having to call an ambulance.

The pump gives much more flexibility for meal times. No more having to eat unwanted snacks, or finish all the food on your plate. Meals can be delayed without problems. Meaning that we can sit down to family meals again without having to always feed Sasha at set times. She has also become much more confident about herself as she no longer worries about unexpected hypos which used to interrupt life regularly. The unpredictability of the blood sugars has ceased to be the problem it was.

During the last few weeks we can go for days with the blood sugar levels in the ranges of 4 -9 mmol. We still have the occasional low or high level but this it minor compared to the fluctuations we had before the pump. If there are out of range levels, these much more easily treated when using pump therapy. Hypos are easier and quicker to treat.

Sasha's first HbA1c after the beginning of pumping April 2005 was 6.6% in June, 5.8% in August and the last HbA1c November was 5.6%.

This is the result of more controlled blood sugars, very few hypoglycaemic or hyperglycaemic levels.

There are no longer the same issues about visiting other children's houses and staying for meals.

Needless to say we and Sasha are very, very happy with the control and the freedom the pump has given our daughter.

She says that she loves pumping and it has made a huge difference to her life, as she is no longer feeling unwell because she was either too high or too low. She feels that SHE is now in control of her life instead of the diabetes being in control.

Kind Regards

Jackie [redacted] mum of Sasha aged 11

Terry [redacted]

I have been a type 1 diabetic for almost 46 years. I started on one injection a day in 1960. This soon changed to two per day, eventually four per day.

I suffered a number of hypos, some required emergency treatment at various A & E depts! Also, extremely high blood sugars (hypers) without good reason.

I started on a D-Tron Plus pump in April 2004.

My quality of life was changed. I've not had a serious low or high Bg since. Also, I can vary my day without the worry when driving.

All this won't make my other associated long term problems go away but will help stop further unnecessary visits to hospitals and doctors. Also, heart and other serious conditions are likely not to affect me like when on MDI treatments because of my stability.

I view all this a long term saving to the NHS, both in time and money.

Many thanks for all your work,

Regards,
Terry [redacted]

I began on a pump in 1999 when 10 years of MDI had failed to work for me. My HbA1Cs were in the mid- to high teens despite blood testing and injections up to 10 times a day. I had developed proliferative retinopathy over the previous 5 years and was registered blind. I also showed signs of kidney damage. I have always led a very active and healthy lifestyle and participated in many sports, sometimes doing up to 30 hours exercise a week. This played havoc with my blood sugar control and it was very difficult to prevent the swings from high to low, especially during and after sports, and this affected my performance considerably. I was permanently tired from the blood sugar swings and went through a stage of depression and insomnia for several years; I also struggled to lose weight despite the exercise and healthy lifestyle.

When I began pump therapy, things changed almost instantly. My HbA1Cs dropped to around 6-7%, I had more energy, I was sleeping through the night, and I was able to fine tune my insulin requirements. Although my blood sugars still show quite marked swings at times, I now have the tools to deal with this a lot more effectively, in particular using the suspend and temporary basal features to lower my insulin when active. I rarely have hypos requiring 3rd party assistance after exercise these days. I am also able to control my dawn syndrome by increasing the rate after breakfast, and to deal with events that would otherwise wreak havoc with my control such as eating at odd times (for example during sports tournaments). I use up to 4 basal rates a day, frequently adjusting the nighttime basals depending on my activity levels and carbohydrate intake during the previous day. My night time basal rates are around half those of my daytime rates, something which was very hard to simulate on MDI.

Since commencing pump therapy, my eyesight has stabilised and I have not required further treatment for the last 4 years. My kidney function has returned to normal also and show no signs of problems. Having been advised by my retinal consultant that I was destined to lose my sight entirely within 6 months (pre-pump), I have no doubts that this would have happened had I not commenced pump therapy and been able to stabilise my blood sugar levels.

Guidance on the use of continuous subcutaneous insulin infusion for the treatment of diabetes (review of Technology Appraisal Guidance No 57, Feb 2003)

Evidence submitted to NICE by Professor John Pickup, as a nominated clinical expert

Address for communication:

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[redacted]

Expertise and conflicts of interest

I am the lead author of the team that first described continuous subcutaneous insulin infusion in 1978 and have published extensively on the subject. I am the Consultant-in-Charge of the Insulin Pump Clinic at Guy's and St Thomas' NHS Foundation Trust, London, which was the first NHS-funded clinic for CSII in the UK and is currently one of the largest adult insulin pump clinics in the UK. I am Professor of Diabetes and Metabolism at King's College, London (Guy's Hospital) and visiting Professor at the University of Strathclyde, Glasgow.

Personal Review of Appraisal

I refer to the sections in the 2003 Appraisal, discuss the context of any need for updating the comments, and make recommendations for the current review committee to consider.

1.1. CSII is recommended as an option...provided that:

- multiple dose insulin (MDI) therapy (including where appropriate the use of insulin glargine) has failed

Context

(i). There has been considerable criticism from patient groups and some doctors about the use of the word 'fail'. Though it has a recognised medical meaning in the sense of not been able to achieve targets for whatever reason, many feel that it implies a criticism of patients. This must be seen against the background that poor control has often erroneously been seen as the fault of the patient.

(ii). MDI is increasingly seen as only a short-hand expression for a package of measures concerning modern optimised diabetes treatment for people with type 1 diabetes, including not only MDI itself but also education, diet and exercise, blood glucose self monitoring and insulin dosage adjustment.

(iii). Glargine has been joined by detemir as a long-acting insulin analogue which should be tried as part of an MDI regimen before considering CSII.

Recommendation

Consider changing to:

....provide that:

- Multiple dose insulin (MDI) therapy (including structured education, diet and exercise, blood glucose self monitoring and insulin dosage adjustment) has been unsuccessful in achieving strict glycaemic control without hypoglycaemia.

1.1. ...haemoglobin A1c level no greater than 7.5% (or 6.5% in the presence of microalbuminuria or adverse features of the metabolic syndrome) without disabling hypoglycaemia

Context

This has been a difficult sentence to understand for many practitioners, partly because no evidence was presented in the appraisal for choosing these cut-off levels of HbA1c or the dependence on microalbuminuria and the metabolic syndrome) and none seems to exist. There is also confusion in what is meant by an 'adverse feature of the metabolic syndrome' – is there a feature which is not adverse? In any case, most will consider that the metabolic syndrome is primarily a concept pertaining to type 2 diabetes (not the target group for CSII).

Recommendation

Consider amending to 'Those for whom MDI has been unsuccessful are considered those where an HbA1c within the target range cannot be achieved without the occurrence of frequent, unpredictable hypoglycaemia'.

2.4. The age standardised prevalence...

Context
The prevalence of diabetes has increased since 2003
Recommendation
Update these estimates

2.9. There are four main types of insulin...

Context and recommendations
Note the introduction of long-acting insulin analogues like glargine and, since 2003, detemir. Inhaled insulin should also be included as a therapeutic option for a minority of people with diabetes.

2.11 Living with diabetes requires...for people receiving insulin therapy, multiple daily injections

Context
This is not strictly true, since most people with type 2 diabetes can often be well managed with twice-daily insulin injections and sometimes with only once-daily injection of insulin.

Recommendation
Consider changing to 'Most people with type 1 diabetes need multiple daily insulin injections to achieve good glycaemic control, and some insulin-requiring people with type 2 diabetes also benefit from a switch to MDI when control is poor on regimens with less frequent insulin injection.

3.5. The additional costs of CSII..Currently about 800 people ....

Context and recommendations
These figures need updating, concerning both the current cost of insulin pumps and supplies in the UK and the estimated number of people with diabetes using CSII in the UK (obtainable from pump manufacturers and INPUT). As the consequence of the Guidance of 2003, most pump users in the UK are now NHS-funded and the proportion who are self-funding or funded through charities has diminished significantly.

It may be appropriate for the Appraisal Committee at this point to record the comparative usage of CSII in different countries [see my evidence in the DOH Report (1), where I show that UK pump usage is still less than 1-2% of those with type 1 diabetes, whilst the percentage usage in many European countries of comparable economic standing and healthcare provision is 10-15%, and the uptake in the USA is >20%]. This is not just to note the low uptake in the UK (which alerts us to the disappointing implementation of the 2003 Guidelines), but also serves to underline the increasing worldwide clinical experience of the treatment.

4.1 Clinical effectiveness

Context
The 2003 Guidelines were only able to conclude that the overall mean difference in HbA1c between MDI and CSII was about 0.6%, favouring pump therapy. Many of the trials used older pumps (sometimes less reliable and with less adjustments) and older insulins (i.e. not monomeric) and might have given suboptimal performance. Little information was available to the Assessment Group on changes in hypoglycaemia, quality of life or CSII in children and adolescents, and none on the impact of MDI using new long-acting insulin analogues. Interestingly, there was no information available on the expected quality of control (HbA1c) during CSII in the recommended group of hypoglycaemia-prone type 1 diabetes.

A considerable number of studies relevant to these issues have been published since 2003 and new information has been accumulated on the following:

(i). Severe hypoglycaemia

I performed a meta-analysis and metaregression study [(2), Pickup and Sutton, submitted for publication, see Appendix 1) selecting trials in the target group of NICE-recommended subjects, i.e. those with significant hypoglycaemia during MDI, published between 1996 and 2006 (i.e. using modern pumps and insulins) and where the duration of CSII was ≥ 6 months (i.e. long enough for significant hypoglycaemia to be recordable). Twenty-two studies in 21 publications (3 RCTs, 19 before/after studies) met the selection criteria. Hypoglycaemia was markedly reduced during CSII compared to MDI (rate ratio 4.19 [95% CI 2.86 to 6.13]), with the greatest reduction in those with the highest initial hypoglycaemia rate on MDI ($p < 0.001$). Mean age ($p = 0.019$) and diabetes duration ($p = 0.025$) were also predictors of hypoglycemia reduction on switching to CSII. Thus hypoglycaemia reduction on switching to CSII in children is still marked and significant, but somewhat less than in adults because of the shorter diabetes duration and initial hypoglycaemia rate on MDI in children.

The effectiveness of CSII in reducing hypoglycaemia was not related to the duration of pump therapy. Before/after studies gave similar results to RCTs.

We found no trials comparing severe hypoglycaemia on CSII with MDI based on glargine or detemir, but 4 additional studies compared HbA1c on glargine-based MDI and CSII (see below).

There is no other meta-analysis of hypoglycaemia during MDI and CSII in the literature.

(ii). HbA1c

In the above meta-analysis (2), the mean difference in HbA_{1c} between treatments was 0.62 (95% CI 0.47 to 0.78)% (i.e. confirming the NICE 2003 Appraisal). There was a similar difference in HbA1c (MDI vs. CSII) with isophane/lente- or glargine-based MDI. This confirms our results from observational studies in individual patients (3), where we found no evidence that MDI based on glargine improved HbA1c in poorly controlled patients treated by isophane-based MDI, but who subsequently enjoyed a substantial reduction in HbA1c on switching to CSII.

The mean difference in HbA_{1c} (MDI vs. CSII) was strongly related to the mean initial HbA_{1c} on MDI ($p < 0.001$), with the worst controlled subjects with an HbA1c of about 9.5 % on MDI having a reduction in HbA1c of about 1.5% on switching to CSII.

The dependence of change in HbA1c on initial HbA1c on MDI is confirmed by recent studies in individual patients from our group (4) and others (5).

It is important that in our meta-analysis we showed that in 10 trials the mean HbA_{1c} on MDI was ≥8.5% (mean 9.0%), in spite of significant severe hypoglycaemia (median hypoglycaemia rate 65 episodes/100 patient-years). This provides further evidence to confirm the common clinical observation and audit data (3) that patients in the main hypoglycaemia-prone target group for insulin pump therapy often maintain a high HbA_{1c} during best attempts with MDI. We have recently shown (4) that a main determinant of HbA1c is the glycaemic variability (e.g. measured as standard deviation of blood glucose values). It is likely that the variability and the consequent risk of hypoglycaemia deters attempts to tighten control with injection therapy. Thus, patients referred for CSII may have a high HbA1c and glycaemic variability but little severe hypoglycaemia. We have shown that not only is within-day but also between-day blood glucose variability is improved on CSII (3). Patients may thus have a larger change in HbA_{1c} on switching to insulin pump therapy than previously recognised.

Recommendations:
Consider noting the following:

1. The rate of severe hypoglycaemic episodes is on average about 4 times less during CSII than during MDI, but the reduction is greatest in those with the highest rate of hypoglycaemia on MDI.
2. The reduction in severe hypoglycaemia remains significant and notable in children but it is somewhat less than in adults (because the rate of hypoglycaemia on MDI is less in children with their lower duration of diabetes).
3. The reduction in HbA1c on switching to CSII from MDI is greatest in the worst controlled patients on MDI.
4. In addition to those with frequent severe hypoglycaemia on MDI, a further group of subjects who benefit from CSII are those with a high HbA1c (usually with high glycaemic variability) on MDI. This should be an additional indication for a trial of pump therapy.

(iii). The impact of long-acting insulin analogues

I have mentioned above that we have found no evidence from meta-analysis and clinical audit that HbA1c is improved by long-acting insulin analogues in hypoglycaemia-prove subjects. The reduction in HbA1c (in our meta-analysis) on changing patients treated by glargine MDI to CSII is similar to the change from isophane regimens (0.63%). Severe hypoglycaemia is more difficult to assess since we found no trials of sufficient duration comparing this complication in glargine- or detemir-based MDI with CSII . However, several studies and a meta-analysis of long-acting insulin analogues have concluded that the frequency of severe hyoglycaemia is unaltered during glargine- or detemir-based MDI vs. isophane regimens (6-10).

Recommendations
Consider noting that present evidence does not indicate that the introduction of long-acting insulin analogues will reduce the need for insulin pump therapy in the target group of people with type 1 diabetes who have not achieved satisfactory control on MDI.

(iv) 4.1.9 to 4.1.11. CSII in children and adolescents

Context
The 2003 Appraisal notes an absence of RCTs in children concerning CSII and little trial data in adolescents. There have been more than 25 studies of insulin pump therapy in children and adolescents since 2002, including 5 RCTs (11-15) ; these have confirmed that CSII is safe and effective in young people with type 1 diabetes.

In our meta-analysis (2) (which had particular selection criteria), 11 studies (42%) were in children or adolescents (3 RCTs). I have mentioned above that children have a lower reduction in hypoglycaemia on switching to CSII because of their shorter duration of diabetes, though hypoglycaemia reduction on pump therapy remains significant and marked. As far as reduction in HbA1c is concerned, the meta-analysis indicates that insulin pump therapy is about as effective in children as it is in adults. In a multivariate regression analysis adjusting for the HbA1c during MDI and the study design, age is a significant predictor of the mean HbA1c difference between MDI and CSII but the effect is small (coefficient 0.0072): a 10 year old might expect the HbA1c difference on switching to CSII to be on average an HbA1c level of about 0.1% less than for a 30 year old.

The Appraisers will want to note the accumulation of reports on CSII in very young children with type 1 diabetes (13,15-19) (< 7 years of age at start of pump therapy), where there are special considerations such as the extreme emotional impact of diabetes in such young children on their parents and caregivers, the huge variability in eating and activity in children, the inability to communicate hypoglycaemia as well as older children and their special vulnerability to hypoglycaemia. CSII is as effective at reducing HbA1c and severe hypoglycaemia in this group as in older age groups and is not associated with an increased risk of ketoacidosis. A 2006 Position Statement on CSII in very young children has concluded that 'all children with diabetes, regardless of age, should be considered potentially eligible candidates for insulin pump therapy' (19).

The Appraisers will also want to note the multinational 'Consensus Statement on the Use of Insulin Pump Therapy in the Pediatric Age Group (in press at the time of writing [20]) which includes much practical advice on performing CSII in children.

Recommendations
Consider noting the above

4.12. CSII in type 2 diabetes

Context
The 2003 Appraisal states that there was insufficient evidence to draw conclusions from studies comparing the effect of CSII with MDI in type 2 diabetes. There have been 3 RCTs since 2003 comparing MDI and CSII in people with type 2 diabetes (21-23). In two of these studies, there was no significance difference between HbA1c during MDI and CSII, and though the third study is more difficult to interpret, there appeared also to be no difference in HbA1c between the two treatments in the completers' cohort. There is little evidence that weight or insulin dose differed on CSII and MDI, and although treatment satisfaction was greater for CSII in one study, it was similar for MDI and pump therapy in another.

This lack of evidence for a benefit of CSII in type 2 diabetes in RCTs must be contrasted with some briefly reported observational studies of people with poorly controlled type 2 diabetes who have been switched from MDI to CSII with a significant reduction in HbA1c and sometimes insulin dose (24). I can confirm from my own clinic that CSII is effective in some type 2 diabetic patients who are poorly controlled and insulin resistant during MDI. One should note that the initial mean HbA1c in two of the RCTs was about 8-8.2% i.e. the subjects were not on average the most poorly controlled. There has been no analysis of baseline effect to determine if the worst controlled subjects had a greater change in HbA1c on switching to CSII.

Recommendation
There is evidence that CSII is as beneficial as MDI in type 2 diabetes, but no indication that it should be used in preference. More research is needed to determine if insulin pump therapy is indicated in certain subgroups of people with type 2 diabetes.

4.2. Cost effectiveness

Context
The 2003 Appraisal records that no economic evaluations have appeared in the literature. At least two analyses in English language journals have appeared since that date (25,26), but these studies fail to take notice of recent evidence on the relationship between clinical effectiveness and initial glycaemic control – for HbA1c and/or frequency of hypoglycaemia on MDI.

This is particularly important as far as HbA1c is concerned because the largest effect is in the worst controlled patients and because a reduction in HbA1c in the poor control region (say HbA1c 9-10% on MDI) occurs on the steep part of the curve relating HbA1c to microvascular risk (27). Since many target-group patients have an elevated HbA1c on MDI (2,3) they will thus expect a large reduction in HbA1c on switching to CSII, and the associated reduction in

microvascular risk is greater than if the same glycaemic control improvement occurred on the flat part of the risk curve (say, 6-8%).

We also showed in our meta-analysis (2) that the rate ratio for hypoglycaemia reduction is about 5-fold greater for a patient experiencing 1 episode of severe hypoglycaemia per year during MDI compared to a person with 1 episode every 10 years.

Recommendation
New cost effectiveness studies need to be done which incorporate into the model the much greater clinical efficacy in the target group of people with type 1 diabetes who are poorly controlled because of hypoglycaemia or an elevated HbA1c.

4.3 Consideration of the evidence
Context
The 2003 Appraisal considered that the evidence from clinical trials showed that either CSII is 'no more effective than MDI or at best the difference is small'. There is now good evidence (see above) that the difference in HbA1c and frequency of severe hypoglycaemia in the target group is both significant and large. The 2003 Appraisal also concludes that benefits from CSII are seen in 'a small subgroup', or 'a selected group of people who were determined to do everything possible to overcome previously inadequately controlled disease', and that 'this group comprises only a very small proportion of people with type 1 diabetes'.
This view is contrary to present evidence on the widespread international use of CSII and its efficacy and a re-assessment of the numbers likely to benefit from CSII (see below).

Recommendation
This section should be amended to take note of the evidence on the efficacy of CSII and either at this point or elsewhere in the Appraisal, the implications for the numbers of people who would benefit.

4.3.3. Quality of life
Context
The Committee drew attention to the contrast between evidence from users of CSII that a more satisfactory quality of life (QoL) could be achieved and the evidence from clinical trials. More evidence has been presented on QoL since 2002, with many reports showing that it is improved during pump therapy (13, 28-31). Nevertheless, it is the case that some trials report no improvement in at least some aspects of QoL when using CSII (32). In this context it is necessary to consider the varying sensitivity and appropriateness of QoL measures and (as with glycaemic control and hypoglycaemia) whether QoL improvements might be different in different sub-groups.

In response to the need for improved QoL instruments for use in assessing new technology, we have recently developed and validated a patient-centred QoL measure that is simple and quick to complete (<5 min), correlates well with the 'gold standard' Diabetes Control and Complications Trial QoL index, and is sensitive enough to detect a significant difference in QoL between MDI and CSII-treated people with type 1 diabetes (33). The index is based on patients nominating five aspects of general- and diabetes-related life which they themselves (not the healthcare professional) judge most important for their overall quality of life, and rating each for current level of satisfaction.

Recommendation
Note the increasing evidence that QoL is improved during CSII compared to MDI but that there is on-going debate and research into the types of QoL measure that are best suited for assessing QoL differences during different treatments, including CSII.

4.3.10. The number likely to benefit from CSII

Context

The 2003 Appraisal states that 'the proportion of people with type 1 diabetes who would be appropriate for and would take up insulin pump therapy would be of the order of 1% to 2% of the total'. The evidence base for choosing the figures of 1-2% was not presented and this limited range has been widely misunderstood and misinterpreted by commissioners of pump services, particularly in so far as it might justify a cap of 2% on the number of insulin pump users in an area.

I have presented elsewhere the evidence base for estimating the numbers of people with diabetes who might benefit from CSII on clinical grounds alone (34). This gives no consideration to the numbers of people with diabetes who might choose CSII as their form of intensive insulin therapy (i.e. patient preference), or affordability. I estimated the proportion of people with type 1 diabetes treated by MDI who are suffering from severe hypoglycaemia, markedly elevated HbA1c, extreme blood glucose variability and unpredictable hypoglycaemia and the dawn phenomenon.

The distribution of severe hypoglycaemia is extremely skewed, with about 5% of people suffering 70% of all episodes (35). There are therefore likely to be some 5% of people with type 1 diabetes treated by MDI with severe, recurrent hypoglycaemia. At least another 5% suffer severe hypoglycemia at such a frequency that it is markedly disabling to them. In fact, about 20% have two or more severe hypoglycaemic episodes per year (35). I estimate that about 15% of type 1 diabetic subjects on MDI have the syndrome of markedly elevated HbA_{1c} and wide swings in blood glucose concentration, often with unpredictable, moderate (non-severe) hypoglycaemia (34). Only a small percentage will have the dawn phenomenon after optimised MDI (about 5%), because there is evidence that this can be improved by regimens using long-acting insulin analogues. These clinical problems are at least as important in children as adults. On present evidence, the proportion of subjects with severe hypoglycaemia or unacceptable hyperglycemia who are improved by regimens using new long-acting insulin analogues is likely to be small (see above). The studies supporting these estimates are given in the cited paper (34).

Some patients are known to be unsuitable for insulin pump treatment because they are unable to perform pump procedures, are psychologically unsuitable or simply decline this treatment option and prefer MDI. Even using the most conservative estimate that this number is as much as one quarter of those with the above clinical problems, a reasonable minimum target for those type 1 diabetic patients who should be offered a trial of insulin pump therapy is thus about 15-20% of type 1 diabetic subjects. This a percentage of patients similar to that already so treated in the USA and several European countries (1).

Recommendation

Consider amending the statement to 'The proportion of people with type 1 diabetes who may benefit from CSII on clinical grounds, or who should be offered a trial of CSII, might be about 15-20 % of the total of those currently treated by MDI. It is recognized that there are likely to be organizational, financial, staffing and other challenges to achieving this suggested level of pump usage in the near future, not only for the UK but for several other countries'.

7 and Appendix C. Implementation and Audit

Context and recommendations

The Appraisal group will want to refer to the recent Dept of Health Report which reviews and recommends procedures for implementing and auditing CSII. Though the 2003 Appraisal recommends some measures for audit, it has been generally difficult to audit CSII in recent years, since there have been no agreed standards against which the outcomes of insulin pump therapy can be compared. However, I present above the evidence for the range of expected changes in severe hypoglycaemia and HbA1c on switching to CSII and it should now be possible to incorporate these as standards into audit programmes (taking due note of the effects of age, initial hypoglycaemia frequency and level of HbA1c on MDI).

In our experience, the number of people on CSII who return to MDI because of failure of pump therapy to improve control or because of a patient request to stop CSII is small, about 2% of those started. An audit target might reasonably be estimated as at least 90% would be expected to remain on CSII. This low rate of discontinuation is probably because of a strict protocol for selecting people for a trial of CSII in our Pump Clinic, and the Appraisal Group might want to consider underlining the benefits of such a protocol. In brief, all patients are seen first by a consultant who assesses whether CSII is a possible therapy, and then patients who wish to consider CSII are entered into a pre-pump assessment programme where a pump nurse and dietitian try again to improve control on MDI (which succeeds in about 10% of cases). This pre-pump assessment has as a component an education programme which includes injection technique (e.g. sites), changing the insulin regimen if necessary, re-teaching blood glucose self monitoring and insulin dose adjustment, and appropriate dietary advice including 'carbohydrate counting'. There is a discussion and demonstration of insulin pump therapy with the patient, and the patient has time to discuss insulin pump therapy with friends and relatives at home. And the healthcare team can assess the psychological and other suitability of the patient for insulin pump therapy. Only if these measures do not improve control and the patient is willing to consider CSII and considered suitable is a trial of pump therapy then offered.

The Appraisal Group may want to consider the patchy implementation of the 2003 Guidelines in the UK (poor in many areas) and how this might be rectified. There are no formal assessments of attitudes to CSII and its implementation in the UK, but a useful pointer to the barriers to uptake can be obtained from a nationwide survey in Denmark (36), which like the UK, is a low-pump-use country. The two main obstacles to implementing CSII were considered to be ignorance of the benefits and safety of CSII, and lack of resources. Both are true of the UK. It is perhaps understandable that many areas of the UK do not have the resources to start a pump service or have not yet put a team in place for delivering a pump service, but it is of considerable concern that, as experience from my clinic shows, patients are often referred to a specialist pump centre because their local consultant 'does not believe in pumps', or 'does not know anything about pumps' or thinks 'pumps are dangerous'.

It is clear that considerable education is necessary about the indications for CSII, and its possible benefits and restrictions. This extends beyond training courses in pump procedures which will be attended mainly by those with an interest in CSII, and the Appraisal Group may want to recommend how education on insulin pump therapy can be extended to the wider medical community

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Appendix 1

Meta-analysis submitted for publication

Severe hypoglycemia and glycemic control in type 1 diabetes: meta-analysis of multiple daily insulin injections versus continuous subcutaneous insulin infusion

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Running title: Severe hypoglycemia during MDI and CSII

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Abstract

Context Continuous subcutaneous insulin infusion (CSII) is a recommended therapy for people with type 1 diabetes who cannot achieve good glycemic control on multiple daily insulin injections (MDI) because of frequent severe hypoglycemia, but the evidence base for this is unclear. The expected change in glycemia (measured by HbA_{1c}) when switching to CSII in this target group is also uncertain.

Objective We performed a meta-analysis and meta-regression of studies comparing severe hypoglycemia frequency and HbA_{1c} in people with type 1 diabetes.

Data sources Medline and Embase electronic databases and cited literature from retrieved articles published from1996-2006.

Study selection Randomised controlled trials (RCTs) or before/after studies, of ≥ 6 months duration CSII and with hypoglycemia frequency >10 episodes/100 patient years on MDI. We excluded studies in type 2, newly diagnosed type 1 and pregnant diabetic subjects. From 61 potentially relevant reports, 22 studies in 21 publications (3 RCTs, 19 before/after studies) met the selection criteria.

Data extraction From text, tables and graphs by two independent observers

Results Severe hypoglycemia during MDI was related to diabetes duration ($p = 0.038$) and greater in adults than children (100 vs. 36 events/100 patient-years, $p = 0.036$). Hypoglycemia was markedly reduced during CSII compared to MDI (rate ratio 4.19 [95% CI 2.86 to 6.13]), with the greatest reduction in those with the highest initial hypoglycemia rate on MDI ($p <0.001$). Mean age ($p = 0.019$) and diabetes duration ($p = 0.025$) were also predictors of hypoglycemia reduction on switching to CSII. The pooled mean difference in HbA_{1c} between treatments was 0.62 (95% CI 0.47 to 0.78)%, with similar difference with isophane/lente- or glargine-based MDI. Mean difference in HbA_{1c} was strongly related to the initial HbA_{1c} on MDI ($p <0.001$).

Conclusion The rate of severe hypoglycemia is about 4 times less during CSII than MDI. The greatest reduction in hypoglycemia on switching to CSII occurs in those with most hypoglycemia on MDI and those with longest duration of diabetes, and the biggest improvement in HbA_{1c} is in those with the highest HbA_{1c} on MDI.

Severe hypoglycemia is a devastating and much-feared complication of type 1 diabetes, with considerable morbidity[1,2]. Despite strenuous efforts to improve glycemic control since the publication of the Diabetes Control and Complications Trial[3], the frequency of severe hypoglycemia in the general type 1 diabetes population is often recorded as higher now than in 1993[4].

Continuous subcutaneous insulin infusion (CSII, insulin pump therapy) is recommended by several national guidelines[5,6] as a therapeutic option for people with type 1 diabetes who fail to achieve satisfactory glycemic control on multiple dose insulin injections (MDI) because of frequent severe hypoglycemia. Surprisingly, the magnitude of the change in severe hypoglycemia and glycemic control (e.g. as measured by glycated hemoglobin, HbA_{1c}) which is to be expected on switching to CSII in this specific recommended group is unclear and not recorded by the guidance. Reports have been unable to compare hypoglycemia during CSII and MDI using meta-analysis because of unsuitable data[7,8]. Furthermore, some trials show no change in hypoglycemia[9] and a 2002 evidence review even concluded that CSII is associated with an increased risk of hypoglycemia[10].

Difficulties include trials comparing CSII and MDI being too short-term for severe hypoglycemia to occur, or using patients with an initial very low rate of hypoglycemia. In some trials, hypoglycemia was a specific exclusion criterion, or early-generation pumps and pump insulins (i.e. not monomeric insulin) were used which may have suboptimal performance.

As far as glycemic control is concerned, a meta-analysis of trials comparing MDI and CSII in patients with type 1 diabetes without the problem of hypoglycemia showed only a relatively small difference in HbA_{1c} between the two therapies, about 0.5%[7]. More recent studies have indicated that the improvement in HbA_{1c} may be much larger in hypoglycemia-prone type 1 diabetic patients, who often maintain an elevated HbA_{1c} on MDI[11].

We therefore performed a meta-analysis of studies comparing the frequency of severe hypoglycemia and the associated HbA_{1c} during MDI and CSII, selecting only trials from the last decade (i.e. using a

high proportion of modern pumps and insulins), in patients with a significant initial rate of severe hypoglycemia (the target population in guidelines) and of adequate duration of pump therapy. We also investigated whether any improvement in glycemic control or hypoglycemia frequency using insulin pump therapy was associated with the level of control achieved on insulin injections.

Methods

Identification and selection of trials

For study of severe hypoglycemia, we selected for inclusion in the meta-analysis only trials in type 1 diabetes of $\geq$ 6 months duration of CSII, where the rate of severe hypoglycemia during MDI was >10 episodes/100 patient years of treatment, and the study was published no earlier than 1996. Severe hypoglycemia was defined as that requiring third party assistance, including unconsciousness, seizure, glucagon adminstration and emergency attendance or admission to hospital. We excluded trials in type 2 diabetes, newly diagnosed type 1 diabetes, and in pregnant diabetic patients. We also identified trials which, although ineligible for study of hypoglycemia (e.g. because of short duration or low hypoglycemia rate), used an MDI regimen based on a long-acting insulin analogue (glargine or detemir), and we analysed these in a comparison of HbA_{1c} during MDI and CSII.

To identify trials, Medline and Embase electronic databases were searched for studies reported from 1996-2006, and cited literature in retrieved articles was also reviewed. The search terms used were insulin pump therapy, insulin infusion system, insulin pump, continuous subcutaneous insulin infusion and CSII.We selected randomised controlled trials and before/after studies in which patients were switched from MDI to CSII and acted as their own control, but we excluded studies with two non-randomised groups who had chosen to be on either therapy (e.g.[12]). Data were examined in text, tables and graphs and extracted by two independent observers, differences in interpretation being resolved by consensus after discussion.

Outcome measures

Severe hypoglycemia was recorded as episodes/100 patient years of treatment. Both the rate on MDI and the rate ratio for episodes on MDI compared to CSII were considered as outcome measures. We assessed overall glycemic control using HbA_{1c} and the mean difference in this quantity on MDI compared with CSII in each trial was used as the outcome measure.

Statistical analysis

Study results were combined using meta-analysis. A preliminary assessment of the degree of heterogeneity between study results was obtained by calculating the I^2 statistic[13] (the proportion of variability attributed to heterogeneity). Where a non-zero value for I^2 was ascertained, random effects models were used to combine studies.

Analysis of hypoglycemia frequency on MDI and the ratio of hypoglycaemia rates during MDI to those during CSII were carried out on a $\ln_e$ scale. Although data from before/after studies and crossover-trials were paired, only aggregate data per treatment were available, and hence standard errors (SEs) of treatment effects from these studies could not be appropriately adjusted for pairing[14] and are therefore conservative.

The mean differences in HbA1c between interventions were meta-analysed using weighted mean differences. We used the methods of Elbourne et al.[14] to take into account the paired nature of the data in deriving a SE of the mean difference, even when this statistic was not reported in the trial. The following hierarchy of methods was used to derive SEs:

(1) Where the SE of the difference was extractable from summary statistics or could be calculated from confidence intervals (CI), this was used directly.
(2) Where no SE of difference or CI was provided but a p value from a paired t-test given, this was used to derive the SE.

(3) Where it was unclear whether the t-test was paired or unpaired, method (2) was used if the result was close to that derived using method 4); otherwise method 4) was used. (Where a p-value was derived from another test such as ANOVA, method 4 was used).
(4) Where no CI or useable p-value was provided, the correlation between outcomes on MDI and CSII observed in the study of Pickup et al.[11] (estimated at 0.5) was used to derive an approximate SE using the formulae provided by Elbourne et al.[14]

We explored potential explanations for between-study heterogeneity using random-effects meta-regression[15]. For MDI hypoglycemia rate, mean duration of diabetes and child/adult study indicators were examined. Covariates investigated in univariate and multivariate modelling of both outcome measures were mean age of patients at the start of the study, mean duration of diabetes prior to study, duration of CSII, study design (binary indicator for randomised or not), starting HbA_{1c} on MDI, and hypoglycemia rate on MDI (hypoglycemia rate outcome only). Since starting HbA_{1c} is part of the outcome definition for the mean difference in HbA_{1c} and hypoglycemia rate on MDI is part of the outcome definition for hypoglycemia rate ratio, and both covariates are measured with error, we adjusted for potential regression towards the mean[16] using meta-regression models which included measurement error in the covariates; a Bayesian approach was used with vague prior distributions evaluated using Markov Chain Monte Carlo methods based on previous work by Arends et al.[17]. (Further details of this analysis are available on request from the 2nd author). When considering MDI hypoglycemia rate, subgroup analysis for children and adults was carried out, in addition to a meta-regression on mean duration of diabetes.

Potential publication bias was assessed by visual inspection of funnel plots and Egger's regression test[18]. Where important study-level covariate effects were identified, the residuals from the meta-regression models were considered on the funnel plots to remove systematic effects on the symmetry, which may confound the relationship between effect size and study precision[19].
STATA (v9.2, StataCorp, College Station, TX) was used for all analyses, except the measurement error model which was fitted using WinBUGS software[20].

Results

Study selection

We identified 61 studies comparing CSII and MDI that reported hypoglycemia rates and were potentially relevant to this meta-analysis. We excluded studies for the following reasons: 23 because of a low rate of severe hypoglycemia on MDI, 8 because of short duration of pump therapy, 6 because the design was not a randomised controlled trial or before/after study, two because the protocol was unclear and one because of apparent duplication of data found in another paper. Twenty one studies were thus eligible for analysis of severe hypoglycemia [9,21-40] but since one trial[21] reported results in two groups – a good and a poor control group – we included this as two data sets, resulting in 22 studies in total. Four additional studies[11, 41-43] were identified that compared glycemic control during MDI using the long-acting insulin analogue glargine and CSII, but where rates of severe hypoglycemia could not be estimated (no studies were found comparing CSII and MDI using the analogue detemir).

Table 1 shows the characteristics of the trials; two were randomised control trials (RCTs) with a parallel group design, four were RCTs with cross-over and 20 were before/after studies.

Severe hypoglycemia during MDI and CSII

All 22 studies reporting hypoglcemia rates used MDI based on isophane- or lente-type intermediate-acting insulin in combination with regular or monomeric insulin at meals. Ten studies (45.5%) were in children or adolescents and 12 studies (54.5%) were in adults. A total of 1414 type 1 diabetic subjects received either MDI or insulin pump therapy for a mean CSII duration of 6-48 months.

The pooled hypoglycemia event rate during MDI was 62 events per 100 patient-years (95% CI 22 to 175). There was large heterogeneity between studies (I^2 = 99.7%) which was, in part, due to an outlying report[38] with a rate of 3,001 events per 100 patient-years (95% CI 2,840 to 3,190), 10-fold greater than the next highest study. Reasons for the extreme results in this study are considered in the

Comment section and all analyses were repeated excluding this study as a sensitivity analysis (this did not change inferences in any case, but all analyses are available on request).

Adult subjects with diabetes had a greater frequency of hypoglycemia on MDI (100 events per 100 patient-years [95% CI 25 to 399]) than children and adolescents (36 events per 100 patient-years [95% CI 25 to 52]), p = 0.036 from meta-regression.

The relationship between mean hypoglycemia rate during MDI and mean diabetes duration was quantified using meta-regression, where a strong linear association (p=0.038) was found (Fig. 1).

Fig. 2 illustrates the random effect meta-analysis for hypoglycemia rates and shows that severe hypoglycemia was markedly reduced during CSII compared to MDI, with an overall rate ratio of 4.19 (95% CI 2.86 to 6.13). The I^2 statistic of 84.2% showed that there was considerable heterogeneity amongst studies. We performed a meta-regression to explore this (Fig. 3a), which showed a linear relationship between the (ln) rate ratio and the hypoglycemia frequency during MDI ($p < 0.001$) which remained highly significant when the outlying study was excluded or when allowing for measurement error in the covariate values. The greatest reduction in hypoglycemia thus occurred in those subjects with the highest initial hypoglycemia frequency. The study by Rodrigues et al.[38], although having a much higher event rate on MDI than other trials, does not appear as an outlier in the meta-regression model with treatment vs. baseline risk adjustment.

Mean age was also a highly significant predictor of treatment effect (p = 0.019) with older subjects having a significantly greater reduction in hypoglycemia on CSII compared to MDI (Fig. 3b). There was also a significant positive relationship (p = 0.025) between mean duration of diabetes and the rate ratio for hypoglycemia (Fig. 3c). There was no strong evidence for relationship between either study duration (p = 0.62) or initial MDI HbA1c (p = 0.15) and the hypoglycemia rate ratio. Before/after studies had a similar overall rate ratio for hypoglycemia to the randomised studies: 4.34 (2.87 to 6.56) vs. 2.89 (1.45 to 5.76) (p = 0.52 from meta-regression).

In a multivariate analysis exploring the simultaneous effect of study level covariates (Table 2), both the hypoglycemia frequency during MDI and mean age remained important predictors of treatment effect. Due to the high degree of association between mean age and mean duration of diabetes, including both in the model induced high autocorrelation, and the latter was therefore removed from analysis. A funnel plot showed no evidence of publication bias (not shown) (Egger's test: p = 0.90).

Glycemic control

Fig. 4 presents the random effect meta-analysis for mean difference in HbA_{1c} between MDI and CSII (first subgroup) and shows that glycemic control was significantly better during insulin pump therapy than during MDI, the pooled mean difference of the HbA_{1c} values being 0.62 (95% CI 0.47 to 0.78)%. Four additional studies[11, 41-43] were identified that compared glycemic control during MDI using the long-acting insulin analogue glargine and CSII (Table 1), but where rates of severe hypoglycemia could not be estimated. The mean difference in HbA_{1c} between glargine-MDI and CSII was similar to that of MDI not based on glargine and CSII: 0.63 (95% CI 0.09 to 1.17)% (Figure 4, second subgroup). Combining both sets of studies produced a mean difference of 0.62 (95% CI 0.47 to 0.76)%. All studies were used in the remainder of the analysis.

Because of heterogeneity (I^2 83.5%), we performed a meta-regression including the covariates listed in the methods section. The initial HbA_{1c} on MDI was highly significantly related to the mean difference in HbA_{1c} between MDI and CSII ($p < 0.001$ for the unadjusted model), with those worst controlled on MDI enjoying the most reduction in HbA_{1c} on switching to CSII (Fig 5). Regression to the mean was minimal with a standard and adjusted meta-regression model both producing a slope of 0.52, and hence measurement error was ignored in the multivariate analysis shown below.

Study design had a significant effect on mean HbA_{1c} difference on the two treatments, with the before/after studies producing a larger difference in HbA_{1c} (0.72, [95% CI 0.55 to 0.90])% than the randomised studies (0.22 (0.12 to 0.31)%, p = 0.043. Mean patient age (p = 0.27) and duration of diabetes (p = 0.42) were not strongly related to HbA_{1c} difference in a univariate meta-regression, but

in a multivariate model (Table 2), initial HbA_{1c} on MDI, study design and age were independent predictors of HbA_{1c} difference.

An initial inspection of a funnel plot for this outcome suggested apparent publication bias (Egger's test, p = 0.004), but after adjusting the effect size of each study for the large covariate effects identified above, re-plotting produced a more symmetrical funnel (available on request), suggesting most of the observed asymmetry was due to confounding factors and not publication bias.

Comment

The meta-analysis we performed showed that the frequency of severe hypoglycemia in type 1 diabetes is on average about 4 times less during CSII than MDI, even though the mean level of glycemia (measured by HbA_{1c}) was significantly less on insulin pump therapy. The analysis was similar for both randomised and before/after studies, and the conservative estimates of SEs for hypoglycemia that we used indicate further confidence in the conclusion that hypoglycemia is reduced during CSII. This improvement in hypoglycemia far exceeds the 10-20% reduction from a treatment approach for this complication that the American Diabetes Association has considered as clinically advantageous[44].

The heterogeneity we found between trials is explained in large part by the greater reduction in hypoglycemia in those worse affected by hypoglycemia on MDI, and in older subjects with longer diabetes duration. It is known that hypoglycemia frequency tends to increase as duration of diabetes increases[45], and we found evidence to confirm this. One of the trials we selected also had a very high rate of hypoglycemia during MDI (3010 events/100 patient years), accounting for additional heterogeneity[38]. The study included three patients with an exceptionally high rate of hypoglycemia during MDI, and excluding these subjects reduced the rate to 645 episodes/100 patient-years.
Our finding of a marked reduction in severe hypoglycemia during CSII has several implications. Firstly, it counters the notion that intensive insulin therapy is intrinsically associated with a

of hypoglycemia or has an unacceptable risk: benefit ratio in those with frequent severe hypoglycemia[46] (in fact, such patients particularly benefit from CSII). Secondly, our result presents standards for expected efficacy of CSII (presently lacking[6]) against which insulin pump services can be audited. In addition, updated cost-effectiveness comparisons of MDI and CSII will now be possible, based on better knowledge of changes in the costs associated with improved hypoglycemia frequency.

We also found that glycemic control, as measured by HbA_{1c}, is significantly better during CSII than MDI (mean difference of about 0.6%), which confirms findings from previous studies[7,8]. However, there was a marked relationship of effect size to the starting HbA_{1c} on MDI, i.e. the worst controlled subjects on injections enjoyed the most improvement on insulin pump therapy. This finding is supported by other reports on individual subjects[47,48]. It should be noted that in 10 trials the mean HbA_{1c} on MDI was ≥8.5% (mean 9.0%) in spite of severe hypoglycemia (median hypoglycemia rate 65 episodes/100 patient-years). This provides further evidence that patients in the main target group for insulin pump therapy often have a high HbA_{1c}, even during best attempts with MDI, perhaps because high associated glycemic variability and the risk of hypoglycemia deters attempts to tighten control with injection therapy. Such patients have a large change in HbA_{1c} on switching to insulin pump therapy[47].

Our study has several potential limitations. The inclusion criteria for studies were arbitrary, e.g. the initial hypoglycemia frequency rate and study duration, but we set these as reasonable cut offs to ensure that only the target group were studied. Our definition of severe hypoglycemia followed that recommended by the American Diabetes Association[44] but there were variations amongst trials which might have influenced the frequency, e.g. the more stringent 'use of glucagon, loss of consciousness, seizure and emergency admission'[37], as opposed to the less stringent additional inclusion of 'uncontrolled shaking and inconsolable crying '[25]. However, analysis by rate ratio for each study should help to minimise the influence of this discrepancy. Also, because of a relatively small number of randomised controlled trials, we combined data from these with results from the less methodologically rigorous before/after design of studies, but we showed that the two designs had

similar rate ratios for severe hypoglycemia . A further limitation is that, due to the reporting of the before/after studies, it was often not possible to derive a standard error for the hypoglycemic rate which took into account the paired nature of the data, and hence these standard errors are conservative.

It is also possible that our selection criteria and the use of trial data over the last 10 years led to results that are not representative of severe hypoglycaemia rates in the currently managed general type 1 diabetes population. However, the all-study pooled hypoglycemia rate in this study of 62 (CI 22 to 175) and adult rate of 100 (CI 25 to 399) episodes/100 patient-years during MDI is comparable to the mean of 95 epidoses/100 patient years for adult subjects of similar diabetes duration reported in a four-center, clinic-based survey of severe hypoglycaemia rates in people with type 1 diabetes treated by MDI according to modern guidelines[45].

We did not find any trials comparing CSII and MDI based on the newer long-acting insulin analogues where severe hypoglycemia could be analysed (e.g. because they were of short duration or had low initial frequency of hypoglycemia), but other studies indicate that severe hypoglycemia is not substantially reduced by switching from isophane- to glargine- or detemir-based regimens[49-53]. It is therefore unlikely on present evidence that the need for insulin pump therapy will be removed by the availability of these analogues.

Conclusion

We conclude that CSII produces a significant and substantial reduction in severe hypoglycemia in type 1 diabetes compared to MDI. The accompanying lowering in HbA_{1c}, which can be about 1.5% in the worst controlled patients, will also afford a marked decrease in the risk of microvascular disease in type 1 diabetes.

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Table 1. Characteristics of trials included in the meta-analysis

Authors	Trial design	No. patients	Child/adult population	Mean age (y)	Mean diabetes duration (y)	Study duration (mo)	Hypoglycemia rate on MDI (episodes/100 pt-y)
Hypoglycemia studies							
Bode et al.[21] (poor control)	B/A	25	A*	39.2*	22.2*	37.2	84
Bode et al.[21] (good control)	B/A	30					183
Kaderman et al.[22]	B/A	33	A	36	16.5	20.9	97
Maniatis et al.[23]	B/A	56	C	17	7.6	12.2	12.3
Rizvi et al.[24]	B/A	5	A	66.4	33	20.9	320
Litton et al.[25]	B/A	9	C	2.8	1.3	12.7	69
Linkeschova et al.[26]	B/A	42	A	33	19.7	28	167
Bruttomesso et al.[27]	B/A	138	A	33.1	13.1	7.4	31
Rudolph and Hirsch[28]	B/A	107	A	36	17	36	73.2
Plotnick et al.[29]	B/A	95	C	12	5.6	28	17.2
Cohen et al.[30]	RCTx	12	C	14.2	2	6	61
Hunger-Dathe et al.[31]	B/A	165	A	34.1	15.2	12	47
Weintrob et al.[32]	RCTx	23	C	11.8	5.8	7	39
Weinzimer et al.[33]	B/A	65	C	4.5	1.8	48	78
McMahon et al.[34]	B/A	100	C	12.5	5.1	16.8	32.9
Siegel-Czarkwoski et al.[35]	B/A	34	A	50	NA	12	20.5
Alemzadeh et al.[36]	B/A	40	C	14.7	6.2	12	20.6
Mack-Fogg et al.[37]	B/A	70	C	9.1	NA	11	46
Sciaffini et al.[9]	B/A	20	C	12.7	5.5	12	25
Rogrigues et al.[38]	B/A	40	A	33.2	14.6	20.5	3010
Lepore et al.[39]	B/A	82	A	37.9	19.7	31.9	35
Hoogma et al.[40]	RCTx	223	A	36.1	14.9	6	50
Glargine-MDI studies							
Doyle et al.[41]	RCTp	16	C	12.8	6.2	4	NA
Bolli et al.[42]	RCTp	28/29	A	NA	NA	6	NA
Hirsch et al.[43]	RCTx	100	A	43	21.8	1.25	NA
Pickup et al.[11]	B/A	14	A	39	22	6	NA

*Age and diabetes duration for all patients; RCTx = randomised controlled trial with cross over; RCTp = randomised controlled trial parallel design; B/A = before after design.

Table 2. Multivariate regression of predictors of hypoglycemia rate ratio (MDI: CSII) and difference in mean HbA1c on MDI and CSII

	Coefficient	SE	p value	CI
Hypoglycemia rate ratio				
Hypoglycemia on MDI	0.50	0.085	<0.001*	0.33 to 0.68
Mean age	0.016	0.0072	0.04*	0.001 to 0.029
Constant	-1.18	0.36	0.002*	-1.88 to -0.43
Difference in HbA1c				
HbA1c during MDI	0.48	0.075	0.0	0.32 to 0.63
Age	0.0072	0.0031	0.028	0 to 0.014
Study design	0.24	0.12	0.051	0 to 0.49
Constant	-3.7	0.59	<0.001	-4.9 to -2.5

*Parameter estimates are derived from Bayesian analysis taking measurement error into account, but p values are from classical analysis and should be considered approximate

Fig. 1

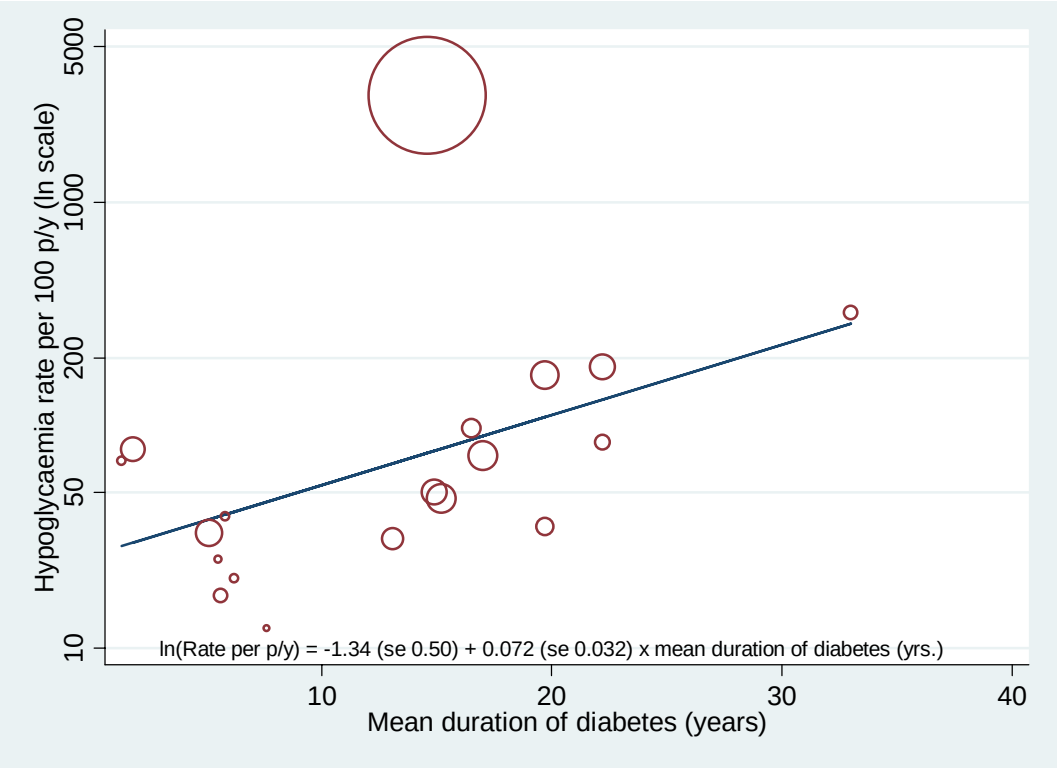

Hypoglycaemia rate per 100 p/y (ln scale)
10
50
200
1000
5000
ln(Rate per p/y) = -1.34 (se 0.50) + 0.072 (se 0.032) x mean duration of diabetes (yrs.)
10
20
30
40
Mean duration of diabetes (years)

Fig.2.

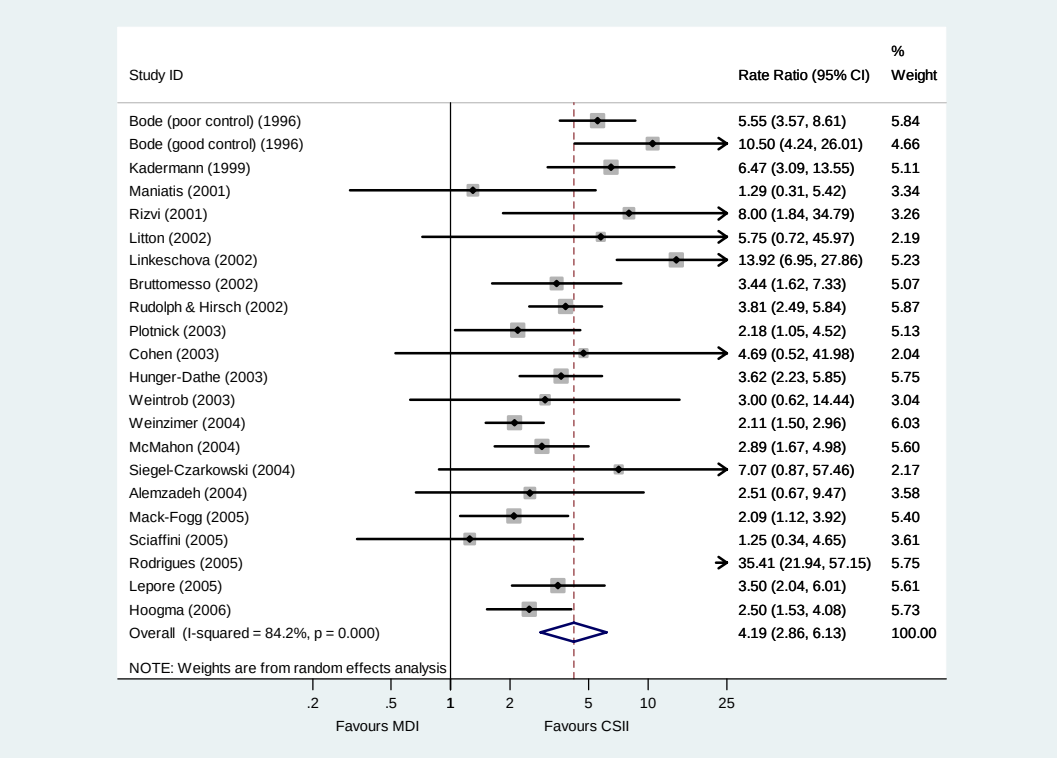
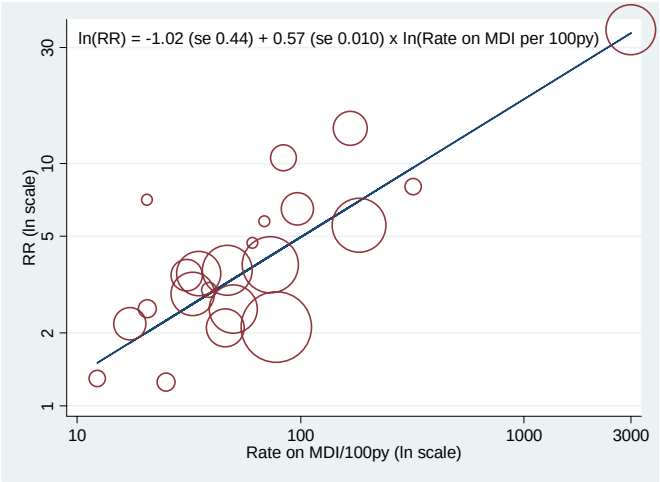
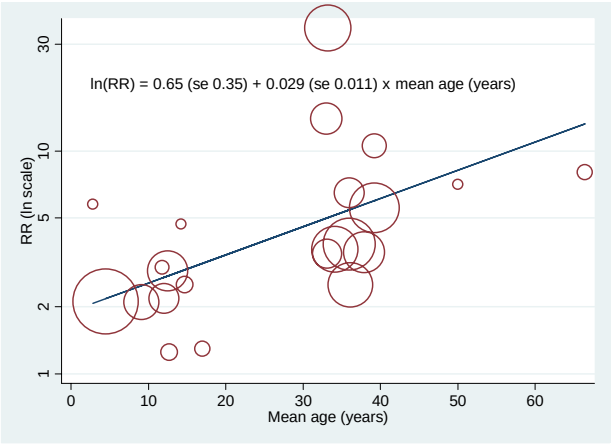

Study ID
Rate Ratio (95% CI)
% Weight
Bode (poor control) (1996) 5.55 (3.57, 8.61) 5.84
Bode (good control) (1996) 10.50 (4.24, 26.01) 4.66
Kadermann (1999) 6.47 (3.09, 13.55) 5.11
Maniatis (2001) 1.29 (0.31, 5.42) 3.34
Rizvi (2001) 8.00 (1.84, 34.79) 3.26
Litton (2002) 5.75 (0.72, 45.97) 2.19
Linkeschova (2002) 13.92 (6.95, 27.86) 5.23
Bruttomesso (2002) 3.44 (1.62, 7.33) 5.07
Rudolph & Hirsch (2002) 3.81 (2.49, 5.84) 5.87
Plotnick (2003) 2.18 (1.05, 4.52) 5.13
Cohen (2003) 4.69 (0.52, 41.98) 2.04
Hunger-Dathe (2003) 3.62 (2.23, 5.85) 5.75
Weintrob (2003) 3.00 (0.62, 14.44) 3.04
Weinzimer (2004) 2.11 (1.50, 2.96) 6.03
McMahon (2004) 2.89 (1.67, 4.98) 5.60
Siegel-Czarkowski (2004) 7.07 (0.87, 57.46) 2.17
Alemzadeh (2004) 2.51 (0.67, 9.47) 3.58
Mack-Fogg (2005) 2.09 (1.12, 3.92) 5.40
Sciaffini (2005) 1.25 (0.34, 4.65) 3.61
Rodrigues (2005) 35.41 (21.94, 57.15) 5.75
Lepore (2005) 3.50 (2.04, 6.01) 5.61
Hoogma (2006) 2.50 (1.53, 4.08) 5.73
Overall (I-squared = 84.2%, p = 0.000) 4.19 (2.86, 6.13) 100.00
NOTE: Weights are from random effects analysis
.2
.5
1
2
5
10
25
Favours MDI
Favours CSII

Fig. 3

a


ln(RR) = -1.02 (se 0.44) + 0.57 (se 0.010) x ln(Rate on MDI per 100py)
RR (ln scale)
1
2
5
10
30
10
100
1000
3000
Rate on MDI/100py (ln scale)

b


ln(RR) = 0.65 (se 0.35) + 0.029 (se 0.011) x mean age (years)
RR (ln scale)
1
2
5
10
30
0
10
20
30
40
50
60
Mean age (years)

c

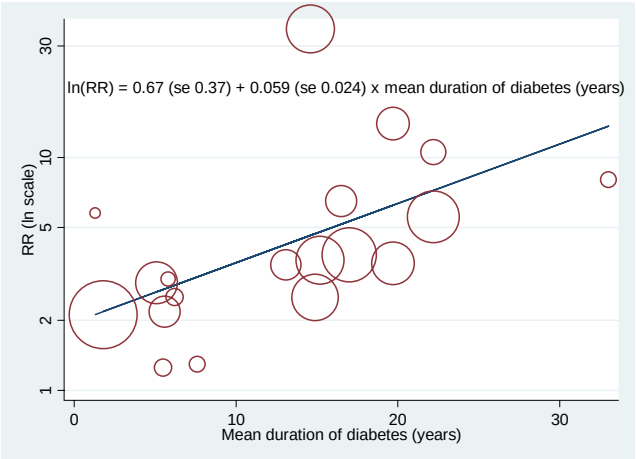

ln(RR) = 0.67 (se 0.37) + 0.059 (se 0.024) x mean duration of diabetes (years)
RR (ln scale)
1
2
5
10
30
0
10
20
30
Mean duration of diabetes (years)

Fig.4.

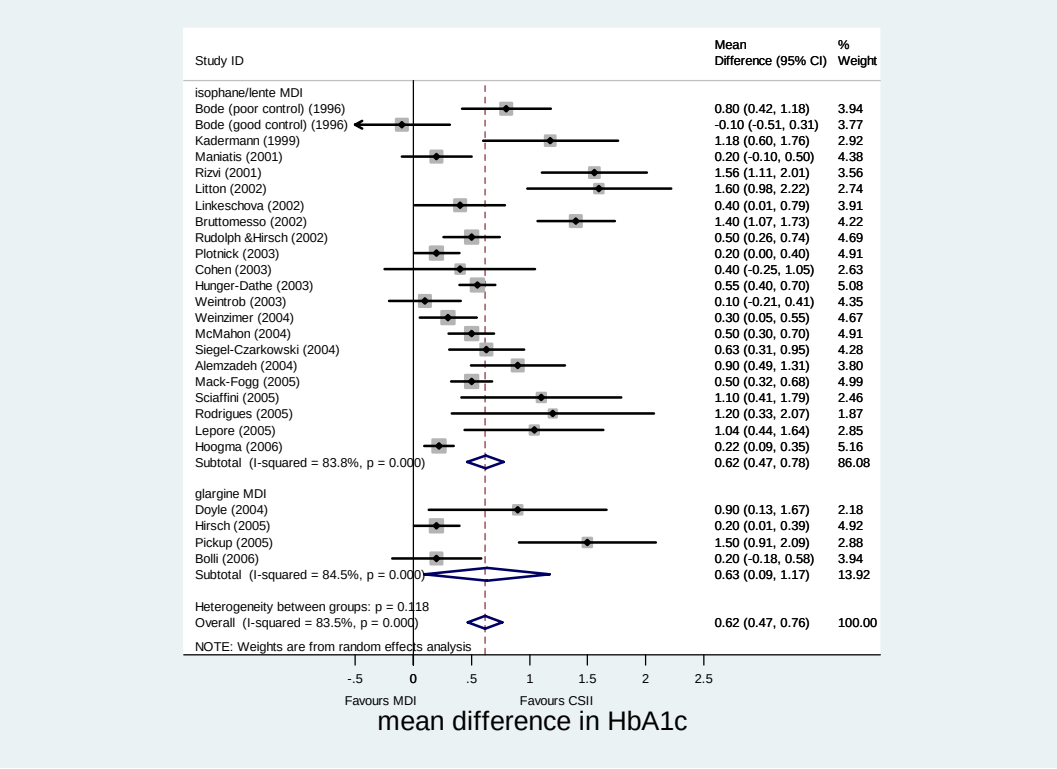

Study ID
Mean Difference (95% CI)
% Weight
isophane/lente MDI
Bode (poor control) (1996) 0.80 (0.42, 1.18) 3.94
Bode (good control) (1996) -0.10 (-0.51, 0.31) 3.77
Kadermann (1999) 1.18 (0.60, 1.76) 2.92
Maniatis (2001) 0.20 (-0.10, 0.50) 4.38
Rizvi (2001) 1.56 (1.11, 2.01) 3.56
Litton (2002) 1.60 (0.98, 2.22) 2.74
Linkeschova (2002) 0.40 (0.01, 0.79) 3.91
Bruttomesso (2002) 1.40 (1.07, 1.73) 4.22
Rudolph &Hirsch (2002) 0.50 (0.26, 0.74) 4.69
Plotnick (2003) 0.20 (0.00, 0.40) 4.91
Cohen (2003) 0.40 (-0.25, 1.05) 2.63
Hunger-Dathe (2003) 0.55 (0.40, 0.70) 5.08
Weintrob (2003) 0.10 (-0.21, 0.41) 4.35
Weinzimer (2004) 0.30 (0.05, 0.55) 4.67
McMahon (2004) 0.50 (0.30, 0.70) 4.91
Siegel-Czarkowski (2004) 0.63 (0.31, 0.95) 4.28
Alemzadeh (2004) 0.90 (0.49, 1.31) 3.80
Mack-Fogg (2005) 0.50 (0.32, 0.68) 4.99
Sciaffini (2005) 1.10 (0.41, 1.79) 2.46
Rodrigues (2005) 1.20 (0.33, 2.07) 1.87
Lepore (2005) 1.04 (0.44, 1.64) 2.85
Hoogma (2006) 0.22 (0.09, 0.35) 5.16
Subtotal (I-squared = 83.8%, p = 0.000) 0.62 (0.47, 0.78) 86.08
glargine MDI
Doyle (2004) 0.90 (0.13, 1.67) 2.18
Hirsch (2005) 0.20 (0.01, 0.39) 4.92
Pickup (2005) 1.50 (0.91, 2.09) 2.88
Bolli (2006) 0.20 (-0.18, 0.58) 3.94
Subtotal (I-squared = 84.5%, p = 0.000) 0.63 (0.09, 1.17) 13.92
Heterogeneity between groups: p = 0.118
Overall (I-squared = 83.5%, p = 0.000) 0.62 (0.47, 0.76) 100.00
NOTE: Weights are from random effects analysis
-.5
0
.5
1
1.5
2
2.5
Favours MDI
Favours CSII
mean difference in HbA1c

Fig.5

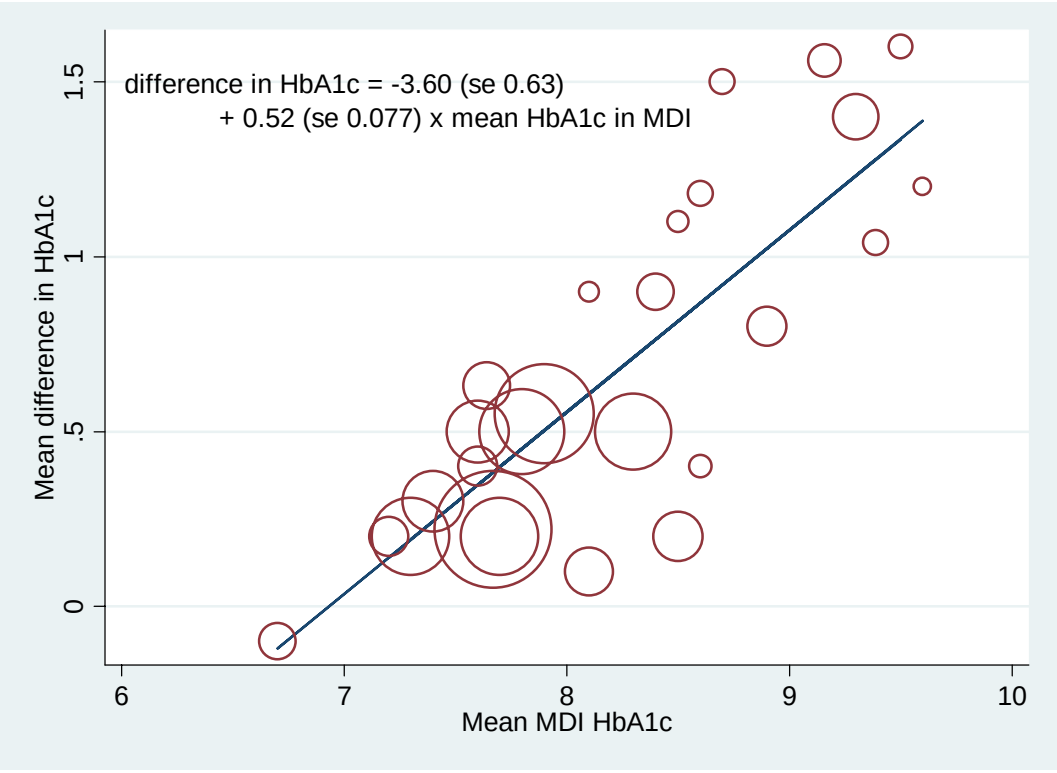

difference in HbA1c = -3.60 (se 0.63)
+ 0.52 (se 0.077) x mean HbA1c in MDI
Mean difference in HbA1c
0
.5
1
1.5
6
7
8
9
10
Mean MDI HbA1c

Figure legends

Fig.1. Random effect meta-regression of (ln) hypoglycemic rate on MDI against mean duration of diabetes as a covariate. Circles are proportional to precision of study estimates.

Fig. 2 Forest plot of random effect meta-analysis for hypoglycemic rate ratio (CSII vs. MDI).

Fig.3. Random effect meta-regression of (ln) hypoglycemia rate ratio (RR) for MDI: CSII with the following covariates: (ln) hypoglycemia rate on (a) MDI, (b) mean age and (c) mean diabetes duration (c).

Fig.4. Random effect meta-analysis for mean difference in HbA1c between MDI and CSII, including subgrouped analysis for studies using isophane/lente insulin and those using glargine-based MDI.

Fig.5. Random effect meta-regression of mean difference in HbA1c with mean HbA1c on MDI as a covariate.

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