HTA report: new devices for the management of glycaemia in young diabetics

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Foreword

This year Agenas produced on behalf of the Ministry of Health (Direzione genralwe dei dispositive medici, del servizio farmaceutico e della sicurezza delle cure), a HTA report on the use of devices in the management of glycaemia in young diabetic people. The report was written in a collaboration with some of Italian regions participating in the Italian Network for Health Tecnology Assessemtn (Rete Italiana di Health Technology Assessment -RITHA) and from a process of consultation with experts, reviewers (internal and external) and other stakeholders.

The report is developed to answer the question: "Are there economically sustainable new devices to enhance the management of diabetes type I in people aged 0-18 and do they provide better health and quality of life to patients and carers?" The topic of the report is Sensor augmented insulin pump (or SAP for short) which is a convergence of two technologies: continuous insulin infusion and real-time continuous glucose monitoring (CGMS). The evidence on clinical effectiveness and safety has been synthesised by a systematic review of literature while, to describe the patterns of use and expected expenditure of the device we performed a contextual analysis in the regions which took part in the assessment. Although SAP therapy has a lot of theoretical advantages compared to the use of either single-component devices or daily injection of insulin with self-montoring, our researchers were unable to identify any evidence that such advantages were converted into clinical benefits or enhancements in quality of life of young diabetics or their families.

Future good quality research aimed at assessing the impact of SAP on clinical and quality of life outcomes is necessary to develop clinical recommendations.

Fulvio Moirano

Executive Director of Agenas

Premessa

Quest'anno Agenas ha prodotto su commissione del Ministero della Salute (Direzione generale dei dispositive medici, del servizio farmaceutico e della sicurezza delle cure) un HTA report sull'uso di device innovativi per la gestione del diabete nei bambini e adolescenti. Il report è stato scritto in collaborazione con alcune delle regioni che partecipano alla Rete Italiana di Health Technology Assessment–RITHA e attraverso un processo di consultazione con esperti, revisori esterni ed interni e altri stakeholders.

Il report è stato sviluppato per rispondere alla domanda: "I nuovi device per il miglioramento della gestione del diabete nella popolazione 0-18 anni, sono economicamente sostenibili e forniscono un miglioramento della salute e della qualità della vita?". La tecnologia oggetto del report è la Sensor Augmented Pump (SAP), risultante dalla convergenza di due tecnologie preesistenti: la pompa ad infusione continua di insulina (CSII) e i sistemi di rilevazione continua del glucosio (CGMS).

Le evidenze relative alla efficacia e sicurezza sono state sintetizzate attraverso una revisione sistematica della letteratura, mentre per descrivere gli scenari d'uso e la spesa attesa è stata realizzata un' analisi di contesto in alcune regioni partecipanti. Sebbene la terapia con SAP abbia una serie di vantaggi teorici sia rispetto alla terapia multiniettiva con auto-monitoraggio, sia rispetto all'utilizzo distinto dei due device che la compongono, i nostri ricercatori non hanno individuato evidenze che provino un chiaro vantaggio clinico e in termini di qualità della vita per i giovani diabetici e le loro famiglie.

Sarà necessaria più ricerca di buona qualità per valutare l'impatto della SAP in termini di outcome clinici e di qualità della vita al fine di sviluppare raccomandazioni cliniche per un uso appropriato.

Fulvio Moirano

Executive Director of Agenas

One-liner

We assessed the clinical effectiveness, safety, patients' acceptatbility and costs of Sensor Augmented Pump versus multiple daily injections therapy.

In breve

Abbiamo valutato l'efficacia clinica, la sicurezza e l'accettabilità e costi della pompa ad infusione continua di insulina collegata al sistema di monitoraggio continuo del livello di insulina (SAP) verso la terapia multiniettiva.

Executive Summary

This HTA report aims to understand if new devices do improve the management of diabetes type I in people aged 0-18 and are economically sustainable for the public system, according to the available evidence. We focused on the most innovative which showed to be the Sensor Augmented Pump. This device is the result of the joint use of continuous subcutaneous insulin infusion (CSII) and continous blood monitoring systems devices (CGMS). We retrived and analysed the evidence on its effectiveness, safety, acceptability, and on direct and indirect costs and information on its marketing status at international, national and regional level. Context specific epidemiological data were also collected in some of the participoating regions on prevalence and incidence of the disease and on short and long term complications of type I diabetes mellitus (T1DM).

Chapter 1 focuses on the health problem, T1DM, in children and adolescents. A section (chapter 2) is dedicated to the descrption of the policy question and the research questions that led our work in this report, highlighting all the dimension of impact we analysed (effectiveness, safety, acceptability etc.). Chapter 3 a detailed description is provided about the technology at stake, its components, functioning and alternatives. Information on authorisation at European and American level can also be found in this section, together with detailed appendices where some producers, who answered our request, describe their products.

In Chapter 3 published evidence about clinical effectiveness and safety has been reviewed. In the first part authors report a summary of conclusions from international HTA reports and clinical practice guidelines on Continuous Insulin Infusion (CSII) and/or Continuous Glucose Monitoring Systems (CGMS). CSII and CGMS are the single components of the SAP and its immediate predecessors so it appeared important to overview the evidence they are based on. In the second part of Chapter 3, the existing evidence on clinical effectiveness and safety of SAP compared against multiple daily injections has been retrieved and analyzed via a systematic review.

In the section dedicated to the epidemiology and contextual analysis (chapter 4) some of the participating Regions and Autonomous Provinces, namely Emilia Romagna, Sicilia, Basilicata and Trento, collected new data on T1DM diffusion in their own context, sharing a common methodology, so that a clearer picture of the actual diffusion of the disease and its main long and short term consequences are given.

Chapter 5 deals with patients' views on SAP and its main component CSII. Indeed those devices can have similar psychosocial impacts on patients and some advantages/disadvantages in flexibility of life style are already experienced when wearing single components. A systematic review of the evidence on SAP versus MDI was performed including all comparative clinical studies involving 0-18 population and considering also Quality of Life (QoL) as an outcome. Only one study fitted the inclusion criteria, and any definitive conclusion can be drown from it about better or equal quality of life with the new

device. To outline pros and cons of wearing an external device HTA reports on simple pump versus MDI reporting QoL information were overviewed and studies measuring QoL with CSII versus MDI with standardised instruments were also described. From the analysis of the qualitative research contained in the selected HTA report, parents/patients who use the pump are very satisfied and say they have many advantages in their/their children life style. Chapter 6 on costing and economic evaluation contains a systematic review of the economic literature on SAP versus MDI and the results of a survey on direct and indirects costs of SAP in some of the participating regions. Although partial, the data show that SAP has still a limited spread. Authors conclude that an economic evaluation privileging QoL aspects is needed to identify also potential age groups or personality types which are more likely to make best use of such an expensive but important device.

Our final recommendation highlights that there is the need to generate new good quality evidence (in design and number of diabetics patients divided for classes of ages) to answer the study question. Clearer guidelines for the appropriate use of SAP should be produced and the evidence base on the use of these expensive and potentially important devices should be developed.

Sintesi

Il presente report di HTA si pone l'obiettivo di valutare le evidenze relative ai nuovi device per la gestione del diabete di tipo 1 (T1DM) nella popolazione pediatrica (0-18) per capire se e quanto essi migliorino la gestione della malattia e siano al contempo sostenibili economicamente. La nostra valutazione si è concentrata sul device più innovativo e disponibile, ad oggi: la pompa ad infusione continua subcutanea di insulina collegata al sistema di monitoraggio continuo del livello di insulina altrimenti detta Sensor Augemented Pump (SAP). Si tratta di una nuova tecnologia, che si compone di due strumentazioni (già esistenti e diffuse) ora in comunicazione tra loro: la pompa ad infusione continua subcutanea di insulina (CSII) e il sistema di monitoraggio continuo del livello di insulina (CGMS). Abbiamo reperito ed analizzato l'evidenza relativa alla efficacia, sicurezza, accettabilità, costi diretti e indiretti e commercializzazione a lievllo internazionale, nazionale e regionale. Sono poi stati raccolti dati epidemiologici in alcune delle regioni partecipanti, sulle conseguenze a breve e lungo termine del diabete mellito di tipo 1 (T1DM).

Nel primo capitolo viene descritto il problema di salute rappresentato dal diabete nel nostro paese e nel mondo, la sua eziologia e diffusione nella popolazione pediatrica e le terapie disponibili. Nella seconda sezione viene sinteticamente descritta la domanda di ricerca affrontata dal report, esplicitando le varie dimensioni di impatto (effucacia, sicurezza, accettabilità, etc.) considerate dal report e di cui si sono analizzate le evidenze disponibili. Il capitolo 3 presenta una descrizione del device oggetto di valutazione e delle sue alternative, con schede dettagliate per ogni marca di device, nonché lo stato autiorizzativo in Italia, Europa e Stati Uniti.

La revisione sistematica della letteratura di efficacia e sicurezza (capitolo 4) si articola in due parti. Una prima sezione dedicata ai "predecessori" e componenti della SAP, cioè alla CSII e ai sistemi di CGMS. Qui gli autori hanno identificato ed esaminato gli HTA report e le lineeguida cliniche più rilevanti dedicate ai due device di cui sopra. Nella seconda parte è stata effettuata la revisione sistematica della letteratura per la SAP versus terapia multi-iniettiva.

Nella parte del report dedicate alla epidemiologia e dati di contesto le Emilia Romagna, Sicilia, Basilicata and la provinicia autonoma di Trento, hanno raccolto una serie di dati sul T1DM nel loro contest, relative alla diffusione e le complicazioni a lungo e breve termine della malattia, in base ad una comune metodologia di raccolta.

La sezione relativa al punto divista del paziente e alle sue prefrenze (capitolo 6) prende in esame la letteratura relativa alla quaklità della vita con SAP versus terapia multiniettiva nella popolazione target, tramite revisione sistematica. Sono poi esaminati gli HTA report relativi alla terapia con CSII contenenti una capitolo sui pazienti e gli studi CSII verus MDI che abbiano usato strumenti standardizzati di misurazione della qualità della vita nella popolazione target. L'assunto è che CSII e SAP abbiano impatti pisco sociali simili e che

molti dei vantaggi e svantaggi della cura basata sull'uso di uno strumento "esterno", siano già presenti con la semplice pompa ad infusione (CSII).

Il capitolo relativo alla raccolta costi e valutazione contiene una revisione sistematica degli studi economici su SAP versus MDI e i dati di una survey sui costi diretti e indiretti del device raccolti a livello regionale.

La nostra raccomandazione riguarda la necessità di generare nuove evidenze di buona qualità dal punto di vista del disegno di studio e del numero di paziwenti divisi per fasce di età. Inoltre si consilgia la produzione di lineeguida sull'utilizzo apporpriatoi della SAP che è uno strumento costoso e potenzialemnte importante per la gestione del diabete.

1.Health problem

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease, characterized by absolute insulin deficiency resulting from immuno-mediated destruction of insulin-producing β-cells in the pancreatic islets of Langherans.

The etiology of the disease is unclear, although a genetic component is evident. The most important genes contributing to the disease susceptibility are located in the HLA class II locus on the short arm of chromosome 6 [Knip M, 2011). Exogenous factors, that can trigger β-cells destruction in genetically predisposed subjects, such as infections, toxins, nutritional components, are also involved in the development of T1DM.

The incidence of T1DM among children is increasing worldwide. The DIAMOND project, initiated by the World Health Organization in 1990, described the incidence of T1DM in children 0-14 years of age in 50 countries worldwide totaling 19,164 cases from a population of 75.1 million children. The lowest incidence (<1/100.000 per year) was reported in the populations from China and South America and the highest incidence (>20/100.000 per year) was reported in Sardinia, Finland, Sweden, Norway, Portugal, the UK, Canada, and New Zealand (Diamond, project). The EURODIAB study showed a great heterogeneity of the incidence during the 1989-2003 period in central and eastern European countries (EURODIAB ACE study Group, 2000). The study of Registry for T1DM in Italy (RIDI), involving the majority of Italian regions, identified 5180 incident cases aged 0-14 years between 1990 and 2003 and highlighted large geographical variations in risk of childhood T1DM within Italy, with the highest incidence in Sardinia (about 34 per 100.000 person/year), intermediate in Central-Southern Italy, and high in Northern Italy, especially in Trento. Italy is one of the countries with more significant variation in the incidence of T1DM, which is fourfold lower in peninsula regions than in Sardinia. The incidence rate was 12,26 per 100.000 person per year and significantly higher in boys than in girls (13.13 vs 11.35). The authors showed a linear increasing temporal trend with annual increment of 2,94% among all age groups and both sexes. The same trend for increased incidence of T1DM was seen across the world in populations studied (+ 4.0% in Asia, + 3.2% in Europe, and + 5.3% in North America). In all the period study the highest incidence rate was found in the group of children of 9-11 years of age. Data from the RIDI underline that the increasing temporal trend involved all age-groups in contrast with studies showing an increased incidence shifted to younger children [Bruno G, 2010).

The replacement therapy in T1DM should mimic exactly the endogenous insulin profile of non diabetic people. The Diabetes Control and Complications Trial (DCCT) established that the intensive treatment, which maintains a good metabolic control achieving near-normal blood sugar levels, delays the onset and reduces the progression of microvascular complications (ADA, 2010). This widely adopted pattern of insulin therapy, called basal-bolus therapy, can be carried out with multiple daily injections (MDI) as well as continuous

subcutaneous insulin infusion (CSII) via an insulin pump, associated with medical nutrition therapy and frequent self-monitoring of blood glucose (DCCT/EDIC research group 2009).

The goal of medical care of children and adolescents with T1DM is to optimize glycemic control and minimize complications, promoting health-related quality of life. To achieve an optimal glucose control the patient with T1DM must be able to access health care providers who have experience in T1DM.

MDI regimens are based on rapid acting insulin with meals combined with new long-acting insulin analogs such as glargine and detemir. Treatment with insulin analogues is associated with a lower risk of hypoglycaemia and less glycaemic variability than treatment with human insulin in patients with type 1 diabetes. After the DCCT study, there has been a widespread use of multiple-dose insulin regimens (four or more daily insulin injections), using a variety of insulin analogs. It is now possible to achieve previously unattainable levels of glycemic control with less risk of severe hypoglycemia.

Continuous subcutaneous insulin infusion (CSII), or insulin pump therapy, provides a treatment option that could assist in the attainment of all of the therapeutic goals in all ages of children In paediatric patients CSII can reduce both glycosylated haemoglobin (HbA1c) levels and frequency of severe hypoglycaemia, without sacrifices in safety, quality of. life, or weight gain, particularly in conjunction with the use of new insulin analogues and improvements in pump technology. Additional risk reduction may be possible with current continuous glucose sensors and could decline further with advances in this technology and the development of "closed-loop" insulin delivery systems [Pinelli L, 2008]. Criteria for pump therapy can be an inadequate glycemic control, "dawn phenomenon," marked daily variations in glucose levels, history of hypoglycemia unawareness or of hypoglycemic events requiring assistance, need for flexibility in lifestyle or particular lifestyle such as athletes, pregnancy or the intention to become pregnant.

Sensor-augmented insulin pump therapy (SAP) is a convergence of two technologies: CSII and real-time continuous glucose monitoring (CGMS). Frequent self-monitoring of blood glucose (SMBG) is a critical component of intensive therapy with insulin pumps and assists patients in their estimation of insulin dosing and food intake. SMBG, however, cannot be performed frequently enough to reliably detect every glycemic excursion. A device for CGMS can be used to improve glucose control by capturing clear trends in the patient glycemic profiles that are not easily identified by intermittent SMBG alone. Just recently patients have been given the ability of viewing their glucose real time, as well as reviewing graphs of recent trends in their glycemic control. The application of real-time alarms warns users of impending hypo- and/or hyperglycemia, allowing for either preventive or corrective action [Lee SW, 2007]. Criteria for SAP are similar to pump therapy and particularly hypoglycemia unawareness. Some authors suggest that the increased use (availability) of continuous glucose sensors is likely to have a significant impact on pediatric diabetes therapy and

education in the near future [Scaramuzza AE, 2011], even if the achievement of a stricter glycemic control than patients using conventional insulin pump depends on the duration of SAP, which in reality is about a week per month because a high level of motivation is required [Hirsch IB, 2008].

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2. Report objectives: policy question and research question

Policy Question

Are there economically sustainable new devices to enhance the management of type I diabetes mellitus (T1DM) in people aged 0-18 and do they provide better health and quality of life to patients and carers?

Research Questions

1) Which is the most innovative device for better management of diabetes type I in people aged 0-18?

2) What is the available evidence on its

- Effectiveness
- Safety
- Acceptability/Quality of Life
- Economic aspects

3) Context analysis (national/regional level)

- How long has the device been used and where?
- How many producers are there?
- When did the device obtain the CE and FDA authorisations?
- What are its price and costs?
- What are Patients' and patients' carers opinions on the device acceptability?

4) Economic evaluation

Is the use of this device economically sustainable from the National/Regional Health Services point of view?

3.Technology, procedure and alternative

3.1 Technology

Since the first half of the 20th century, the traditional therapy for T1DM has been represented by multiple daily injection (MDI), for which the Diabetic patient auto-injects during the course of the day different (type and) doses of insulin, also depending on the quantity of food taken. In the years, therapy for T1DM has been evolved towards systems in which insulin pumps is used to deliver, in different types of boluses, a dose of insulin calibrated over the glycaemic level of the patient using a blood glucose analyser at the moment of the infusion.

Recently, new therapies have been delivered using the sensor-augmented pump (SAP) system that combines Continuous Subcutaneous Insulin Infusion (CSII) and Continuous Glucose Monitor (CGM) technologies [Bergenstal et al. 2011].

CSII infuses insulin in microvolume pulses and can deliver insulin at a slow and continuous basal rate and in bolus doses. Most of the time, a pump operates at the basal infusion rate (the insulin level needed to ensure sufficient glucose transport to satisfy an individual's energy requirements overnight and between meals) [HPCS 2011].

Blood glucose levels are usually checked at least four times a day. In order to measure blood glucose level, different types of monitoring methods can be used: frequent self-monitoring of blood glucose (SMBG) or CGM. They involve different devices:

- SMBG test strips cartridge, or cuvette saturated with a drop of capillary blood taken by a finger puncture are used to analyze intermittently level of glucose in blood [HPCS 2011].
- CGM is used to analyse in continuous level of indulin allowing a longerterm analysis of glucose level by the insertion into subcutaneous fat of a needle (containing a glucose-dependent enzyme generating glucose-dependent electrical currents), a transmitter connected to the needle (translating and relaying data by infrared technology) and a separate receiver that displays the glucose profile.

Results of continuous glucose monitoring system (CGMS) have to be calibrated with a number of self-monitoring measurements of blood glucose. Thbis is always necessary since there could be a slight difference between the glucose levels measured within subcutaneous fat and the level of glucose into blood. The first CGMS allowed only 'offline' interpretation of the glucose profiles after disconnecting the sensor and uploading the results. In the past years, 'off-line' or 'real-time' CGMS have become available, allowing direct feedback of glucose levels and direct intervention. In Appendix 2 a detailed description of the technologies is provided.

3.2 Alternative therapies

The traditional therapy for T1DM has been represented by Multiple dose injection (MDI) therapy, also known as multiple daily injections. MDI is an alternative term for the basal/bolus regime of injecting insulin. Basal-bolus insulin regimens attempt to replicate normal insulin secretion through the use of a long-acting insulin analogue to cover basal insulin needs along with bolus injections of rapid-acting insulin analogue with food intake and to correct increases in blood glucose levels [Tamborlane 2012].

The therapy implicates injecting a long acting insulin once or twice daily as a background (basal) dose and having further injections of rapid acting insulin at each meal time depending on the quantity of food taken. Multiple daily injection therapy will usually involve at least four injections a day.

3.2 The marketing status

As described in the Appendix 1, we identified three producers of SAP systems:

- Animas Corporation - Animas® Vibe™ (CSII) and Dexcom G4™ (CGM);
- Medronic - Paradigm® Veo™ 554/754 (includes CSII and CGM in a single device);
- Roche - Accu-Chek® Combo (CSII) and DexCom Seven® Plus (CGM).

All systems has CE-mark but none has FDA approval. In Appendix 2 a detailed description of the technologies is provided.

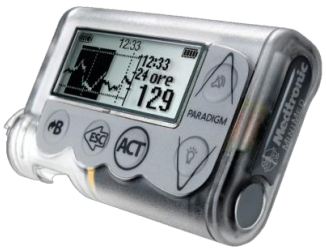
Fig.1 Sensor Augmented Pumps

Animas

Animas® Vibe™ (CSII)

Dexcom G4™ (CGM)

Medtronic



Paradigm® Veo™ 554/754 (includes CSII and CGM)

Enlite® Sensor and MiniLink® transmitter

Roche

Accu-Chek® Combo (CSII)

Dexcom® SEVEN® PLUS (CGM)

Table 1. Regulatory status of the technologies

Producer	Device/model	Italian National Classification of Medical Devices (CND)	Medical Devices Database and Repertory (Italian Ministry of Health)	CE Certificate	FDA
Animas Corporation – Dexcom	Animas® Vibe™	Z1204021601 - Microinfusori Portatili Per Insulina.	449841/429075/ 499993/499844/ 499842/499845/ 499989/499840/ 499990 (models differ in colour)	from June 2011	No
	Dexcom G4™	Z12040115 - Sistemi Per Monitoraggio Della Glicemia	446804	from June 2011	
Medtronic	Paradigm® Veo™ 554	Z1204021601 - Microinfusori Portatili Per Insulina	214158	from July 2010	No
	Paradigm® Veo™ 754		214177		
Roche Diagnostics – Dexcom	Roche – Accu-Chek® Combo	Z1204021601 – Microinfusori portatili per insulina	206397	from April 2010	No
	Dexcom Seven® Plus	Z12040115 – Sistemi per monitoraggio della glicemia	277400	from November 2008	

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4. Clinical effectiveness and safety

This chapter is divided into two main parts. The first part provides an overview of the published literature on CSII and/or CGMS. As the objective of the present HTA report was to assess safety and efficacy of the sensor-augmented systems in children and adolescents with T1DM, it seemed appropriate to provide a summary of conclusions from international HTA reports and clinical practice guidelines on the immediate predecessors of this innovative technology, i.e.continuous subcutaneous insulin pumps and devices for continuous glucose monitoring. In the second part a systematic review of studies on SAP versus MDI is provided, and results discussed.

4.1 Overview of HTA reports and systematic reviews produced by HTA Agencies on Continuous subcutaneous insulin injection (CSII) pumps and devices for continuous glucose monitoring systems (CGMS) for children and adolescents with T1DM

4.1.1 Objectives

To overview recommandations from recent HTA reports and clinical practice guidelines in patients with TDM1, on the separate use of:

- Continuous Subcutaneous Insulin Infusion (CSII) pumps
- Continuous Glucose Monitoring Systems (CGMS)

4.1.2 Methodology

A systematic search of Health Technology Assessment (HTA) reports, Horizon Scanning (HS) and systematic reviews (when produced by HTA Agencies) on Continuous Subcutaneous Insulin Infusion (CSII) pumps or Continuous Glucose Monitoring Systems (CGMS) was performed. No time limit for publication was applied.

Inclusion criteria were: HTA reports, Horizon Scanning (HS) and systematic reviews (the latest ones only when produced by HTA Agencies) evaluating efficacy and safety of CSII pumps or CGMS in children and/or adolescents with T1DM. Papers in English, French, Italian and Spanish were considered for the inclusion. Given the rapid evolving nature of considered

devices when more than one report and/or systematic review were available from the same HTA Agency, only the most recent publication was included.

The quality of the included papers was analysed according to the following criteria: description of the research strategy, type of limits applied, inclusion and exclusion criteria, description and quality assessment of the included studies.

In addition to the systematic search of the literature for HTA reports, HS and systematic reviews, most relevant clinical practice guidelines on diabetes mellitus were searched, retrieved and analysed and recommendations on CSII pumps and/or CGMS reported. Databases and websites that were consulted and complete research strategy are reported in Appendix 3.

4.1.3 Results

Continuous Subcutaneous Insulin Infusion (CSII) pumps

HTA Reports

The literature search identified 4 HTA reports,[1-4] and 1 horizon scanning.[5] One report[6] was excluded because an older version of a more recent document.

Overall results and conclusions of included HTA reports and HS are reported below in chronological order, while a summary of findings and conclusions are reported in Appendix 4 - Table 1.

- The HTA report produced by the Andalusian Agency for Health Technology Assessment (AETS) in 2000[1] evaluated the efficacy of both external (CSII) and implantable (peritoneal) insulin pumps in specific populations of patients with T1DMM (i.e. pregnant women and children and adolescents). Secondary objectives were the identification of best suited patients for pumps' use and impact on quality of life. Literature search methods are fully described (studies published between 1990 and 2000, in English or Spanish and indexed by Medline). The search retrieved 48 studies; 36 studies evaluated the efficacy and safety of either external (CSII) or implantable (peritoneal) pumps and 12 studies evaluated impact on patients' quality of life. Authors did not provide any details on the design of included studies. Among the retrieved studies, two considered CSII pumps in a total of 158 children and/or adolescents with type 1 diabetes. The report concludes that metabolic control and its related benefits obtained

through intensive insulin therapy are equally achievable with multiple injections or infusion pumps. Use of and indication for CSII pumps inplace of MDI appears to be related more to patients' preferences and characteristics rather than to therapeutic necessity or improvement in quality of life. However it is acknowledged that some authors suggest using pumps during pregnancy or in those patients who have not been able to achieve a good metabolic control with use of multiple injections. Finally, AETS recommends that public reimbursement of CSII should be restricted to patients who respond to specific selection criteria, the most important being compliance with an intensive insulin therapy from 6 to 12 months before CSII initiation.

- The Succint and Timely Evaluated Evidence Review (STEER) published in 2002[2] tried to answer the following research question: "What are the clinical effects of continuous insulin infusion pumps compared with multiple injection and conventional insulin therapy in people with T1DM?". The literature search covered Medline, Embase and the Cochrane Library and was updated at November 2001; however, inclusion and exclusion criteria were not described. The report included one systematic review (judged of good quality) and one RCT (on 96 patients with type 1 uncontrolled diabetes) both evaluating conventional therapy versus intensified treatment (only aggregated data for MDI and CSII are available). According to the retrieved evidence, the Authors conclude: "we found no reliable evidence about benefits of continuous subcutaneous insulin infusion compared with multiple insulin injections for clinically important outcomes, although limited evidence suggested that infusion may improve glucose control, but increase risk of ketoacidosis compared with multiple injections. We found good evidence that both continuous infusion and multiple insulin injection, described collectively as intensive insulin therapy, reduce clinical complications and achieve tighter blood glucose control compared to conventional therapy in people with type 1 diabetes, but are associated with greater risk of hypoglycaemia and ketoacidosis."
- National Institute of Clinical Excellence (NICE) HTA 2004 (Colquitt 2004).[6] This report was updated by a subsequent more recent NICE HTA report published by Cummins et al. in 2010 (see below).
- In 2005 the Agency of the Evaluation of Technologies and Means of Intervention of Healthcare (Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé, AETMIS) of Quebec produced an HTA report assessing efficacy, safety and cost-effectiveness of CSII compared to MDI for intensive insulin therapy in type 1 diabetes (AETMIS 2005).[3] Authors clearly and completely described the applied methods: they applied the same search strategy of an HTA report previously published by NICE (Colquitt 2004)[6] to retrieve articles published between January 2002 and July 2004. They included RCT, cohort and case-series of at least 10 weeks' duration, published in English, French, Spanish, Italian and

German comparing CSII versus MDI in patients with type 1 DM. Studies on pregnant women, newly diagnosed type 1 DM patients and on patients with type 2 DM were excluded. Additional studies were hand-searched from retrieved publications. To complete the safety profile, national incident report databases (from USA, GB and Canada) were also consulted. Patients' (or patient's parents') and health professionals' perspective were explored by means of a survey and interviews (see Chapter 4 "Patients views"). The report included 2 meta-analyses, 4 economic analyses, 13 primary studies on adult patients (3 RCTs and 10 observational studies and 21 primary studies on children and/or adolescents (5 RCTs and 16 observational studie) comparing CSII to MDI with either insulin glargine or insulin NPH. According to the available evidence, authors conclude that NPH-based MDI remain the standard treatment for both paediatric and adult diabetic patients, although - for the general population of adult diabetics - the pump may offer a modest advantage in terms of glycemic control. For both adult and paediatric patients, selected on the basis of inadequate glycemic control (HbA1c level ≥ 8.5%), there is some evidence that CSII may be associated with improvement of HbA1c. The survey on patients' (or patients' parents) and health professionals' perspectives revealed that most of them are in favour of insulin pumps. The analysis on the warnings concerning pumps' malfunctioning concluded that "it therefore seems that the insulin pump is still prone to technical problems, but the nature and severity of their impact on the patients' health cannot be accurately assessed." The available evidence concerning the impact on prevention of long-term complications and on improvement of quality of life was judged not sufficient to give an informed opinion of the cost-effectiveness of the insulin pump for target populations. Finally, AETMIS recommends that:

1. the preferred therapeutic approach to type 1 diabetes in both adults and children should be based on intensive therapy with multiple daily insulin injections;
2. therapy by continuous subcutaneous insulin infusion should be recognized in Québec as a treatment modality that might be indicated for a limited, selected group of type 1 diabetics (various selection criteria based on expert opinions are cited in the report);
3. the *Ministère* consider setting up a multidisciplinary task force (including *Diabète Québec*, and the clinical and research communities) responsible for: a. identifying consensus criteria for patient selection and for prescribing and monitoring insulin pump therapy; b. designating clinics that would participate in the implementation of pump therapy and determining the composition and role of the professional team required; c. developing common candidate selection, patient education and follow-up tools; d. monitoring the

implementation of pump therapy; and e. re-evaluating the use of pump therapy in Québec some time after it is introduced;

4. the consensual criteria for the use of the pump be reviewed periodically […];

- The HTA report by Health Services Assessment Collaboration published in 2008 (HSAC 2008)[4] was aimed at evaluating effectiveness, safety and cost-effectiveness of CSII when compared to optimised MDI in type 1 and 2 DM. The HTA report updated the systematic review of Colquitt et al (Colquitt 2004).[6] Literature strategy and inclusion and exclusion criteria are clearly exposed. Medline, Embase and the Cochrane Library were systematically search for RCTs on efficacy and safety (published from January 2002 to August 2007 inclusive) testing CSII versus optimal MDI (at least three injections/day) for almost 10 weeks in type 1 and 2 DM. Economic data were retrieved from papers indexed by Medline and Embase and published through January 2008. Using the same economic model used by Colquitt et al. (Colquitt 2004)[6] adapted to the New Zealand's context, a cost-effectiveness analysis was performed. Among the 11 included RCTs, 3 compared the efficacy of CSII or MDI in children and/or adolescents with type 1 diabetes. According to the available evidence, Authors concluded that CSII pumps could be associated to a better glycaemic control and less episodes of severe hypoglycaemia whilst, in relation to economics aspects, they point out that favourable conclusions from the available literature are heavily influenced by the magnitude of clinical benefit assumed. Finally, Authors highlight that available studies were affected by many potential biases impacting on their internal validity.

- The HTA report by NICE published in 2010 (NICE 2010)[5] evaluated effectiveness and cost-effectiveness of CSII in type 1 and 2 diabetes mellitus; it updates a previous one published in 2004.[6] The Authors carried out a systematic review of the literature and an economic evaluation; MEDLINE, EMBASE, The Cochrane Library (all sections), the Science Citation Index (for meeting abstracts only) and the website of the 2007 American Diabetes Association were searched for studies published between 2002 and June 2007. The systematic review included RCTs comparing the use of CSII with MDI either in patients with type 1 diabetes or in those with type 2 diabetes. Trials shorter than 12 weeks were excluded. Some recent observational studies were also included and reviewed for data on long-term outcomes, discontinuation rates and adverse events; studies on quality of life and the cost-effectiveness assessment of CSII were also included. Information on the patient's perspective was obtained from a collection of commentaries by members (or their parents) of a British pump-users organization – Insulin Pump Therapy (INPUT)[19]-, from a review of existing literature on patients' preference and QOL and from the summary of findings of the previous NICE HTA report (see Chapter 4 "Patients views"). Economic evaluation comprised both a review of

existing literature on cost-effectiveness of CSII and a cost-effectiveness analysis that used the Center for Outcomes Research and Evaluation (CORE)[20] model (i.e. an economic model that can be briefly summarised as being an Internet-based model, built upon 15 sub-models that simulate the main complications of diabetes; each sub-model is a Markov model using Monte Carlo simulation and incorporating the time, the state, the time in state and transition probabilities that are typically diabetes type dependent, as derived from published sources).

The HTA report included 16 RCTs: 8 compared CSII versus analogue-based MDI in either type 1 or type 2 diabetes and 8 small RCTs compared CSII versus NPH-based MDI in type 1 diabetes (6 out of 8 including only children and/or adolescents for a total number of patients: 126, range: 16-42). Also 48 observational studies (28 out of 48 only on young children and/or adolescents with a number of patients ranging from 8 to 161 and a follow-up from 6 months to 5 years), 6 studies in pregnancy and 4 systematic reviews were included in the report.

Authors highlight that most of the RCTs had a small number of patients and a short duration; moreover, considering only type 1 diabetes, RCTs comparing the use of CSII with the most effective available treatment (i.e. MDI with analogue insulins) resulted to be still lacking, in particular in young patients. The perspective of pump users was analysed interviewing parents of 10 children aged 5-8 years and included in INPUT. Most of the retrieved cost-effectiveness studies used the CORE model applying it only to adults (as the model cannot be applied to children). Authors developed their own CORE model as well and, assuming an improvement in HbA1c level of 0.9%, and a reduction in severe hypoglycaemic episodes from 62 to 31 per 100 patient/years, the cost per QALY gained resulted in around £36,587.

Authors identified the following research needs for young patients with type 1 diabetes:

- RCTs with larger numbers of patients, of longer durations and with structured educational programs available for all the patients comparing CSII versus MDI with insulin analogues;
- an economic model specific for young patients
- in-depth assessment of possible difficulties in managing diabetes in schools.

Authors concluded that "based on the totality of evidence, using observational studies to supplement the limited data from randomised trials against best MDI, CSII provides some advantages over MDI in type 1 diabetes. For both children and adults, these are:

1. better control of glucose levels as reflected by HbA1c level, with the size of improvement depending on the level before starting CSII,
2. fewer problems with hypoglycaemia,
3. quality of life gains, such as greater flexibility of lifestyle.

There are benefits for families. However, the benefits of CSII come at an extra cost of about £1,700 per annum. There is no evidence that CSII is better than analogue-based MDI in type 2 diabetes, or in pregnancy […]."

Clinical Practice Guidelines

Twelve Clinical Gudelines[7-18] expressing recommendations on CSII pumps were retrieved.

Seven of the twelve guidelines have a "comprehensive approach", meaning that they include all type of diabetes, all ages and consider characteristics of specific sub-population; two guidelines take into consideration T1DM and T2DM, one focusing specifically on CSII, the other focusing on pregnant woman; the remaining three focused on T1DM, one of which only on children and young people. The twelve guidelines have been published between 2004 and 2011 (nine of twelve between 2008 and 2011). Six were developed in Europe (5 in UK and 1 in Italy) and six in north America (5 in USA and 1 in Canada). Seven were produced by governmental institutions and five by patients or professional associations.

All retrieved guidelines consider CSII as an option for those patients with DM1 that, despite an appropriate use of MDI, do not achieve HbA1c targets and/or experience severe or disabling hypoglycaemia. Moreover all guidelines highlight the importance of patients being motivated and of a trained healthcare team being present supporting patients and families. No guideline recommends CSII for DM2. Table 2 at Appendix 4 reports a summary of the recommendations.

Continuous Glucose Monitoring Systems (CGMS)

HTA reports, HSs and systematic reviews

Overall results and conclusions of included HTA reports, HSs and systematic reviews are reported below in chronological order, see Table 3 at Appendix 4.

- The Horizon Scanning (HS) produced by the Agencia de Evaluación de Tecnologías Sanitarias de Andalucía (AETSA) in 2005 (AETSA 2005)[2121] evaluated the efficacy and safety of continuous glucose monitoring system (CGMS) for paediatric and adult patients with diabetes mellitus type 1 (DM1). Literature search methods are generally described: searched databases (Medline, Embase, CRD, EMEA, FDA, EuroScan, INAHTA and ClinicalTrial.gov) and assessment of methodological quality of the identified studies (adapted version of U.S. Preventive Services Task Force and SIGN – Scottish Intercollegiate Guidelines Network)[28] are reported. Six studies in paediatric population (patients' number ranging from 11 to 191) and 5 in adult population have been included. A control group was present only in one study on paediatric population and in two studies on adult population. The methodological quality of the studies was considered moderate or moderate-low. concerning paediatric population, reviewers found that the CGMS and SMBG have good correlation (Pearson's coefficient over 0.80); correlation is higher for hyperglycaemic episodes, but frequency and duration of hypoglycaemic episodes appear overestimated. Sensitivity and specificity were found to be acceptable but with high rate of false positive. Contradictory results have been found on glycaemic control; moreover higher quality studies didn't find significant difference on the improvement of HbA1c. No improvement in quality of life nor in fear of hypoglycaemic episodes have been found.
- The HS produced by Australia and New Zealand Horizon Scanning Network (ANZHSN) in 2006 (ANZHSN)[2122] updated a previous document with the latest available evidence derived from Randomised Controlled Trials (RCTs) on safety, effectiveness, cost-effectiveness and ethical considerations associated with continuous glucose monitoring devices for diabetic patients. Literature search methods are described: time limits (until 15th March 2006) and searched databases (Cinahl, Medline, CRD, Cochrane Database of Systematic Review, CENTRAL and others) are reported. While no criteria for studies' methodological quality assessment are given, all studies are graded according to the dimensions of evidence defined by the National Health and Medical Research Council[29] and/or levels of evidence for assessing diagnostic accuracy.[30] Thirteen studies have been included in the report, but only four are on paediatric patients with T1DM (number of patients ranging from 11 to 191). Of these, two evaluate only diagnostic accuracy, one effectiveness and safety and one effectiveness, safety and Quality of life. The methodological quality of the studies was considered

essentially low. Conclusion and advisory are reported for mixed population: "There is significant potential for the uptake of CGM devices given the worldwide clinical need and burden of disease. There is a need to develop more affordable and viable CGM devices with sound performance standards and to show more beneficial clinical effectiveness and safety outcomes. Evidence from RCTs, though somewhat contradictory and limited by small and select patient groups, indicates some effectiveness in glycaemic control and increased safety, due to greater awareness of glycaemic variation. However these devices seem to be less accurate, particularly during hypoglycaemic episodes, can cause minor skin reactions and do not improve diabetes related quality of life compared to SMBG. CGM is useful as an adjunct to conventional SMBG in selected patients with difficulties in maintaining glycaemic control. However, at this stage, CGM will not replace conventional SMBG in the majority of patient".

- The HTA produced in 2009 by the California Technology Assessment Forum (CTAF)[2323] updates a previous HS produced by the Agency and published in 2003 and reviews the scientific literature on the use of continuous blood glucose monitoring (CGM) devices in patients with diabetes mellitus. Literature search methods are described: language limits (English), time limits (from 2003 to January 2009), searched databases (PubMed, Embase, Cochrane Clinical Trial Database, Cochrane Database of Systematic Review, DARE) are reported. Criteria used to assess methodological quality of included studies are not described. Twenty-two studies have been included in the report: 11 RCTs and 11 observational studies. Of these, three RCT and four observational studies are on paediatric population and two RCT are on mixed-age population (number of patients ranging form 1 to 60). The three RCTs (all small trials, ranging from 27 to 36 participants) did not find any difference in glycaemic control for the intervention group (CGM users) compared to the control group. Reviewer concluded that "the largest RCT to date of CGM devices for adults and children was well designed and analyzed, and it found conclusive benefit only for adults 25 years and older. While in this study, and in other smaller RCTs there is evidence that both children and adults spend less time in a hypoglycemic glucose range when using a CGM device compared to usual care frequent SMBG, there is little evidence that the use of a CGM device confers an ultimate health benefit in terms of HbA1C, as measure for overall glycemic control. It may be that for children and adolescents this is in large part due to difficulty with device adherence and not with the device itself. However, a health technology is only as good as its actual clinical application, and the evidence has not yet shown conclusive benefit for children, adolescents, and even young adults". Authors recommend that "continuous glucose monitoring devices do not meet CTAF (California Technology Assessment Forum) criteria for safety, effectiveness and improvement in health

outcomes for the management of diabetes mellitus in children, adolescents and pregnant women".

- The Systematic review produced by the Agència d'Informació, Avaluació i Qualitat en Salut (AIAQS)[24] in 2010 evaluated the efficacy and safety of real time continuous glucose monitoring system (rt-CGMS) in comparison with the self-monitoring blood glucose system (SMBGS) in adults and paediatric patients with T1DM (DM1). Literature search methods are fully described: time limits (from 2006 to July 2010), inclusion and exclusion criteria, searched databases (Medline, CRD, TripDatabase, DARE, CENTRAL and many others) and assessment of methodological quality of the identified studies (according to SIGN criteria, Scottish Intercollegiate Guidelines Network).[28] Fourteen randomized controlled trials and 2 before and after studies were selected. Of these studies, 7 were carried out in adults, 2 in children and 7 in mixed-age sample (number of patients ranging from 10 to 154). The methodological quality of the studies was considered moderate. About paediatric population, reviewers conclude that the use of rt-CGMS requires some additional conditions - such as frequent use of the sensor or use in combination with a CSII - to be considered of some efficacy.
- The systematic review produced by the Agència d'Informació, Avaluació i Qualitat en Salut (AIAQS) in 2010[25] analyzed the scientific evidence on the efficacy and safety of Medtronic-MiniMed CGMS in comparison to the self-monitoring blood glucose system in adults, paediatric patients and pregnant women with DM1, as well as pregnant women with gestational diabetes mellitus (GDM) and proposed indication criteria for the use of this technology. Literature search methods are fully described: time limits (until October 2009), inclusion and exclusion criteria, searched databases (Medline, CRD, TripDatabase, DARE, CENTRAL and many others) and assessment of methodological quality of the identified studies (Scottish Intercollegiate Guidelines Network – SIGN).[28] Two meta-analyses, 12 randomized controlled trials and 1 before and after study were selected. Among primary studies, 5 included adult patients, 5 paediatric patients, 3 adults and paediatrics population (number of patients ranging from 11 to 40). No studies carried out in pregnant women were included. The methodological quality of the studies was considered moderate to low. Regarding paediatric population, reviewers conclude that the limited evidence available, both in improving metabolic control and in reducing the frequency of hypo- and hyperglycemias with the retrospective Medtronic-Minimed CGMS does not allow making conclusions about its effectiveness. Moreover, according to Authors: "Considering the available evidence, the CGMS in real time should be restricted to the following potential candidates: DM1 adult patients with a lack of glycaemic control treated with an intensive insulin therapy including a 3 months review."

- The HTA produced in 2011 by the Washington State Health Care Authority (WA HTA 2011)[2626] analyzed self-monitoring of blood glucose (SMBG) in individuals with insulin dependent diabetes, 18 years of age or under. Literature search methods are fully described: language limits (English), time limits (until July 2010), inclusion and exclusion criteria and searched databases (PubMed, EMBASE, CINAHL, ClinicalTrials.gov, NIH Reporter, The Cochrane Library, EconLIT, PsychINFO, AHRQ, National Guideline Clearinghouse and INAHTA). The method used for assessing the quality of evidence of individual studies as well as the overall quality of evidence incorporate aspects of rating scheme developed by the Oxford Centre for Evidence-based Medicine,[31] principles outlined by the GRADE Working Group[32] and recommendations made by the Agency for Healthcare Research and Quality (AHRQ).[33] Following the assessment of the quality of each individual study included in the report, an overall "strength of evidence" for the relevant question or topic is determined. Globally 43 articles were included in the HTA, but only 4 RCTs (number of patients ranging from 29 to 156) and 10 observational studies deal with CGM safety, efficacy and effectiveness. The "strength of evidence" of CGM+SMBC compared to SMBG alone is low for efficacy and effectiveness and moderate for safety; there is no evidence available on cost-effectiveness.

Reviewers conclude the following:

  - from the available evidence it is not clear what specific role these devices [CGM] might play in patients 18 years old or younger or which individuals may most benefit from this technology.
  - It is not clear to what extent improvement in overall glycemic control within CGM groups is clinically meaningful or how it may affect other long-term health outcomes. The short follow-up period applied by current trials to date precludes any conclusions on long-term benefits of CGMS.

- The HTA produced by the Ontario Medical Advisory Secretariat in 2011[27] analyzed the effectiveness and cost-effectiveness of continuous glucose monitoring combined with self-monitoring of blood glucose compared with self-monitoring of blood glucose alone in the management of diabetes. Literature search methods are fully described: language limits (English), time limits (January 1, 2002 until September, 15 2010), inclusion and exclusion criteria, searched databases (OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, CINAHL, the Cochrane Library, and INAHTA). Assessment of methodological quality of the identified studies was conducted using GRADE methodology.[31] Two studies (number of patients 132 and 138, respectively) of moderate quality have been included: in both, the use of CGM was associated with insulin pump therapy

in a mixed-age population. Data on paediatric sub-population alone are not reported. Reviewers conclude that there is "moderate quality evidence that CGMS + SMBG:

- is not more effective than SMBG alone in the reduction of HbA1c using insulin infusion pumps for Type 1 diabetes;
- is not more effective than SMBG alone in the reduction of hypoglycemic or severe hypoglycemic events using insulin infusion pumps for Type 1 diabetes."

No studies on cost-effectiveness were found. Several studies examined the relative effectiveness and cost-effectiveness of *continuous subcutaneous insulin infusion* when compared to multiple daily injections of insulin. However, none evaluated the *continuous monitoring* of blood glucose levels compared to standard self-monitoring. For this reason economic analysis was limited to evaluation of impact on costs due to CGM transmitter and blood glucose sensor over a 5-years period, resulting in an estimated overall increase of $159.9M per year for all type-1 diabetic patients living in Ontario.

Clinical Practice Guidelines

Eight Gudelines[7,8,10,13-18] expressing recommendations on CGMS were retrieved.

Five of the eight guidelines have a "comprehensive approach", meaning that they include all type of diabetes, all ages and considers characteristics of specific sub-population while others two guidelines take into consideration only T1DM in all ages, and one focused only on pregnant woman. The eight included guidelines have been published between 2004 and 2011 (six upon eight between 2008 and 2011). One was developed in Italy, three in UK and four in USA. Four were produced by governmental institutions and four by patients or professional associations.

All documents consider CGMS as a supplemental tool of (and not a substitute for) self-monitoring blood glucose (SMBG) through finger stick testing especially in patients with hypoglycaemia unawareness and/or frequent hypoglycaemic episodes. See Table 4 (Appendix 4) for a summary of the recommendations.

4.2 Systematic review

4.2.1 Objectives

The objective of the systematic review was to assess effectiveness and safety of the combined use of continuous subcutaneous insulin injection (CSII) and continuous glucose monitoring (CGMS) devices (sensor-augmented pump - SAP) when compared to standard practice, that is intermittent whole blood finger-stick glucose monitoring plus multiple dose injections (MDI), in children and adolescents with type I diabetes mellitus.

4.2.2 Methods

Inclusion criteria

Types of studies: we included systematic reviews and primary studies assessing the effectiveness and safety of the devices. Among primary studies only randomized controlled trials (RCT) and quasi-randomized prospective controlled trials were included. Studies had to be full reports, have a minimum sample size of 10 participants and a minimum follow-up of 6 weeks (as it takes a minimum of 6 weeks to detect a meaningful change in HbA1c (Hoecks 2011).

Types of participants: children and adolescents (0-18 years old) with type I diabetes mellitus as defined by WHO criteria. We also included studies considering adult population with type I diabetes and indirectness was taken into account when evaluating results.

Types of interventions: CSII+CGMS devices (SAP) Versus Standard practice (MDI with three or more insulin injections per day) plus intermittent whole blood finger-stick glucose monitoring

Types of outcome measures:

Primary outcomes

Short-term effectiveness outcomes

- glycemic control (glycosylated hemoglobin A1c (HbA1c), daily mean blood glucose, fasting blood glucose or postprandial blood glucose)
- diabetic ketoacidosis

- endocrine function (normal growth, height and weight, change in Body Mass Index, sexual maturation)
- hospitalisation
- emergency hospital admission

Short-term safety outcomes

- Frequency of hypoglycaemia
- Severity of hypoglycaemia
- Hypoglycaemic awareness
- Type, number and severity of adverse events

Short-term patient-reported outcomes

- Quality of life (measured using a validated instrument) of patients and/or carers
- Participation in physical activity
- School participations/ absence
- Eating disorders
- Compliance
- Clinic attendance

Short-term technical performance outcomes

- Ability and sensibility in time responding after the subject started eating
- Reduction in the amount of insulin administered
- Failure in communication between pump and monitor
- Failure in the alarm systems
- Lipid regulation
- Right estimation of glucose level (accuracy of measure)
- Failures in the quantity of insulin administrated

Long-term effectiveness outcomes

- Cardiovascular function (blood pressure)
- Ocular function (retinopathy, juvenile cataract)
- Renal function (microalbuminuria)
- Diabetes late complications

- Mortality

Secondary outcomes

- Time spent in different glucose strata (hypoglycaemic, euglycaemic, hyperglycaemic)
- Insulin requirement to maintain glycemic control
- Education (Diabetes knowledge)

Search methods for identification of studies

Electronic searches

Six databases were searched to identify both systematic reviews and RCTs of interest: The Cochrane Library, MEDLINE, EMBASE, CINAHL, Health Technology Assessment Database (HTA Database - Centre for Reviews and Dissemination CRD) and Database of Abstracts of Reviews of Effects (DARE - Centre for Reviews and Dissemination). The key words described the participants' disease and interventions. See appendices for details of search strategies: Appendix 5. Ongoing studies were searched in the following databases: Current Controlled Trials (www.controlledtrials.com - with links to other databases of ongoing trials) and the National Research Register (www.update-software.com/National/nrr-frame.html). See appendices for details of strategy: Appendix 6.

Searching other resources

Reference lists of identified articles were checked for additional references. In case of missing and/or unclear data in published papers we contacted the authors. The search was limited to 2005 onwards as the use of the real-time devices had not routinely started before this period (Hoecks 2011). Only documents in English, Italian, French and Spanish were included.

Data collection and analysis

Selection of studies

We used Reference Manager program (version 10) to manage the references. Two reviewers (SM and LV) independently selected the studies to be included following these steps:

1. exclusion on the basis of title and abstract;
2. full text retrieving of the potentially relevant studies;
3. reading of the selected articles and application of the inclusion criteria.

The results of the selection were compared and differences discussed. Resolution of the differences in the paper selection was achieved by mutual agreement.

4.2.3 Data extraction and management

Data were extracted related to study design, study population, intervention, comparator, outcomes and results using a standard extraction template. Data extraction from included studies was carried out using single study tables of evidence. Extraction was performed by two independent reviewers. The results of the extraction were compared and differences discussed. Resolution of the differences in the extraction was achieved by mutual agreement.

Assessment of risk of bias in included studies

The following criteria were used for the quality assessment of different study designs:
- systematic reviews criteria drawn from the AMSTAR checklist (Shea 2007);
- randomized controlled trials criteria suggested by the Cochrane Handbook (Higgins 2009) in particular random sequence generation and allocation concealment (allocation bias), blinding of participants, personnel (performance bias) and outcomes' assessors (detection bias), incomplete or selective reporting (attrition and reporting bias), authors' conflict of interest and role of the sponsor, if any, were taken into account and evaluated.

Measures of treatment effect

According to the nature of the outcome considered (continuous or dichotomous) the effect of both intervention and control were evaluated as head to head comparison in terms of absolute mean differences in values or frequency of each outcome.

Data synthesis

Studies were analyzed and synthesized by outcome. As no meta-analyses were available, only a range of estimates (minimum and maximum values) was provided.

4.2.4 Results

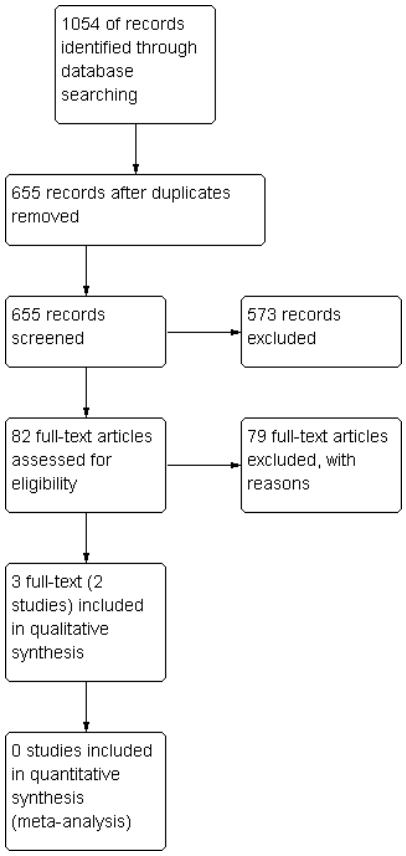
Description of studies

See: Characteristics of included studies (Appendix 7); Characteristics of excluded studies (Appendix 8).

Results of the search

The systematic search conducted up to April 2012 produced 1054 records. From these, 82 potentially eligible papers were retrieved in full-text for further examination. The remaining studies were excluded because they were duplicates or they were not pertinent to the research question, had a very short duration or a number of patients < 10, had not the required right study design for inclusion (narrative reviews, observational studies or guidelines). After reviewing the full text of the 82 selected studies, the comparison between SAP and standard treatment was tackled in only 1 systematic review (Langendam 2012) and 2 RCTs. The study selection process is summarized in the PRISMA flow diagram (Moher 2009; see Figure 1).

Figure 1 Study flow diagram



As the systematic review included the two primary studies, authors decided to exclude it and to analyse in details only the two primary studies. One RCT (STAR-3 study) was published by Hermanides (Hermanides 2011) and included only adult patients. The other RCT, including both adults and children and adolescents, resulted in two publications (Bergenstal 2010, Slover 2011). The paper by Bergenstal (Bergenstal 2010) carried out the analysis for two subgroup populations: a) children and adolescents, b) adults. The paper by Slover (Slover 2011) carried out the analysis stratifying non-adult population in children (7-12 years of age) and adolescents (13-18 years of age). Thereafter we refer to this RCT as STAR-3 study.

Additional search of ongoing studies identified only 1 RCT (Ongoing studies) of potential interest but, as the recruitment is still ongoing, it was not possible to obtain any preliminary data (Appendix 3).

Included studies

To date, only two RCTs (STAR-3, Hermanides 2011) investigating the effectiveness of sensor-augmented insulin pump (the so-called semi-closed/open loop system) versus multiple daily insulin injections (MDI) together with standard monitoring of blood glucose (SMBG) have been published and therefore were included. The characteristics of the two included primary studies are described and summarised in Appendix 7.

Both studies investigated the same device which integrates an insulin pump with continuous glucose monitoring, MiniMed Paradigm REAL-Time System, Medtronic. Both had, as primary outcome, the change of glycated hemoglobin level in each group from baseline to the study end. Only one study (STAR-3) included both children (from 7 years of age) and adults and provided separate analyses of outcomes according to patients' age.

The first study (STAR-3) is a 1-year, multicenter, randomised open trial that enrolled 485 patients either adults (329 patients) or children (82, aged 7-12) and adolescents (74, aged 13-18) with uncontrolled type I diabetes mellitus (i.e. glycated hemoglobin level between 7.4% and 9.5%) despite multiple daily injections therapy. Patients that had used an insulin pump in the three years preceeding the randomization or that had two or more documented events of severe hypoglycemia without warning of impending low glucose levels were excluded. Patients were randomised in blocks stratified according to the age group (children: 7-18 years and adults: 19-70 years) either to a device integrating a subcutaneous insulin pump (CSII) releasing insulin aspart with continuous glucose monitoring (CGM) (Sensor-augmented pump - SAP - group) or to multiple daily injections (MDI) with insulin glargine and aspart and standard blood glucose monitoring (SBGM) through finger sticks (injection-therapy group). All subjects completed 1-week of CGM studies at baseline, 6 months, and 12 months. All subjects were blinded to the baseline CGM study results and MDI subjects were blinded also to the 6- and 12-month results. The primary outcome of the study was the change from baseline in the glycated hemoglobin (HbA1c) level at 1 year whilst severe rates

of hypoglycemia (that, for the study purpose, was defined as an episode requiring assistance and confirmed by documentation of a blood glucose value of less than 50 mg per deciliter - 2.8 mmol per liter - or recovery with restoration of plasma glucose) were analyzed as a secondary outcome.

In the first two weeks, patients randomised to SAP were placed on insulin pump alone and glucose sensors were introduced thereafter. During the 5 weeks after randomization patients completed an online insulin-pump training and attended additional visits for insulin-pump and sensor training. Authors state that all the patients received the same visits' and controls' schedule (3, 6, 9 and 12 months after randomization) but the trial was open. At each follow-up visit glucose data were reviewed, therapy was adjusted, glycated hemoglobin was measured, and data on adverse events were collected. Baseline characteristics of the enrolled 485 patients were similar for the two study groups except for adults, mean weight (higher in the intervention group) and student status (more frequent in the control group). At baseline, the mean glycated hemoglobin, for children and adults, was 8.3% in both study groups.

The second study (Hermanides 2011) included 83 adult patients (aged 18-65 years) diagnosed with Type 1 diabetes at least 1 year prior to study participation, currently treated with optimized multiple daily injections (MDI), but having anHbA1c $\geq$ 8.2% at screening, despite repeated attempts to improve this value. Hearing problems or impaired vision that might hinder recognition of alarms, substance abuse other than nicotine, abdominal skin abnormalities that might hinder subcutaneous insertion, current treatment for any psychiatric disorder other than depression, treatment with CSII in the 6 months prior to study entry, pregnancy, heart failure, cancer or kidney disease, and concomitant participation in another therapeutic study were all criteria for exclusion.

Before randomization, patients underwent blinded 6-day continuous subcutaneous glucose monitoring measurements and treatment advice was given on the basis of downloaded data. Patients were then randomised to a 26-week treatment with a sensor-augmented insulin pump (SAP-group) or to multiple daily injections plus self-blood monitoring through finger-sticks. Patients were trained to use the SAP system within 2 weeks after randomization and to change both the insulin catheter and glucose sensor every 3 days. At 13 and 26 weeks, patients visited the investigating centre: data from the sensor were downloaded and, if necessary, therapy adjustments were made based on the downloaded data. Patients in the multiple daily injection group received standard care, which included multiple daily injection therapy with rapid-acting insulin analogue before meals and long-acting analogues or human insulin; they were advised to self measure blood glucose at least three times daily and received a blinded 6-day of CGBM before their 13- and 26-week visits.

Excluded studies

Studies were excluded because they tested comparisons different from the one we selected (SAP versus MDI+SMBG), because of their design (narrative reviews, observational studies), because number of patients and/or duration of follow-up were insufficient (number of patients < 10 and follow-up duration < 6 months). One systematic review was also excluded as Authors decided to analyse in details the two included primary studies of interest comparing SAP versus MDI plus SBGM (Langendam 2012). See Characteristics of excluded studies (Appendix 8).

Risk of bias in included studies

Figure 2 and Figure 3 present a summary of the results of the risk of bias assessment.

Figure 2: Risk of bias summary: review authors' judgements about each risk of bias item for each included study. (NB la figura è stata sostituita)

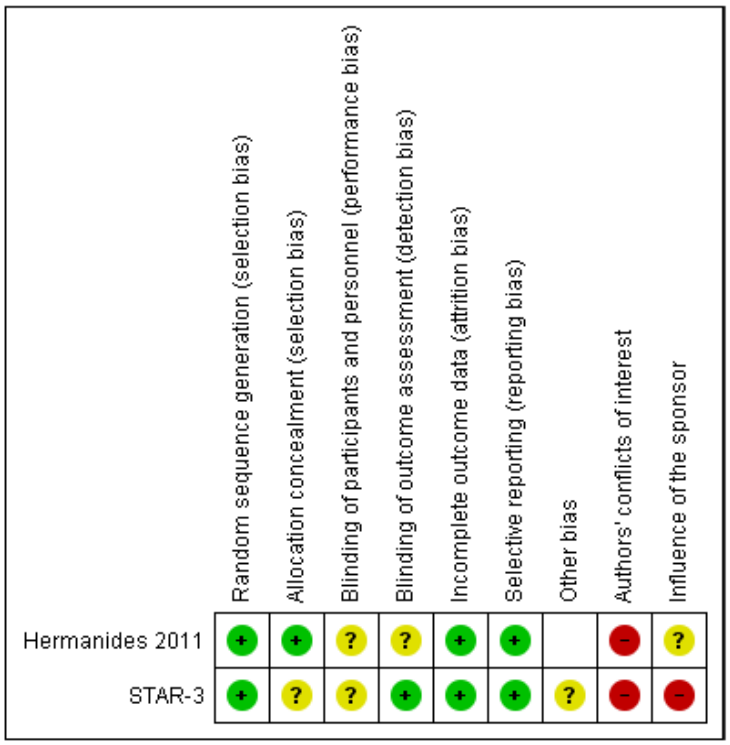
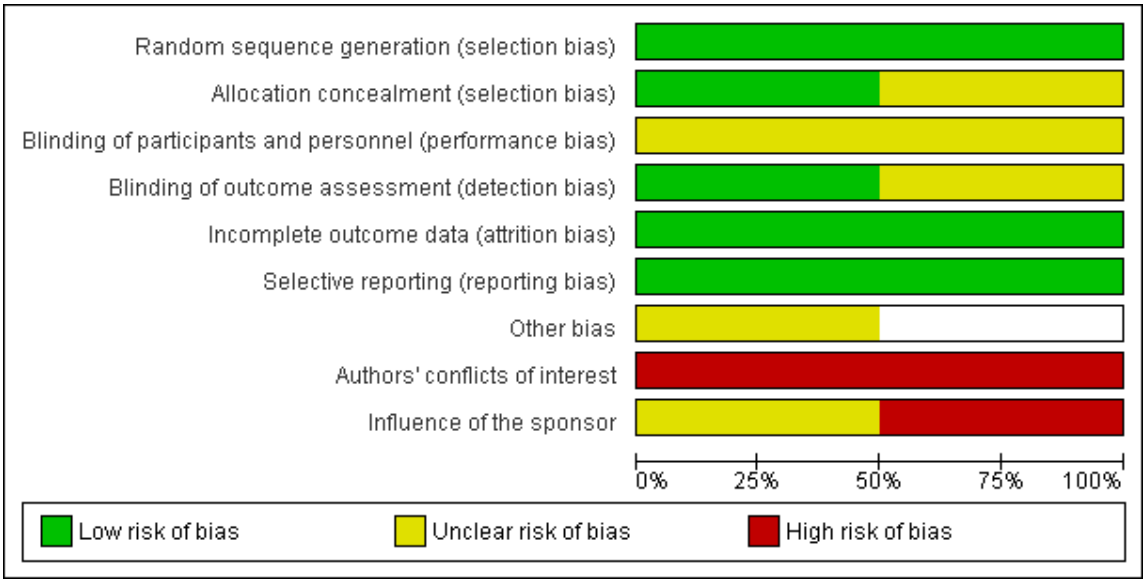


Figure 3: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation (selection bias)

For both studies information and methods for the random sequence generation were considered appropriate. Thus bias due to randomization was judged low. Information on allocation concealment led to judgement of a low risk of bias for Hermanides (Hermanides 2011) but of an uncler risk for STAR-3 (Bergenstal 2010, Slover 2011).

Blinding (performance bias and detection bias)

Both studies were open. Lack of blinding is not likely to introduce risk of bias for the glycaemic control outcomes (HbA1c, severe hypoglycaemia, ketoacidosis) as these outcomes can be measured instrumentally. However, subjective outcomes like health-related quality of life and patient satisfaction as well as the behaviour of health professionals towards patients could be different.

Incomplete outcome data (attrition bias)

Overall, drop-out rates and risk of selective drop-out were relatively low: drop-out rates and relevant reasons were reported in both studies.

Selective reporting (reporting bias)

The studies were free of selective reporting as the results of all the pre-specified outcomes were reported.

Other potential sources of bias

Imbalance in baseline characteristics

In one study (STAR-3 in Bergenstal 2010) among adult patients weight and student status differed between groups.

Authors' conflicts of interest

Several authors of both studies received honoraria, grant support and consulting fees from the device manufacturer (Medtronic) leading to a potentially high risk of conflict of interest.

Influence of the sponsor

Both studies were financially supported by the manufacturer of the SAP system by a grant; other firms supplied insulins for CSII or glucometers.

In the study by Hermanides (Hermanides 2011) authors declare that the funding source had an advising role in trial design details and drafting of the report, that it was only involved in the collection of the sensor data but not in the conduct of the analyses, interpretation of the data or in the decision to approve publication or not.

The STAR-3 study (in Bergenstal 2010) reported that data management and statistical analyses were conducted by an independent clinical research organization which transferred all the data to the sponsor; Authors had access to data but were supported by the sponsor also in the editorial process.

Effects of interventions

STAR-3 study (Bergenstal 2010, Slover 2011)

After 12 months of treatment, the Hb1Ac level decreased to 7.5 in the SAP-therapy group (absolute reduction from baseline: 0.8%, standard error: 0.8%), as compared with 8.1% in the injection-therapy group (absolute reduction from baseline: 0.2%, standard error: 0.9%), for a between-group difference in favour of the SAP-therapy group of –0.6% (95% Confidence Interval: –0.7% to –0.4%; P<0.001). Among adult patients, the absolute reduction in the mean glycated hemoglobin level was 1.0±0.7% in the SAP-therapy group and 0.4±0.8% in the injection-therapy group, resulting in a between-group difference in the SAP-therapy group of –0.6% (95%CI: –0.8 to –0.4; P<0.001). Among children and adolescents, there was an absolute reduction in glycated hemoglobin of 0.4±0.9% in the SAP-therapy group but an increase of 0.2±1.0% in the injection-therapy group, a between-group difference favoring the SAP-therapy group of –0.5% (95%CI, –0.8 to –0.2; P<0.001). An increased frequency of sensor use in all patients was associated with a greater reduction in glycated hemoglobin levels at 1 year (p = 0.003 with adjustment for the baseline glycated hemoglobin level). Among children and adolescents randomised to SAP, at the end of the study period the use of sensor was reported for

66% and 46% of patients, respectively and over the entire 12-month study, sensor use was higher in children than in adolescents (p = 0.025).

Severe hypoglycaemia rates reported for adults and children were similar: 13.1 per 100 person-year in the SAP group and 13.48 per 100 person-year in the injection-group. Among children and adolescents, severe hypoglycaemia rate was higher in those treated with SAP when compared with those assigned to the injection-therapy group (8.95 and 4.95 per 100 person-year in the SAP and in the injection-group, respectively) even if the difference didn't reach the statistical significance. There were no severe hypoglycemic events in either study group among children who had a glycated hemoglobin level of 7% or less at 1 year.

The continuous blood glucose monitoring showed that SAP and injection-group had similar values of Area Under the Curve (AUC) of glucose value <70 mg/dL (<3.9 mmol/L) whilst the SAP-group had statistically significant lower blood glucose values >180 mg/dL (>9.9 mmol/L).

The incidence of diabetic ketoacidosis was in general very low ($\leq$ 0.01 events per 100-person year) and not different between groups.

Patients who reached the target glycated hemoglobin value (<7% for adults; <7.5% for adolescents; <8% for children) were significantly more in the SAP-group (67 out of 244, 27%) than in the injection-group (23 out of 241, 10%) (P<0.001 for comparison between groups). When analysed according to patiens' age, statistical significance was maintained both for adults (57/166 adults, 34%, in the SAP-therapy group and 19/163 adults, 12%, in the injection-therapy group, P<0.001) and for the children and adolescents (35/80, 44%, in the SAP-therapy group and 16/80, 20%, in the injection-therapy group, P = 0.005).

Reported adverse events include two hospital admissions in the SAP-therapy group for cellulitis related to insertion-site infections and one death from sudden cardiac arrest in a patient in the injection-therapy group who had a history of cardiovascular disease.

Hermanides 2011

After 6 months of treatment, the Hb1Ac level decreased to 7.23 in the SAP-therapy group (absolute reduction from baseline: 1.23%, standard deviation: 1.01%), compared to 8.46% in the injection-therapy group (absolute reduction from baseline: 0.13%, standard deviation: 0.56%), a between-group difference in favour of the SAP-therapy group of –1.10% (95% Confidence Interval: –1.47% to –0.73%; P<0.001). The total daily insulin dose was 46.7 (standard deviation 16.5) units per day in the SAP-therapy group and 57.8 (standard deviation 18.1) units per day in the multiple daily injection group, with a baseline and centre-adjusted difference in change between the groups of -11.0 units per day (95% Confidence interval -16.1 to -5.9, P < 0.001). The percentage of time spent in

hyperglicemia decreased to 21.6% (standard deviation 12.2%) in the SAP-therapy group as compared to 38.2% (standard deviation 21.5%) in the injection-therapy group, for a between-group difference in favour of the SAP-therapy group of –16.5% (95% Confidence Interval: –25.2% to –9.5%; P<0.001). The number of hyperglycaemic events decreased to 2.1 (standard deviation 0.6) in the SAP-therapy group as compared to 2.2 (standard deviation 0.7) in the injection-therapy group, for a between-group statistically not significant difference in favour of the SAP-therapy group of –0.2% (95% Confidence Interval: -0.2 to 0.5; P=0.30).

Patients who reached a glycated hemoglobin value of 7% or less were significantly more in the SAP-group (34%) if compared to injection-group (0%) (P<0.001 for comparison between groups);

Percentage of time spent in hypoglycemia was 2.7% (standard deviation 3.4%) in the SAP-therapy group compared to 2.5% (standard deviation 3.5%) in the injection-therapy group, with a between-group statistically not significant difference in favour of the injection-therapy group of –0.2% (95% Confidence Interval: –1.9% to 1.4%; P=0.79). Number of hypoglycaemic events was 0.7 (standard deviation 0.7) in the SAP-therapy group as compared to 0.5 (standard deviation 0.5) in the injection-therapy group, with a between-group statistically not significant difference in favour of the SAP-therapy group of –0.1 (95% Confidence Interval: -0.5 to 0.2; P=0.40). Severe hypoglycaemia events were similar for both groups (9% - 19 episodes per 100 person years - in in the SAP group and 3% - 6 episodes per 100 person years - in the injection-group; P=0.21).

Two serious adverse events occurred in the sensor-augmented insulin pump group and five in the multiple daily injection group. Only one serious adverse event was reported as being related to the device in the SAP group (patient admitted to the hospital for ketoacidosis because of pump failure). Other serious adverse events were: surgery for aorta bifurcation prosthesis, hemianopsia, respiratory tract infection, and ketoacidosis (2) in the multiple daily injection group and acute gastritis in the sensor-augmented insulin pump group. Twenty patients reported 26 probable or possible device-related adverse events. Of these, 17 patients reported skin-related problems (itch／exanthema／infection／redness／plaster allergy／bruising／haematoma) at the sensor or insulin infusion site.

Among patient-reported outcomes, only the scores of the “Diabetes Treatment Satisfaction Questionnaire” and of the “Perceived frequency of hyperglycaemia improved significantly more in SAP-group compared to the multiple daily injection group (see Appendix 1).

Table. 1 Summary of findings: Short-term effectiveness outcomes

Patients/population: uncontrolled type I diabetes mellitus

Intervention: CSII+CGM devices (SAP)

Comparators: MDI plus intermittent whole blood finger-stick glucose monitoring

Ref.	No. of participants	Study design	Risk of Bias	Indirectness	Inconsistency	Imprecision	SAP	Comparator	Difference b/w groups (95% CI)	P	Quality of Evidence
Outcome: difference in HbA1c (52 weeks vs baseline)											
STAR-3	156 children (out of 485 patients including 329 adults)	open RCT	Serious[2]	No	NA	No	-0.4% (SD 0.9)	+0.2% (SD 1.0)	-0.5% (-0.8 to -0.2)	<0.001	Moderate
Outcome: difference in HbA1c (26 weeks vs baseline)											
Hermanides 2011	83 (all adults)	open RCT	No[3]	Serious[1]	NA	No	-1.23% (SD 1.01)	-0.13 (SD 0.56)	-1.10% (-1.47 to -0.73)	<0.001	Low
Outcome: patients reaching target HbA1c (52 weeks)											
STAR-3	156 children (out of 485 patients including 329 adults)	open RCT	Serious[2]	No	NA	No	44%	20%	NR	<0.005	Moderate
Outcome: patients reaching target HbA1c (26 weeks)											
Hermanides 2011	83 (all adults)	open RCT	No[3]	Serious[1]	NA	No	34%	0%	NR	<0.001	Low
Outcome: diabetic ketoacidosis (rate per 100 person-yr)											
STAR-3	156	ope	Serio	No	NA	Serious	0.02	0.02	NR	0.20	Low

	children (out of 485 patients including 329 adults)	n RCT	us[2]								
Outcome: diabetic ketoacidosis (number of events in 52 weeks)											
STAR-3	156 children (out of 485 patients including 329 adults)	open RCT	Serious[2]	No	NA	Serious	1	2	NR	0.49	Low
Outcome: diabetic ketoacidosis (number of events in 26 weeks)											
Hermanides 2011	83 (all adults)	open RCT	No[3]	Serious[1]	NA	Serious	1	2	NR	NR	Very Low
Outcome: change in BMI (52 weeks vs baseline)											
STAR-3	156 children (out of 485 patients including 329 adults)	open RCT	Serious[2]	No	NA	No	adolescents +1.31 (SD 0.26) children +1.07 (SD 0.19)	adolescents +0.44 (SD 0.26) children +1.24 (SD 0.29)	NR	0.043 0.519	Moderate
1 all participants are adults; 2 role of the sponsor: Authors didn't have direct access to the study data, sponsor's editorial assistance to Authors; 3 role of the sponsor: Authors declare that the study was financially sponsored but it was an investigator-initiated trial and the sponsor had no role in the data handling and discussion.											

Table 2. Summary of findings: short-term safety outcomes

Patients/population: uncontrolled type I diabetes mellitus

Intervention: CSII+CGM devices (SAP)

Comparators: MDI plus intermittent whole blood finger-stick glucose monitoring

Ref.	No. of participants	Study design	Risk of Bias	Indirectness	Inconsistency	Imprecision	SAP	Comparator	Difference b/w groups (95% CI)	P	Quality of Evidence
Outcome: severe hypoglycaemia (rate per 100 person-year)											
STAR-3	156 children (out of 485 patients including 329 adults)	open RCT	Serious[3]	No	NA	No	8.92	4.95	NR	0.35	Moderate
Hermanides 2011	83 (all adults)	open RCT	No[4]	Serious[1]	NA	No	19	6	NR	0.21	Low
Outcome: severe hypoglycaemia (number of events in 52 weeks)											
STAR-3	156 children (out of 485 patients including 329 adults)	open RCT	Serious[3]	No	NA	No	7	4	NR	0.53	Moderate
Outcome:severe hypoglycaemia (number of events in 26 weeks)											
Hermanides 2011	83 (all adults)	open RCT	No[4]	Serious[1]	NA	Serious	4	1	NR	0.21	Very Low
Outcome: number of hypoglicaemia (episodes/day in 26 weeks)											
Hermanides 2011	83 (all adults)	open RCT	No[4]	Serious[1]	NA	No	0.7 (SD 0.7)	0.6 (SD 0.7)	0.1 (-0.2 to 0.5)	0.40	Low
Outcome: serious adverse events (number of events in 52 weeks)											

STAR-3	485 (156 children, 329 adults)	open RCT	Serious[3]	Serious[2]	NA	No	2 hospital admissions for cellulitis related to insertion-site infections	1 death from sudden cardiac arrest in a patient who had a history of cardiovascular disease			Low
Outcome: serious adverse events (number of events in 26 weeks)											
Hermanides 2011	83 (all adults)	open RCT	No[4]	Serious[1]	NA	No	ketoacidosis because of pump failure (1), acute gastritis (1)	surgery for aorta bifurcation prosthesis (1), hemianopsia (1), respiratory tract infection (1)			Low
Outcome: other adverse events (number of events in 26 weeks)											
Hermanides 2011	83 (all adults)	open RCT	No[4]	Serious[1]	NA	No	20 patients reported 26 probable or possible device-related adverse events (17 patients skin-related problems at the sensor or insulin infusion site)				Low

1. All participants are adults

2. 68% of patients are adults

3. role of the sponsor: Authors didn't have direct access to the study data, sponsor's editorial assistance to Authors;

4. role of the sponsor: Authors declare that the study was financially sponsored but it was an investigator-initiated trial and the sponsor had no role in the data handling and discussion.

Discussion

Two RCTs (STAR-3, Hermanides 2011) - for a total of 568 participants - investigating the effectiveness of sensor-augmented insulin pump (SAP) versus multiple daily insulin injections (MDI) together with standard monitoring of blood glucose (SMBG) have been included. Both studies have an open design. One study recruited both adults (329 participants, 68% of the sample) and children/adolescents (156 participants) with uncontrolled type I diabetes mellitus and followed them for 52 weeks. Another study recruited only adults (83 participants) with uncontrolled type I diabetes mellitus and followed them for 26 weeks.

According to data judged to be of *moderate quality*, 52 weeks use of SAP versus MDI with SMBG seems to reduce HbA1c in children (-0.5%, CI 95% -0.8 to -0.2).

According to data judged to be of *low quality*, 26 weeks use of SAP versus MDI with SMBG seems to reduce HbA1c in adults (-1.10%, CI 95% -1.47 to -0.73)

According to data judged to be of *moderate quality*, 52 weeks use of SAP versus MDI with SMBG seems to increase the number of children reaching target HbA1c (44% versus 20%, p<0.005).

According to data judged to be of *low quality*, 26 weeks use of SAP versus MDI with SMBG seems to increase the number of adults reaching target HbA1c (34% versus 0%, <0.001).

According to data judged to be from *very low* to *low quality,* SAP versus MDI with SMBG seems not to increase the risk of diabetic ketoacidosis.

According to data judged to be from *low* to *moderate quality,* SAP versus MDI with SMBG seems not to increase the risk of severe hypoglycaemia.

One study (STAR-3 in Bergenstal 2010) reported two hospital admissions in the pump-therapy group for cellulitis related to insertion-site infections; another study (Hermanides 2011) observed skin-related problems at the sensor or insulin infusion site (17 out of 43 patients).

Firm conclusions cannot be drawn about the effect of SAP on of quality of life since only one study with 83 adult patients (Hermanides 2011) assessed this outcome.

No data were found on the following:

- short-term effectiveness outcomes

- Hospitalisation
- Emergency hospital admission

- short-term safety outcomes

- Hypoglycaemic awareness

- short-term patient-reported outcomes

- Quality of life (measured using a validated instrument) of patients and/or carers

- short-term technical performance outcomes

- Ability and sensibility in time responding after the subject started eating
- Reduction in the amount of insulin administered
- Lack of failure in communication between pump and monitor
- Lack of failure in the alarm systems
- Lipid regulation
- Right estimation of glucose level (accuracy of measure)
- Failures in the quantity of insulin administrated

- long-term effectiveness outcomes

- Cardiovascular function (blood pressure)
- Ocular function (retinopathy, juvenile cataract)
- Renal function (microalbuminuria)
- Diabetes late complications
- Mortality
- Costs

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5.Epidemiological background and context analysis

5.1 Epidemiological background

According to WHO (World Health Organization) the latest estimate of the number of patients with any type of diabetes (Type 1 or Type 2) worldwide is about 177 million people. The increasing prevalence of this disease is due to population growth, aging, urbanization, increasing prevalence of obesity and physical inactivity and the WHO predicts that by 2025 the number of people with diabetes could double [Swan, 2009]. Type 1 diabetes accounts for about 10 - 15 % of all diabetes and is increasing at a rate of approximately 3% per year [Diabetes Outreach, 2009].

Two international collaborative projects, the Diabetes Mondial study (DiaMond) [DIAMOND, 2006] (see Chapter 1) and the Europe and Diabetes study (EURODIAB) [Patterson, 2009] began in the 1980s, demonstrated an increasing trend in incidence of type 1 diabetes in most regions of the world over the last few decades and increases seem to be the highest in the youngest age group. Table 1 shows the data of EURODIAB study: the total number of cases registered during 1989-2003, the age-standardized incidence rates in the three 5-year periods and the annual incidence increase in 20 different countries of Europe.

Italy is not represented in this study and Italian data on type 1 diabetes are generally lacking. The data reported in the yearbook 2011 [ISTAT, 2011 accessed 24 may 2012] of the Italian National Institute for Statistics (ISTAT) estimate that patients affected by type 1 or 2 diabetes over 18 years of age, represent the 4.9% of the Italian population, amounting to about 3 000 000 people.

Table 1. Numbers of cases during 1989-2003 for 20 EURODIAB centers, age-standardized incidence rates, annual incidence increase. Adapted from [EURODIAB, 2005]

Key: P1=1989–93; P2=1994–98;P3=1999–2003

Country	Region	Number of cases	Standardised incidence per 100 000 (P1; P2; P3)	Increase per year (95% CI)
Austria	Whole nation	2215	9,0; 9,9; 13,3	4·3% (3·3 to 5·3)
Belgium	Antwerp	318	10,9; 12,9; 15,4	3·1% (0·5 to 5·8)
Czech Republic	Whole nation	3479	8,7; 11,7; 17,2	6·7% (5·9 to 7·5)
Denmark	Four counties	657	17,0; 16,3; 22,9	3·2% (1·4 to 5·1)
Finland	Two regions	1306	39,9; 50,0; 52,6	2·7% (1·4 to 4·0)
Germany	Baden Württemberg	3362	11,0; 13,0; 15,5	3·7% (2·9 to 4·5)
Germany	Düsseldorf	922	12,5;15,3; 18,3	4·7% (3·1 to 6·3)

Country	Region	Number of cases	Standardised incidence per 100 000 (P1; P2; P3)	Increase per year (95% CI)
Hungary	18 counties	2152	8,8; 10,5; 11,5	2·9% (1·9 to 3·9)
Lithuania	Whole nation	996	7,3; 8,2; 10,3	3·8% (2·2 to 5·3)
Luxembourg	Whole nation	148	11,4; 12,3; 15,5	2·4% (–1·4 to 6·3)
Norway	8 counties	1380	21,1; 20,5; 24,6	1·3% (0·1 to 2·6)
Poland	Katowice	1156	5,2; 7,9; 13,0	9·3% (7·8 to 10·8)
Romania	Bucharest	378	4,7; 6,1; 11,3	8·4% (5·8 to 11·0)
Slovakia	Whole nation	1874	8,2; 10,3; 13,6	5·1% (4·0 to 6·3)
Slovakia	Whole nation	504	7,9; 9,2; 11,1	3·6% (1·5 to 5·7)
Spain	Catalonia	1923	12,4; 13,6; 13,0	0·6% (–0·4 to 0·6)
Sweden	Stockholm county	1374	25,8; 25,6; 34,6	3·3% (2·0 to 4·6)
UK	Northern Ireland	1435	20,0; 24,7; 29,8	4·2% (3·0 to 5·5)
UK	Oxford	1615	17,1; 21,7; 22,4	2·2% (1·1 to 3·4)
UK	Yorkshire	2117	16,0; 19,7; 23,3	3·6% (2·6 to 4·6)

Key: P1=1989–93; P2=1994–98;P3=1999–2003

One Italian study [Bruno, 2010], based on the data of the Registry for Type 1 Diabetes Mellitus in Italy (RIDI) concerning children 0–14 years old in the years 1990–2003, reports the incidence rates of type 1 diabetes among Italian children 0–14 years old in different geographical areas of Italy (Table 2).

Table 2. Incidence rates of type 1 diabetes among Italian children 0–14 years old in the years 1990–2003 by geographical area of residence. Adapted from [Bruno, 2010]

Geographical area of residence	Incident cases (n)	Person-years at risk (n)	Incidence rates per 100,000 person-years (95% CI)
Northern Italy	945	8 006 808	11,80 (11,07–12,58)
Turin	419	3 823 910	10,96 (9,96–12,06)
Liguria	280	2 377 687	11,78 (10,47–13,24)
Pavia	93	768 584	12,10 (9,87–14,83)
Modena	74	613 452	12,06 (9,61–15,15)
Trento	79	423 175	18,67 (14,97–23,27)
Central-Southern Italy	2 728	30 550 760	8,93 (8,6–9,27)
Firenze-Prato	214	1 923 090	11,13 (9,73–12,72)
Marche	284	2 696 075	10,53 (9,38–11,83)
Lazio	678	7 522 247	9,01 (8,36–9,72)
Umbria	145	1 255 832	11,55 (9,81–13,59)
Abruzzo	115	1 196 101	9,61 (8,01–11,54)
Campania	1 292	15 957 414	8,10 (7,67–8,55)
Island			
Sardinia	1 507	3 688 76	40,86 (38,84–42,97)

5.2. Context analysis in some Italian regions

Italy is divided into nineteen Regions and two self-governing Provinces. The context analysis that we present involved 3 out of 19 regions and 1 out of 2 self-governing Provinces.

5.2.1 Methods

For each Region or Province participating in the analysis a general method was applied to calculate:

- incidence and prevalence of type 1 in children and adolescents;
- frequency of short-term and prevalence of treated long-term complications in type 1 diabetic population;

Possible variations to the method and specific limitations in the analysis due to local unavailability of electronic datasets are described.

5.2.1.1 Incidence and prevalence of type 1 in children and adolescents

For the present report the current prevalence and incidence of type 1 diabetes for children and adolescents (age<18 years) have been estimated analyzing the two Regional Prescription Drug Database, Assistenza Farmaceutica Territoriale (AFT) and Farmaceutica a Erogazione Diretta (FED). From the AFT- Prescription Drug Database and from the FED-Prescription Drug Database, patients receiving insulin supplied by National Health System, Sistema Sanitario Nazionale (SSN) from a retail/community pharmacy or from an hospital pharmacy were identified.

As the two Prescription Drug Databases were set up in different time (AFT in 2002 and FED in 2008) the study period considered for the analysis is 2008-2011, to avoid bias due to incompleteness of recorded information.

The identification of prevalent cases and incident cases of children and adolescents with type 1 diabetes was carried out by selecting from Regional Prescription Drug Database (AFT and FED) the patients with a prescription of insulin (ATC codes A10A) and without prescription of oral antidiabetics (ATC codes A10B) during the study year (2011,2010,2009,2008) and the

previous three years (2010-2008 for 2011, 2009-2007 for 2010, 2008-2006 for 2009, 2007-2005 for 2008) [Arno, 2007].

5.2.1.2 Prevalence of short-term and long-term complications in diabetic population

Type 1 diabetes is a complex pathology which, if not appropriately managed, can lead to serious short-term and long-term complications. By carefully managing patient's blood glucose levels, the patient can stave off or prevent the short- and long-term complications. If the patient has already developed diabetes complications, controlling the blood glucose levels can help to manage the symptoms and prevent further damage.

Current standards for diabetes management reflect the need to maintain glucose control as near to normal as safely possible. Even though most target recommendations for glycaemic control have been based on data obtained from studies of adult patients with diabetes, the ideal goal of near-normalization of blood glucose levels in children and adolescents is generally the same as that for adults even if special consideration must be given to the unique risks of hypoglycaemia in young children [Silverstein, 2005].

The Diabetes Control and Complications Trial (DCCT) [Diabetes Control and Complications Trial Research Group, 1993] demonstrated that intensive diabetes treatment delays the onset and slows the progression of diabetic complications in subjects with insulin-dependent diabetes mellitus from 13 to 39 years of age.

The complications of diabetes are separated into 2 macro-categories:

- Short term complications
- Long-term complications

The most important short term complications include: ketoacidosis, hypersmolarity, coma and uncontrolled diabetes.

Long-term complications are classified in macrovascular complications (ischemic heart disease, peripheral arterial disease, stroke, myocardial infarction, peripheral revascularization and amputation) and microvascular complications (renal and ocular).

Short-term complications

To quantify the frequency of hospitalization for short-term complications (acute complications) in the period 2008-2011 for patients with type 1 diabetes a cross sectional analysis for each year of study (2008-2011) was carried out according to the following steps:

1. selection of patients with type 1 diabetes from Prescription Drug Database (AFT and FED) in the period 2008-2011;
2. selection of patients with complications (short -term) for diabetes (type 1 and type 2) from Hospital Discharge Records Database (SDO) in the period 2008-2011;
3. record linkage for each year (2008-2011) between the dataset of patients with type 1 diabetes and that of patients with complications for diabetes.

The selection of patients with type 1 diabetes was carried out by selecting from Regional Prescription Drug Database (AFT and FED) the patients with a prescription for insulin (ATC codes A10A) and without prescription of oral antidiabetics (ATC codes A10B) during the study year (2011, 2010, 2009, 2008) and the previous three years (2010-2008 for 2011, 2009-2007 for 2010, 2008-2006 for 2009, 2007-2005 for 2008) [Arno, 2007].

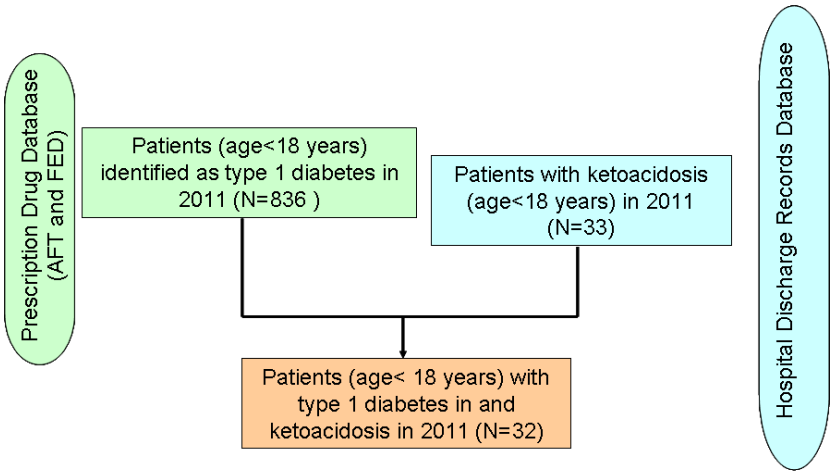
The selection of patients with complications (short-term) for diabetes was carried out selecting from Hospital Discharge Database (SDO) the patients who had an ICD-9-CM diagnosis of complications (2008-2011). Codes used to select the patients with short-term complications are reported in Appendix 11. The analysis was stratified by age (age<18 and age>=18 year).

Record-linkage between the dataset (AFT and FED) of patients with type 1 diabetes with that of patients with short-term complications has allowed quantifying the short-term complications for patients with type1 diabetes.

An example of record-linkage is provided in Figure 4 showing the result of linkage between the two data sources (SDO and AFT/FED) in 2011:

- from the AFT/FED 836 patients <18 years with type 1 diabetes have been identified;
- from the SDO database 33 patients <18 years hospitalized for ketoacidosis have been identified
- Record-linkage of patients present in both databases resulted in 32 patients<18 years with type 1 diabetes hospitalised for the ketoacidisis complication

Figure 4. Example: RER patients (age<18 years) with type1 diabetes and ketoacidosis-2011



The analysis was performed for patients resident in Emilia-Romagna region and Sicily Region. All data were analyzed using the SAS system for Windows software, release 9.1.

Long-term complications

To quantify the prevalence of treated long-term complications (patients with hospitalizations or outpatient procedures) for patients with type 1 diabetes in 2011 a retrospective cohort study was carried out according to the following steps:

1. selection of patients with type 1 diabetes (age>17 years) from the Prescription Drug Databases (AFT and FED) for 2011;
2. selection of patients with complications (long-term) for diabetes from Hospital Discharge Records Database (SDO) and Outpatient Database (ASA) in the period 2006-2011;
3. record - linkage between the dataset of patients with type 1 diabetes in 2011 and that of patients with complications for diabetes in the period 2006-2011.

The selection of patients with type 1 diabetes in 2011 was carried out by selecting, from the Regional Prescription Drug Databases (AFT and FED), patients with a prescription of insulin (ATC codes A10A) in 2011 and without prescriptions of oral antidiabetics (ATC codes A10B) during the study year (2011,2010,2009,2008) and the previous three years (2010-2008 for 2011, 2009-2007 for 2010, 2008-2006 for 2009, 2007-2005 for 2008) [Arno, 2007].

The selection of patients with complications (long-term) for diabetes was carried out selecting from Hospital Discharge Database (SDO) and Outpatient Database (ASA) the patients who had an ICD-9-CM diagnosis of complications in the period 2006-2011. Codes used to select the patients with long-term complications are reported in Appendix 1.

The long-term complications analyzed were:

micro-vascular

- retinopathy
- kidney disease and dialysis

macro-vascular

- stroke
- myocardial infarction
- ischemic heart disease
- peripheral revascularization
- amputation

The analysis was performed only for patients resident in single Regions and older than 17 years. All data were analyzed using the SAS system for Windows software, release 9.1.

5.2.2 Results

5.2.2.1 The context of the Emilia-Romagna Region

Emilia-Romagna is a northeast Italian region with 9 Provinces, covering an area of over 22 446 km^2. It has a resident population of 4 395 606 (update: 1st January 2010), 2 135 966 male and 2 259 640 female. The Regional Health Service comprises 11 Local Health Trusts, 4 University Hospital Trusts (AOSP), 4 Research Hospitals (Istituto di Ricovero e Cura a Carattere Scientifico, IRCCS).

5.2.2.1.1 Diabetic pediatric centers in Emilia-Romagna Region

Currently in Emilia-Romagna region there are 11 diabetic paediatric centres, 1 in every local health trust. Figure 1 shows the geographical location of the 11 paediatric diabetic centres.

Figure 1. Geographical location of the paediatric diabetic centres

5.2.2.1.2 Estimate of incidence and prevalence of type 1 diabetes for Emilia-Romagna children and adolescents (age<18 year)

One study [Zucchini, 2011] on type 1 diabetes on children and adolescents estimated type 1 diabetes 0-14 years incidence and the prevalence for the age 0-17 years for the period 2005–2010 in the area of Bologna, Imola and Ferrara. The preliminary results reported that the incidence per 100 000 person-years increased from 14.1 in 2005 to 16.8 in 2010 with an annual increase of 4% year and prevalence was significantly higher in the Ferrara area (175 cases/100 000 inhabitants with age<18 years), than in the Bologna area (114/100 000 inhabitants with age<17 years).

For the present report the current prevalence and incidence of type 1 diabetes for children and adolescents (age<18 years) in Emilia-Romagna Region have been estimated analyzing the two Regional Prescription Drug Database, Assistenza Farmaceutica Territoriale (AFT) and Farmaceutica a Erogazione Diretta (FED).

Figure 2 shows the number of cases and the number of new cases with type 1 diabetes, while Figure 3 shows the incidence rate and prevalence rate estimated in the study period. Considering the children and adolescents population of Emilia-Romagna Region and the number of cases and new cases with type 1 diabetes the incidence rate and prevalence rate were estimated and reported in Table 3 and Figure 2.

For 2011 the incidence and prevalence rates of Type 1 diabetes in Emilia-Romagna region among children and adolescents are estimated at 18 per 100000 inhabitants and 120 per 100 000 inhabitants, respectively.

Table 3. Number of cases, new cases, prevalence rates and incidence rates of children and adolescents with type 1 diabetes in Emilia-Romagna region-2008-2011

Study Year	Emilia-Romagna population (age<18 years)	Cases with type 1 diabetes (age<18 Year)	New cases (age<18 Year)	Prevalence rate (age<18 year) *100 000	Incidence rate (age<18 year)*100 000
	N	N			
2008	650045	810	367	125	56
2009	667922	789	151	118	23
2010	684231	839	169	123	25
2011	695043	836	126	120	18

Figure 2. Number of cases (prevalence) and of new cases (incidence) of children and adolescents with type 1 diabetes in Emilia-Romagna region-2008-2011

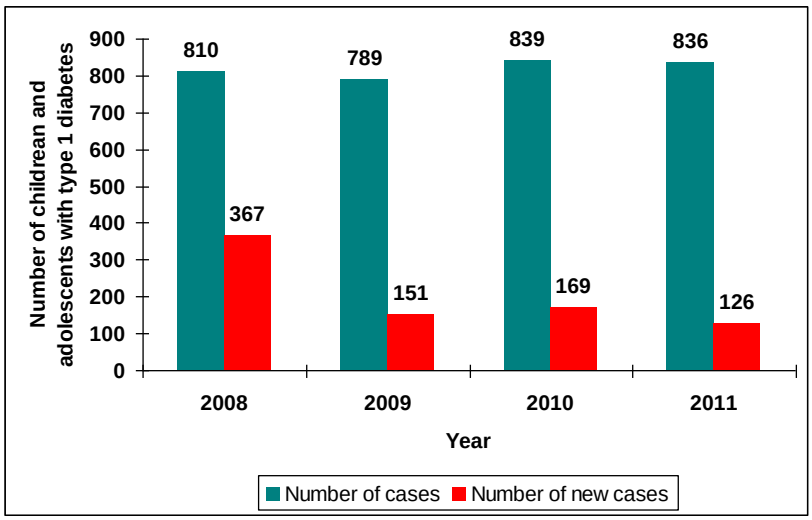
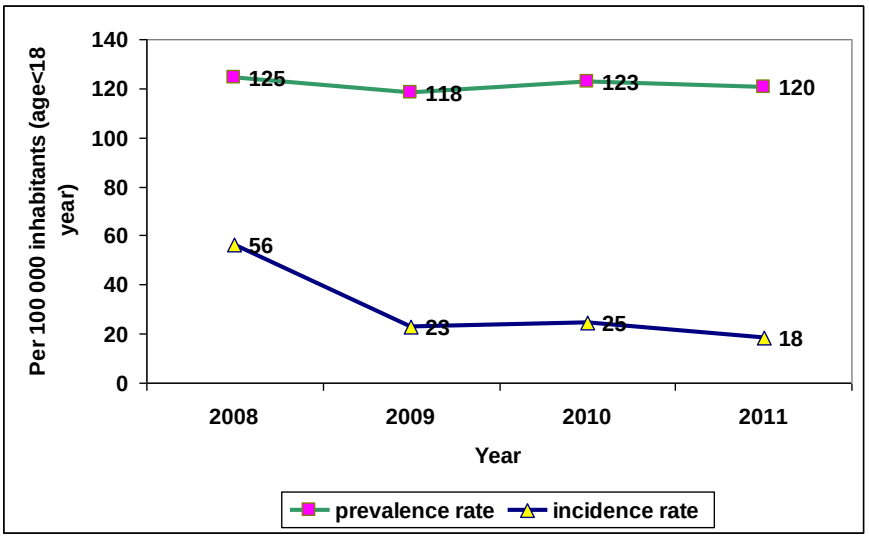


Figure 3. Prevalence rates and incidence rates for children and adolescents (age<18 year) with type 1 diabetes in Emilia-Romagna -2008-2011 (/ 1000 inhabitans)



5.2.2.1.3 Short- and long-term complications for Emilia-Romagna region patients with type 1 diabetes

Short-term complications

The number of patients with type 1 diabetes, stratified by age, selected from Regional Prescription Drug Database (AFT and FED) in the period 2008-2011 are reported in Table 4 and Figure 5.

Figure 5. Number of **patients** with type 1 diabetes stratified by age in the period 2008-2011

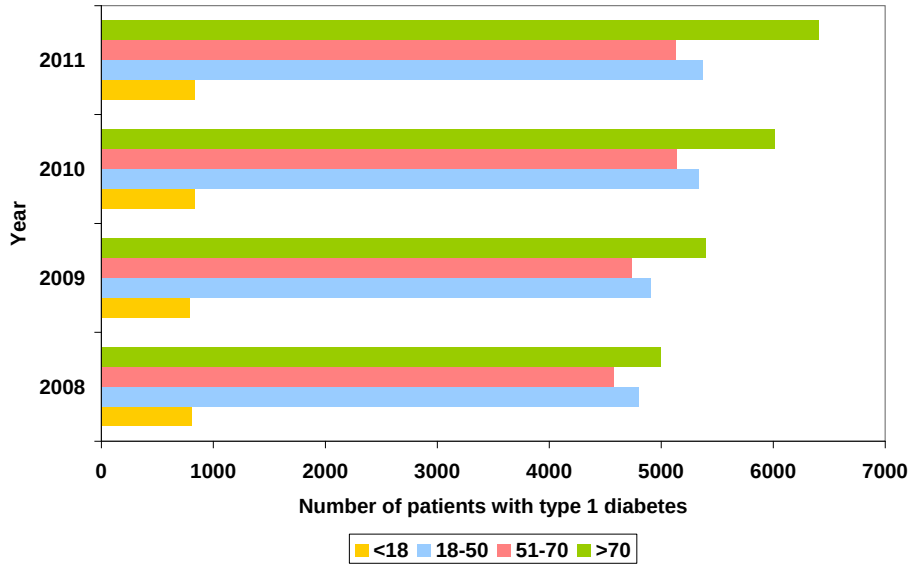


Table 4. Number of patients with type 1 diabetes stratified by age (data source: Regional Prescription Drug Database AFT and FED)

Year	Age	Patients with type 1 diabetes (N)	Patients with type 1 diabetes (%)
2008	<18	810	5,3
	18-50	4796	31,6
	51-70	4577	30,1
	>70	5000	32,9
	ALL	15 183	100,0
2009	<18	789	5,0
	18-50	4904	31,0
	51-70	4737	29,9
	>70	5394	34,1
	ALL	15 824	100,0
2010	<18	839	4,8
	18-50	5335	30,8
	51-70	5144	29,7
	>70	6011	34,7
	ALL	17 329	100,0
2011	<18	836	4,7
	18-50	5371	30,3
	51-70	5133	28,9
	>70	6408	36,1
	ALL	17 748	100,0

Figure 6 shows the short-term complications for children and adolescents (age<18 years) in the period 2008-2011. Ketoacidosis and uncontrolled diabetes were the most common complications with a percentage respectively of 3.8% and 5% in 2011.

Figure 6. Short-term complications for children and adolescents (age<18 years) in the period 2008-2011.

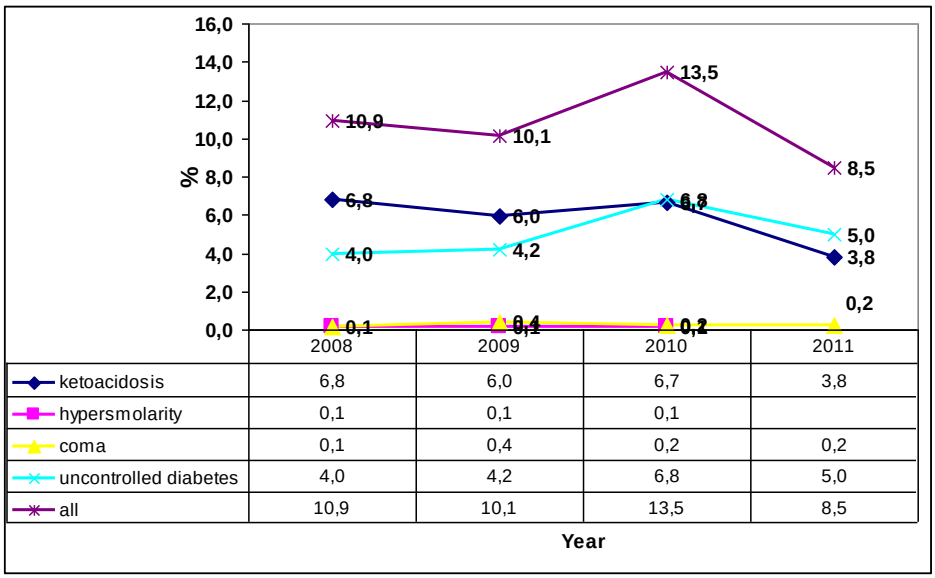
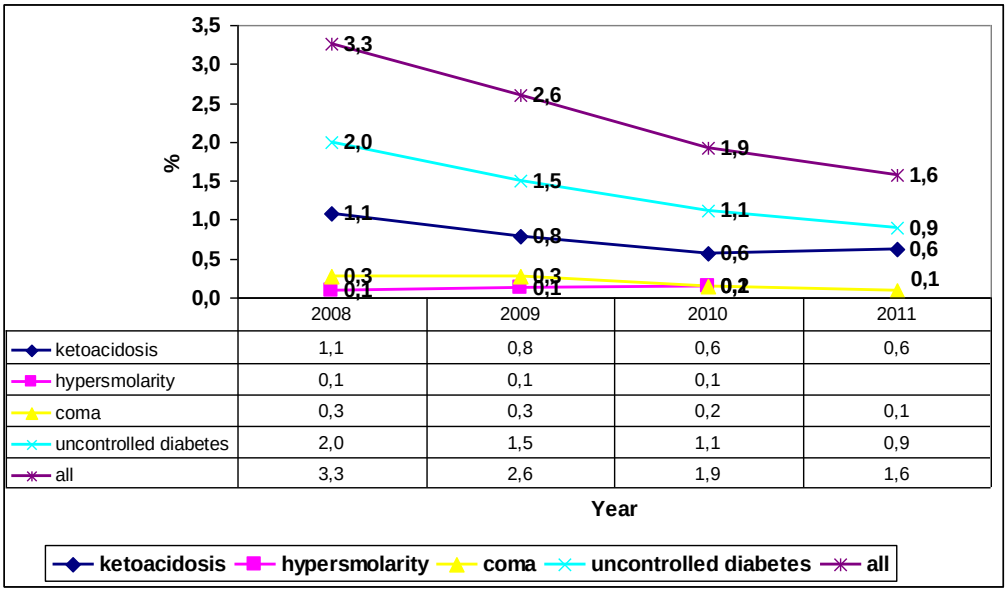


Figure 7 shows the short-term complications for adults (age>=18 years) in the period 2008-2011. For this sub-population the short-term complications were less frequent than in children and adolescents.

Figure 7. Short-term complications for adults (age>=18 years) in the period 2008-2011



Long-term complications

Retinopathy requiring treatment, dialysis and amputation are long-term complications occurring mostly in the 51-70 years age group while kidney disease requiring treatment, stroke, myocardial infarction and peripheral revascularization are late long-term complications occurring mostly in the >70 years age group .

Figure 8 and Figure 9 show for the cohort of patients of 2011 the prevalence cases and the prevalence rate of treated retinopathy (hospitalizations or outpatient procedures) over the period 2006-2011. An overall prevalence rate of 10.7% was detected with a peak of prevalence of 16.1% in the 51-70 years age group.

Figure 10 and Figure 11 show the prevalence cases and the prevalence rate of treated kidney disease (hospitalizations or outpatient procedures) over the period 2006-2011 for the cohort of patients of 2011. An overall prevalence rate of 14.5% was detected with a peak of prevalence of 21.5% in the class >70 years.

Figure 12 and Figure 13 show for the cohort of patients of 2011 the prevalence cases and the prevalence rate of dialysis (hospitalizations or outpatient procedures) over the period 2006-2011. An overall prevalence rate of 2.4% was detected with a peak of prevalence of 3.8% in the class 51-70 years.

Figure 14 and Figure 15 show the prevalence cases and the prevalence rate of stroke (hospitalizations or outpatient procedures) over the period 2006-2011 for the cohort of

patients of 2011. An overall prevalence rate of 12.8% was detected with a peak of prevalence of 22.5% in the class >70 years.

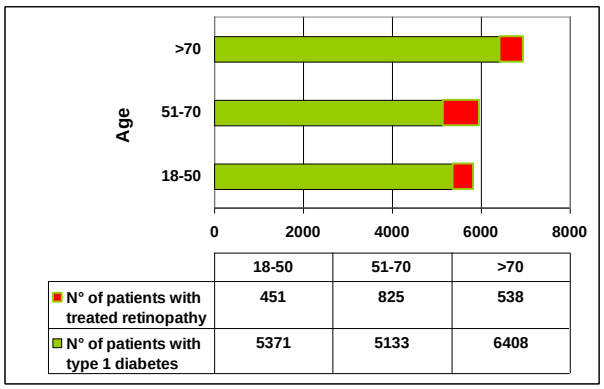
Figure 16 and Figure 17 show the prevalence cases and the prevalence rate of myocardial infarction (hospitalizations or outpatient procedures) over the period 2006-2011 for the cohort of patients of 2011. An overall prevalence rate of 5.5% was detected with a peak of prevalence of 8.3% in the class >70 years.

Figure 18 and Figure 19 show the prevalence cases and the prevalence rate of ischemic heart disease (hospitalizations or outpatient procedures) over the period 2006-2011 for the cohort of patients of 2011. An overall prevalence rate of 16.8% was detected with a peak of prevalence of 25.8% in the class >70 years.

Figure 20 and Figure 21 show the prevalence cases and the prevalence rate of peripheral revascularization (hospitalizations or outpatient procedures) over the period 2006-2011 for the cohort of patients of 2011. An overall prevalence rate of 12.0% was detected with a peak of prevalence of 16.9% in the class >70 years.

Figure 22 and Figure 23 show the prevalence cases and the prevalence rate of amputation (hospitalizations or outpatient procedures) over the period 2006-2011 for the cohort of patients of 2011. An overall prevalence rate of 2.5% was detected with a peak of prevalence of 3.7% in the class 51-70 years.

Figure 8. Number of patients treated for retinopathy -stratified by age



	18-50	51-70	>70
N° of patients with treated retinopathy	451	825	538
N° of patients with type 1 diabetes	5371	5133	6408

Figure 9. Prevalence rate of patients treated for retinopathy -stratified by age

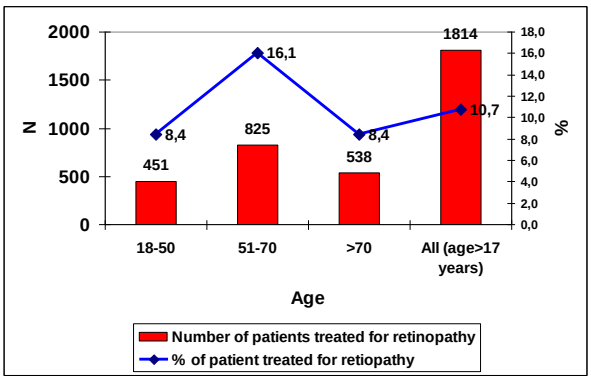
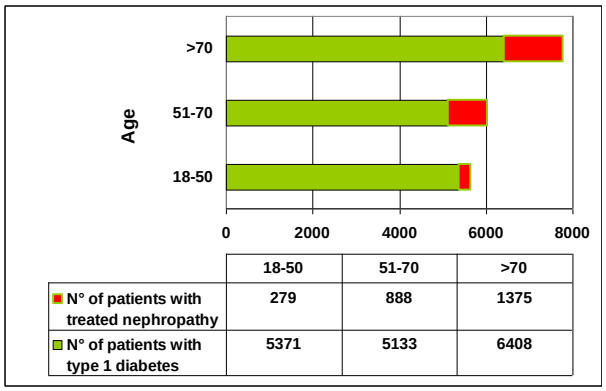


Figure 10. Number of patients treated for kidney disease-stratified by age



	18-50	51-70	>70
N° of patients with treated nephropathy	279	888	1375
N° of patients with type 1 diabetes	5371	5133	6408

Figure 11. Prevalence rate of patients treated for kidney disease-stratified by age

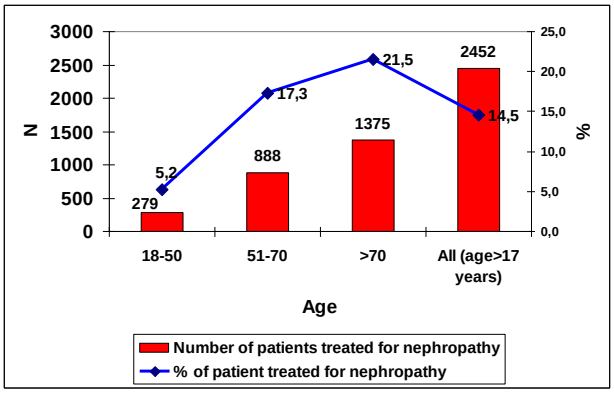
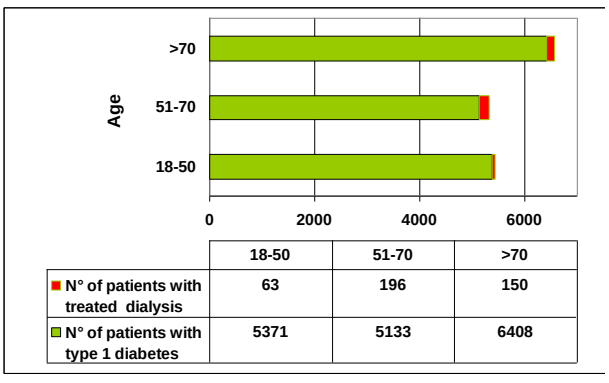


Figure 12. Number of patients undergoing dialysis -stratified by age



	18-50	51-70	>70
N° of patients with treated dialysis	63	196	150
N° of patients with type 1 diabetes	5371	5133	6408

Figure 13. Prevalence rate of patients undergoing dialysis -stratified by age

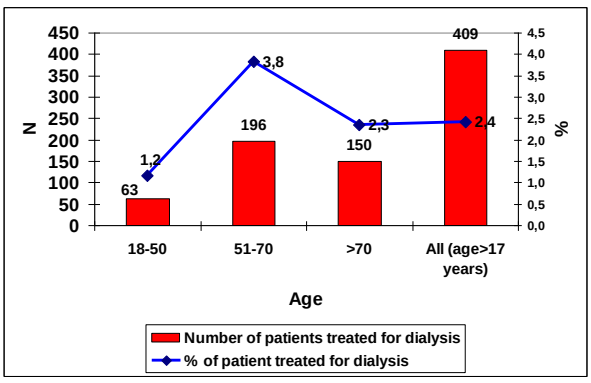
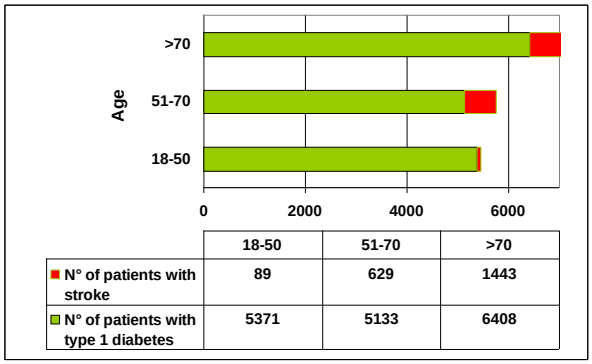
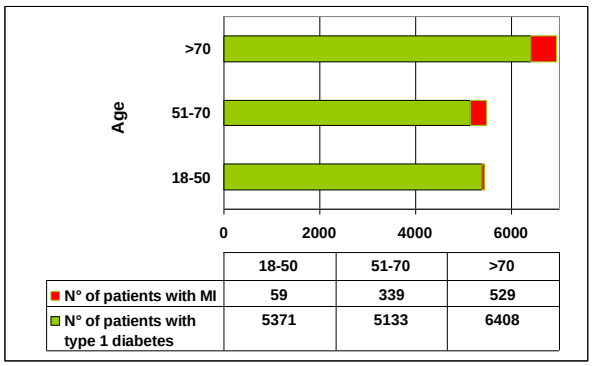


Figure 14. Number of patients with stroke -stratified by age



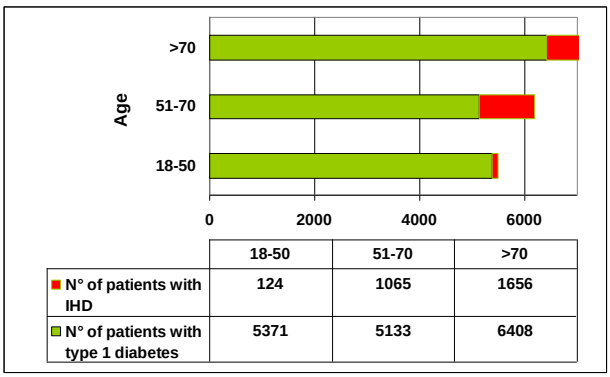
	18-50	51-70	>70
N° of patients with stroke	89	629	1443
N° of patients with type 1 diabetes	5371	5133	6408

Figure 16. Number of patients with myocardial infarction-stratified by age



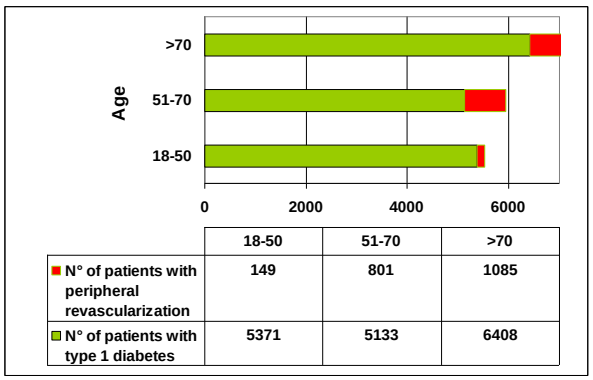
	18-50	51-70	>70
N° of patients with MI	59	339	529
N° of patients with type 1 diabetes	5371	5133	6408

Figure 18 . Number of patients with ischemic heart disease-stratified by age



	18-50	51-70	>70
N° of patients with IHD	124	1065	1656
N° of patients with type 1 diabetes	5371	5133	6408

Figure 20. Number of patients with peripheral revascularization-stratified by age



	18-50	51-70	>70
N° of patients with peripheral revascularization	149	801	1085
N° of patients with type 1 diabetes	5371	5133	6408

Figure 21. Prevalence rate of patients with peripheral revascularization-stratified by age

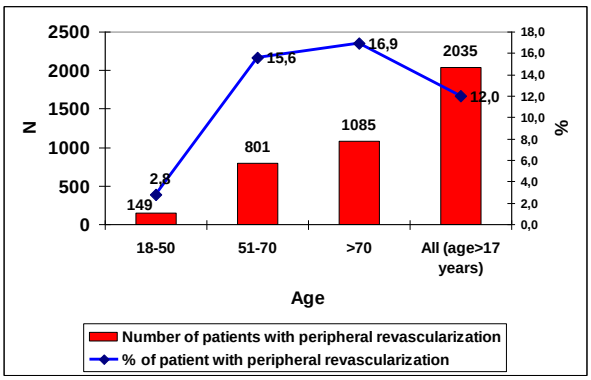
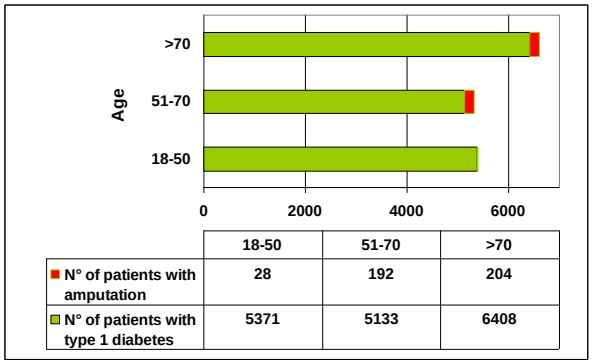
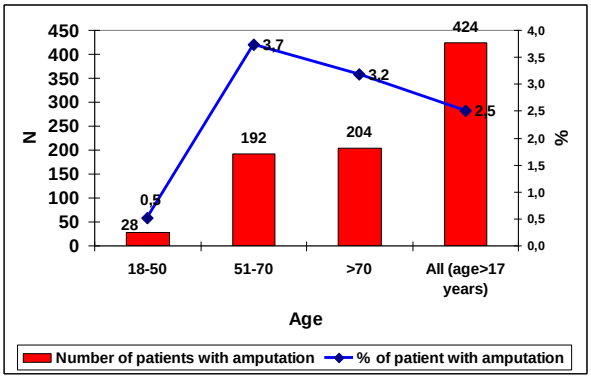


Figure 22. Number of patients undergoing amputation -stratified by age



	18-50	51-70	>70
N° of patients with amputation	28	192	204
N° of patients with type 1 diabetes	5371	5133	6408

Figure 23. Prevalence rate of patients undergoing amputation-stratified by age



5.2.2.2 The context of Basilicata Region

Basilicata, also known as Lucania, is a region of Southern Italy. It covers about 10,000 km^2 and in 2011 had a population slightly under 600,000. The region is divided into two provinces: Potenza and Matera. The Regional Health Service comprises 2 Local Health Trusts, 1 Regional Hospital Trust and 1 Research Hospitals (Istituto di Ricovero e Cura a Carattere Scientifico, IRCCS).

5.2.2.2.1 Number and typology of diabetic centers

In Basilicata region there are 6 diabetic centers, 2 of which are pediatric centers. Both pediatric centres are located in Potenza area: at "San Carlo" regional hospital and "Madre Teresa di Calcutta" ambulatory.

Figure 1. Geographical location of the pediatric diabetic centers in Basilicata.

5.2.2.2.2 Estimate of incidence and prevalence of type 1 diabetes for Basilicata children and adolescents (age<18 year)

Current prevalence and incidence of type 1 diabetes for children and adolescents (age<18 years) in Basilicata Region have been estimated by selecting from two Regional Prescription Drug Database, Assistenza Farmaceutica Territoriale (AFT) and Farmaceutica a Erogazione Diretta (FED) patients with a prescription of insulin (ATC codes A10A) and without prescription of oral antidiabetics (ATC codes A10B) .

Table 1. Number of cases, new cases, prevalence rates and incidence rates of children and adolescents with type 1 diabetes in Basilicata region in 2008-2011

Study Year	Basilicata population (age<18 years)	Cases with type 1 diabetes (age<18 Year)	New cases (age<18 Year)	Prevalence rate (age<18 year) *100 000	Incidence rate (age<18 year) *100 000
2008	102.753	150	60	146	58
2009	100.911	112	26	111	26
2010	99.063	98	17	97	17
2011	96.979	115	28	112	29

Figure 2. Number of cases (prevalence) and of new cases (incidence) of children and adolescents with type 1 diabetes in Basilicata region 2008-2011

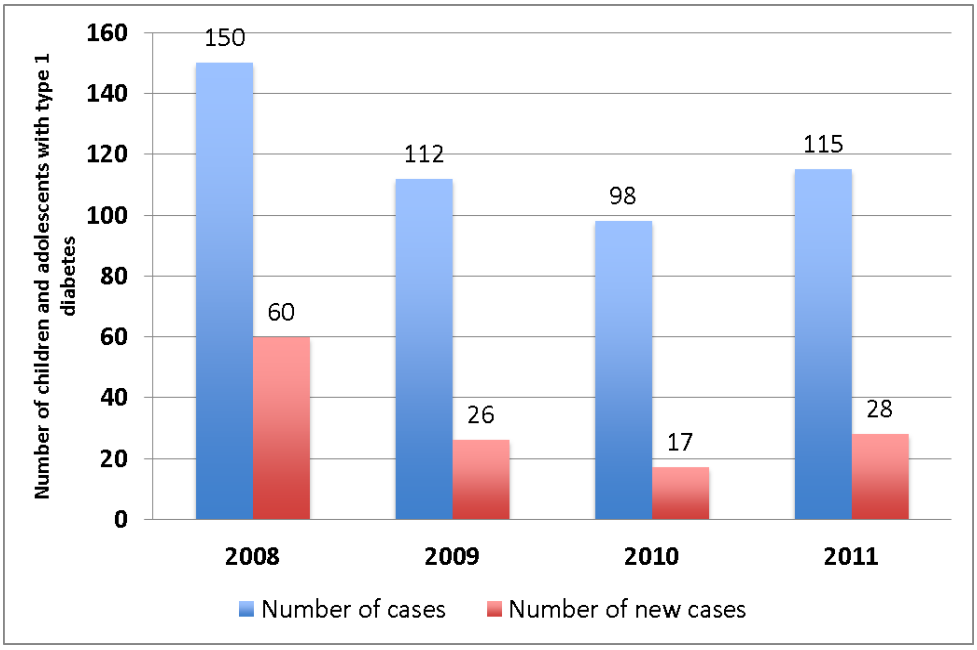
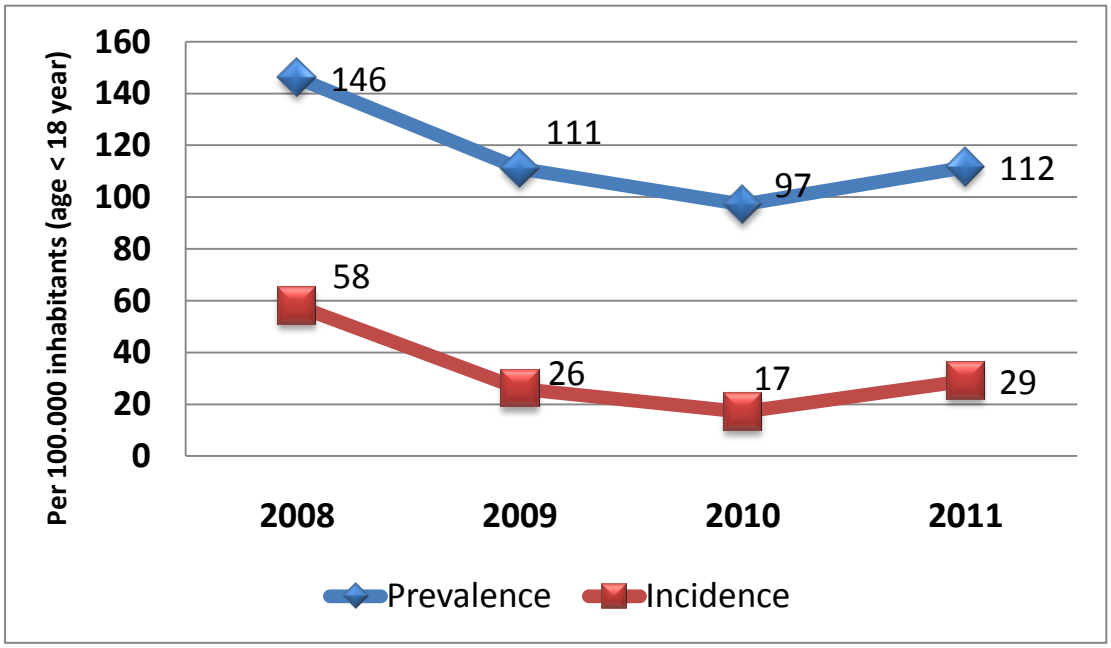


Figure 3. Prevalence rates and incidence rates for children and adolescents (age<18 year) with type 1 diabetes in Basilicata 2008-2011 (per 100.000 inhabitants)



5.2.2.2.3 Short- and long-term complications for Basilicata patients with type 1 diabetes

Short-term complications

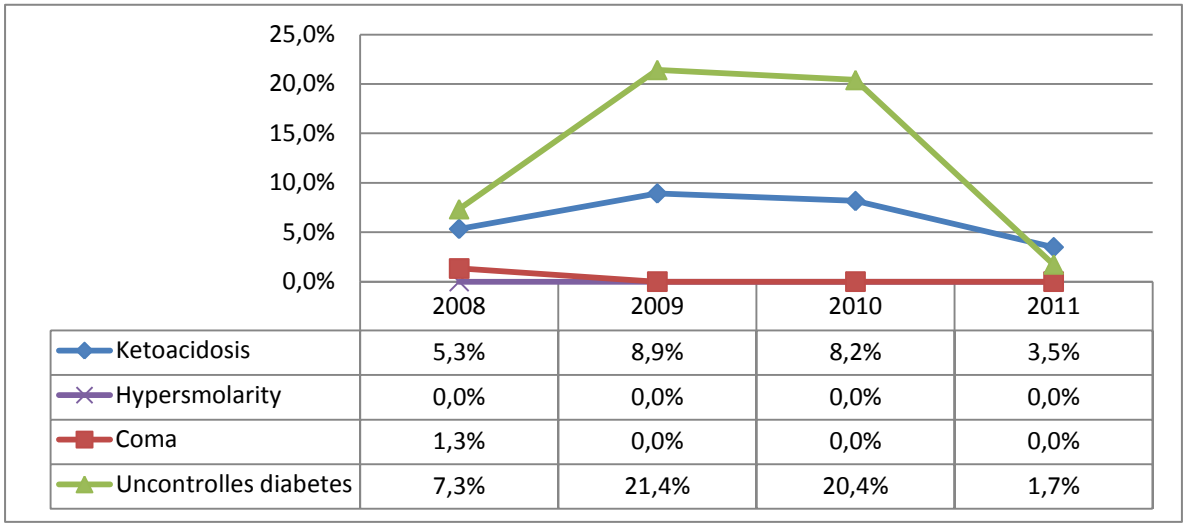
The number of patients with type 1 diabetes, stratified by age, selected from Regional Prescription Drug Database (AFT and FED) in the period 2008-2011 are reported in Table 2.

Table 2. Number of patients with type 1 diabetes stratified by age (data source: Regional Prescription Drug Database AFT and FED)

Year	Age	Patients with type 1 diabetes (N)	Patients with type 1 diabetes (%)
2008	<18	150	2.6
	18-50	776	13.7
	51-70	1.930	34.1
	>70	2.811	49.6
	ALL	5.667	100.0
2009	<18	112	2.0
	18-50	725	13.3
	51-70	1.828	33.4
	>70	2.804	51.3
	ALL	5.469	100.0
2010	<18	98	1.8
	18-50	727	13.6
	51-70	1.683	31.5
	>70	2.829	53.0
	ALL	5.337	100.0
2011	<18	115	2.1
	18-50	739	13.2
	51-70	1.673	29.8
	>70	3.082	54.9
	ALL	5.609	100.0

Figure 4 shows the short-term complications for children and adolescents (age<18 years) in the period 2008-2011. Ketoacidosis and uncontrolled diabetes were the most common complications with a percentage respectively of 3.5% and 1.7% in 2011.

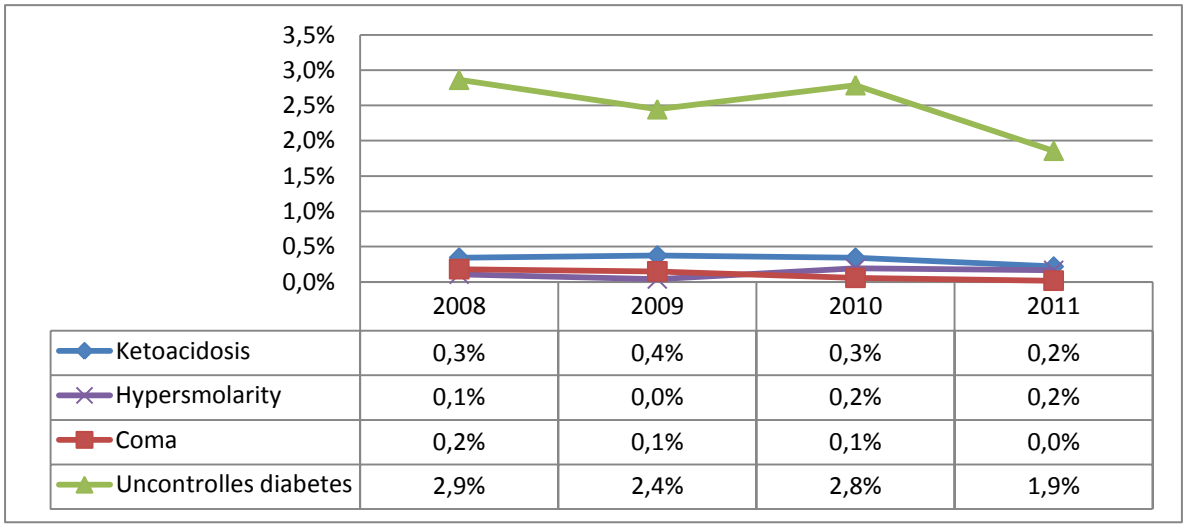
Figure 4. Short-term complications for children and adolescents (age<18 years) in the period 2008-2011.



	2008	2009	2010	2011
Ketoacidosis	5,3%	8,9%	8,2%	3,5%
Hypersmolarity	0,0%	0,0%	0,0%	0,0%
Coma	1,3%	0,0%	0,0%	0,0%
Uncontrolles diabetes	7,3%	21,4%	20,4%	1,7%

Figure 5 shows the short-term complications for adults (age>=18 years) in the period 2008-2011. For this sub-population the short-term complications were less frequent than in children and adolescents.

Figure 5. Short-term complications for adults (age>=18 years) in the period 2008-2011



	2008	2009	2010	2011
Ketoacidosis	0,3%	0,4%	0,3%	0,2%
Hypersmolarity	0,1%	0,0%	0,2%	0,2%
Coma	0,2%	0,1%	0,1%	0,0%
Uncontrolles diabetes	2,9%	2,4%	2,8%	1,9%

Long-term complications

In Basilicata region population, peripheral revascularization and amputation are long-term complications occurring mostly in the 51-70 years age group while ischemic heart disease, kidney disease requiring treatment, retinopathy requiring treatment and stroke are late long-term complications occurring mostly in the >70 years age group.

Figure 6 and Figure 7 show for the cohort of patients of 2011 the number of cases and the prevalence rate of treated retinopathy (hospitalizations or outpatient procedures). An overall prevalence rate of 6.6% was detected with a peak of prevalence of 7.9% in the >70 years age group.

Figure 8 and Figure 9 show the number of cases and the prevalence rate of treated kidney disease (hospitalizations or outpatient procedures) for the cohort of patients of 2011. An overall prevalence rate of 16.1% was detected with a peak of prevalence of 18.6% in the class >70 years.

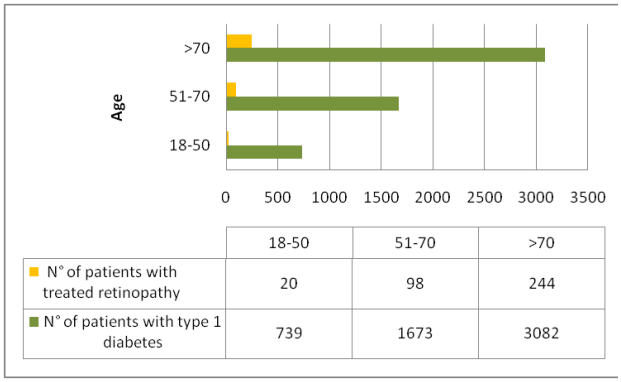
Figure 10 and Figure 11 show the number of cases and the prevalence rate of stroke (hospitalizations or outpatient procedures) for the cohort of patients of 2011. An overall prevalence rate of 8.8% was detected with a peak of prevalence of 12% in the class >70 years.

Figure 12 and Figure 13 show the number of cases and the prevalence rate of ischemic heart disease (hospitalizations or outpatient procedures) for the cohort of patients of 2011. An overall prevalence rate of 13.2% was detected with a peak of prevalence of 15.4% in the class >70 years.

Figure 14 and Figure 15 show the number of cases and the prevalence rate of peripheral revascularization (hospitalizations or outpatient procedures) for the cohort of patients of 2011. An overall prevalence rate of 6.8% was detected with a peak of prevalence of 8.1% in the class 51-70 years.

Figure 16 and Figure 17 show the number of cases and the prevalence rate of amputation (hospitalizations or outpatient procedures) for the cohort of patients of 2011. An overall prevalence rate of 1.3% was detected with a peak of prevalence of 1.7% in the class 51-70 years.

Figure 6. Number of patients treated for retinopathy -stratified by age



	18-50	51-70	>70
N° of patients with treated retinopathy	20	98	244
N° of patients with type 1 diabetes	739	1673	3082

Figure 7. Prevalence rate of patients treated for retinopathy -stratified by age

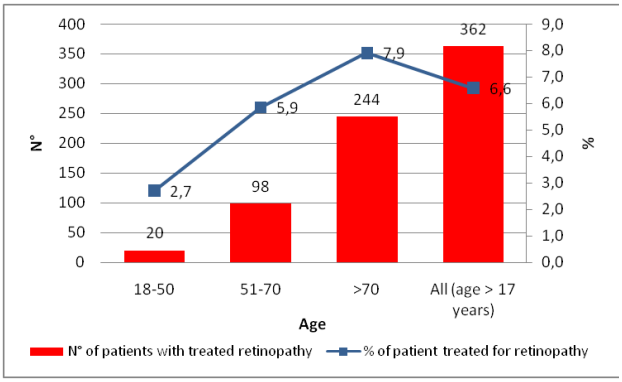
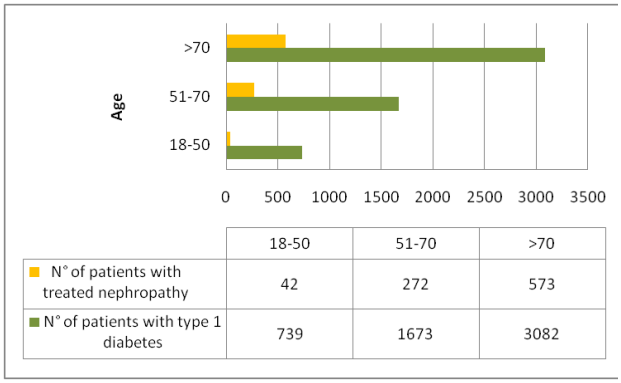


Figure 8. Number of patients treated for kidney disease-stratified by age



	18-50	51-70	>70
N° of patients with treated nephropathy	42	272	573
N° of patients with type 1 diabetes	739	1673	3082

Figure 9. Prevalence rate of patients treated for kidney disease-stratified by age

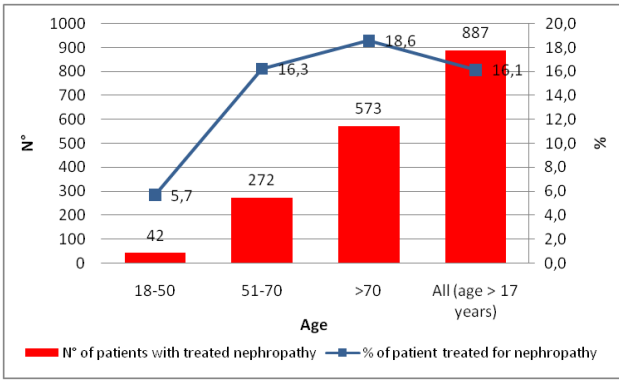
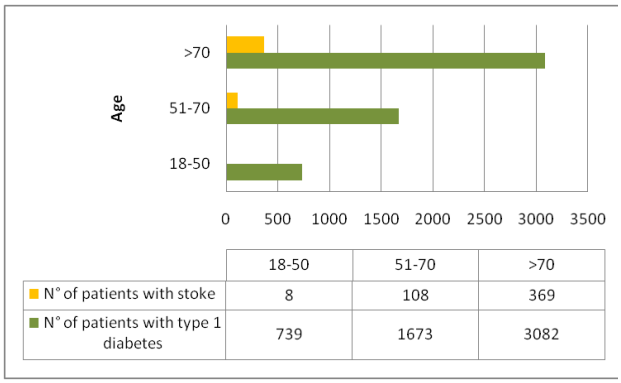


Figure 10. Number of patients with stroke - stratified by age



	18-50	51-70	>70
N° of patients with stoke	8	108	369
N° of patients with type 1 diabetes	739	1673	3082

Figure 11. Prevalence rate of patients with stroke -stratified by age

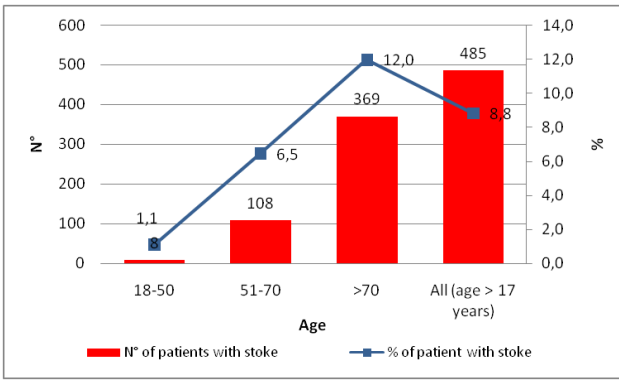
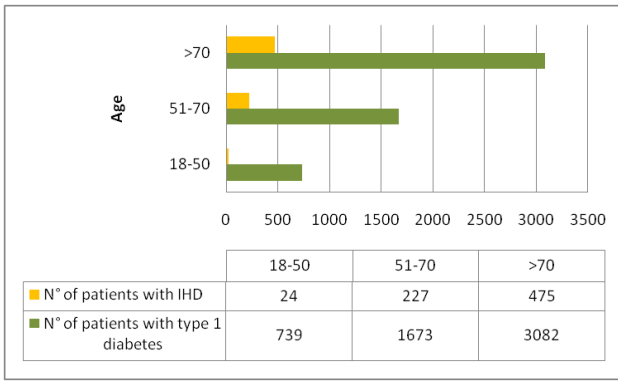


Figure 12 . Number of patients with ischemic heart disease-stratified by age



	18-50	51-70	>70
N° of patients with IHD	24	227	475
N° of patients with type 1 diabetes	739	1673	3082

Figure 13 . Prevalence rate of patients with ischemic heart disease-stratified by age

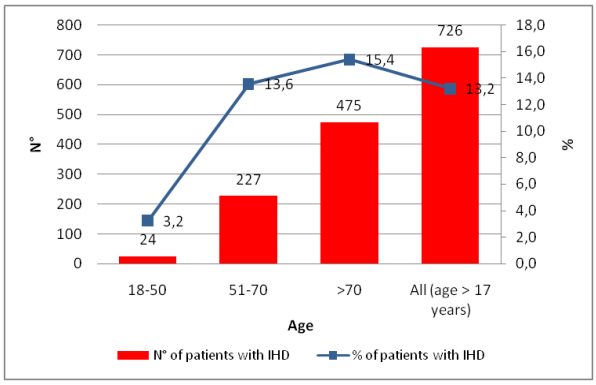
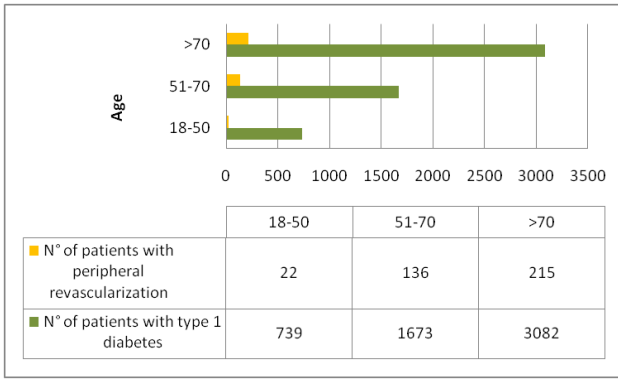


Figure 14. Number of patients with peripheral revascularization-stratified by age



	18-50	51-70	>70
N° of patients with peripheral revascularization	22	136	215
N° of patients with type 1 diabetes	739	1673	3082

Figure 15. Prevalence rate of patients with peripheral revascularization-stratified by age

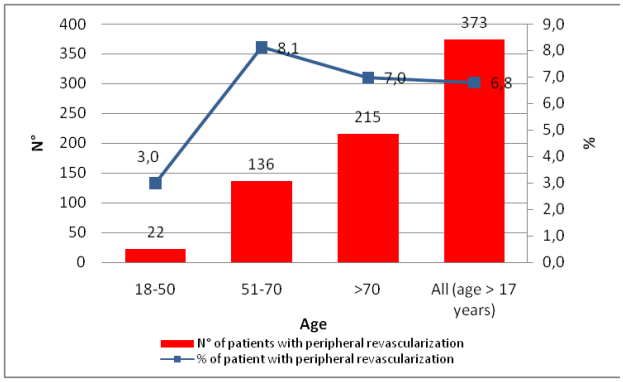
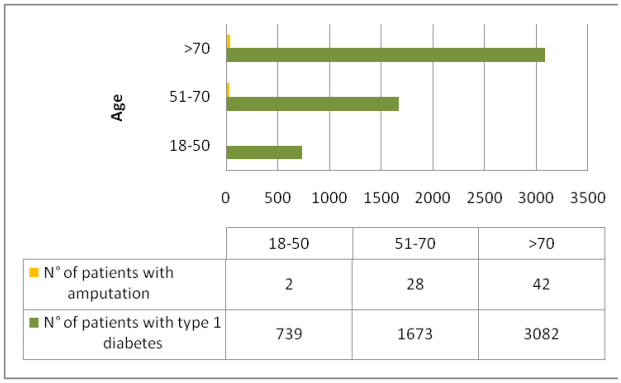
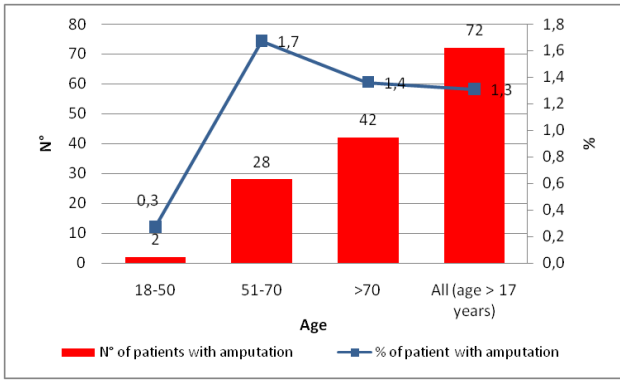


Figure 16. Number of patients undergoing amputation -stratified by age



	18-50	51-70	>70
N° of patients with amputation	2	28	42
N° of patients with type 1 diabetes	739	1673	3082

Figure 17. Prevalence rate of patients undergoing amputation-stratified by age



5.2.2.3 The context of the Trento Province

5.2.2.3.1. Diabetic pediatric centres in Trento Province

Trento Province (PAT) is a northeast Italian autonomous province that covers an area of 6 212 km2, has a resident population of 529 457 (update: 1st January 2011), 258 741 male (48,9%) and 270 716 female (51,1%).

The Provincial Health Service comprises 1 main hospital (Ospedale Santa Chiara, Trento) and 6 smaller local hospitals (Arco, Borgo Valsugana, Cavalese, Cles, Rovereto, Tione).

Currently in PAT there is a single pediatric (0-18) diabetic centre, located at the Ospedale Santa Chiara in Trento.

5.2.2.3.1 Estimate of incidence and prevalence of type 1 diabetes for PAT (age<18 year)

For the present report the current prevalence and incidence of type 1 diabetes for paediatric and juvenile patients in PAT have been estimated analyzing the local RIDI (Registro Italiano per il Diabete mellito Insulino-dipendente), kept by the provincial Epidemiological Observatory. The register contains information about all type 1 diabetic patients living in the Province of Trento. Information is provided according to two age classes: 0-14 and 0-29. In the case of data not available from the RIDI, the register of the Paediatric Diabetic Centre (PDC) of the province has been used. Table 1 shows the number of cases and the number of new cases with type 1 diabetes, the incidence and prevalence rate according to the two data source, i.e. RIDI and PDC. Results coming from the two data source are comparable.

Total population for 2008, 2009 and 2010 were estimated starting from data about total population in 2005 and 2011, considering no changes in population distribution.

Table 1. Number of cases, new cases, prevalence rates and incidence rates of children and adolescents with type 1 diabetes in PAT-2008-2011 for different age classes.

Year	Age class	Total cases	New cases	Incidence (cases/ 100 000)	Prevalence (cases/ 100 000)	Source (PDC=paediatric diabetic centre)
2008	0-14	N/D	15	19,1	N/D	RIDI
	0-29	N/D	21	13,2	N/D	RIDI
	0-18	149	19	20,1	158,0	PDC
2009	0-14	N/D	11	13,7	N/D	RIDI
	0-29	N/D	16	9,9	N/D	RIDI
	0-18	150	14	14,7	157,6	PDC
2010	0-14	N/D	12	14,8	N/D	RIDI
	0-29	N/D	17	10,4	N/D	RIDI
	0-18	157	12	12,5	163,5	PDC
2011	0-14	N/D	N/D	N/D	N/D	RIDI
	0-29	N/D	N/D	N/D	N/D	RIDI
	0-18	156	13	13,4	161,0	PDC

Figure1. Number of cases (prevalence) and of new cases (incidence) of children and adolescents with type 1 diabetes in PAT-2008-2011

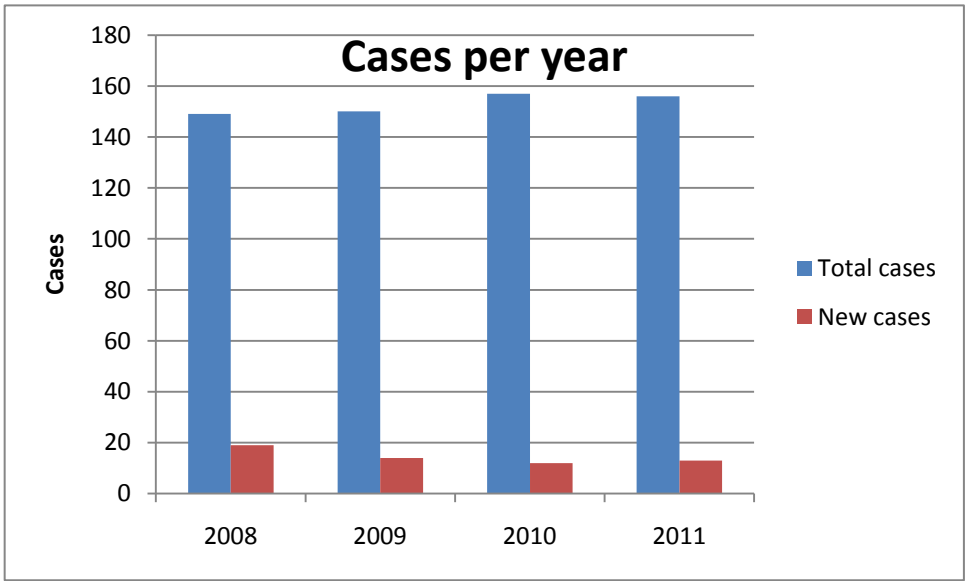


Figure 2. Incidence for different age classes in PAT-2008-2011

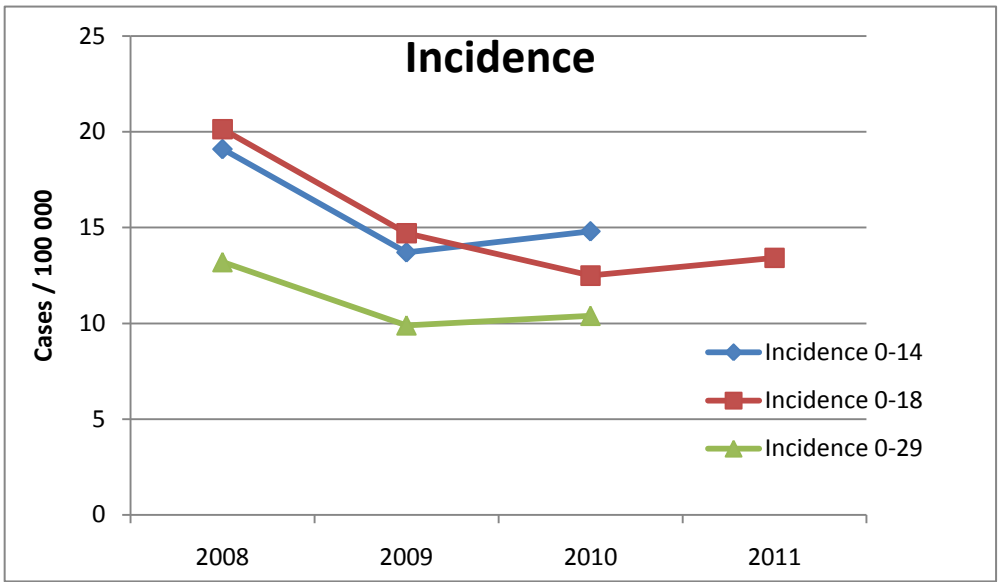
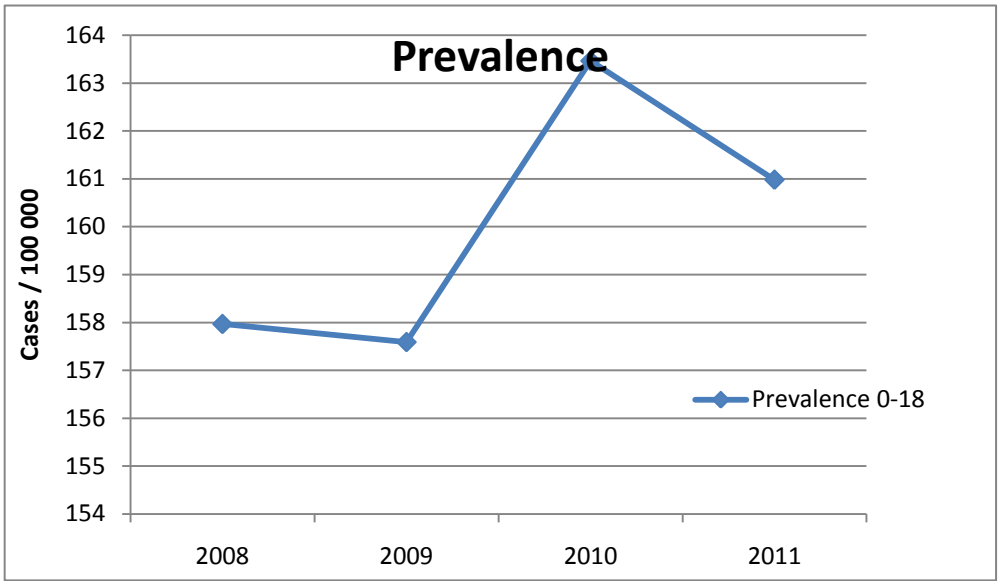


Figure 3. Prevalence for different age classes in PAT-2008-2011



5.2.2.3.3 Short-term complications for PAT patients with type 1 diabetes

Methods we applied to estimate complications of type 1 diabetes are somehow different from the general one described at page XX (section 1.3.1). Only short-term complications were estimated for the PAT since neither the RIDI nor the PDC register contain information about long-term complications.

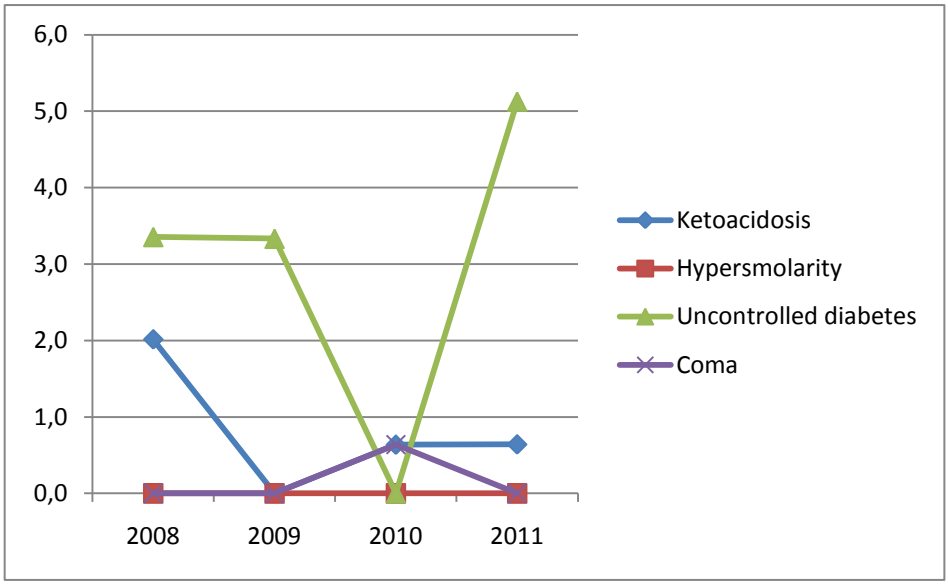
To quantify the frequency of hospitalization for short-term complications (acute complications) in the period 2008-2011 for patients with type 1 diabetes, the register of the PDC in Trento has been used in order to investigate the total number of hospitalizations due to ketoacidosis, uncontrolled diabetes (including hypoglycemia and glycemic unbalance), coma and hypersmolarity. The total number of patients with type 1 diabetes was extracted from the same data source.

The number of cases, the number of patients with type I diabetes and the incidence of short-term complication for the period 2008-2011 are reported in Table 2.

Table 2. Cases of short term complications (hospitalization) of type I diabetes in paediatric patients (0-18) in PAT 2008-2011

Year	Total number of paediatric diabetic patients	Ketoacidosis		Hypersmolarity		Uncontr. diab.		Coma	
		cases	Incidence (%)	cases	Incidence (%)	cases	Incidence (%)	cases	Incidence (%)
2008	149	3	2,0	0	0	5	3,4	0	0
2009	150	0	0,0	0	0	5	3,3	0	0
2010	157	1	0,6	0	0	0	0,0	1	0,6
2011	156	1	0,6	0	0	8	5,1	0	0

Figure 4. % of hospitalization due to short-term complications for children and adolescents (age<18 years) in the period 2008-2011.

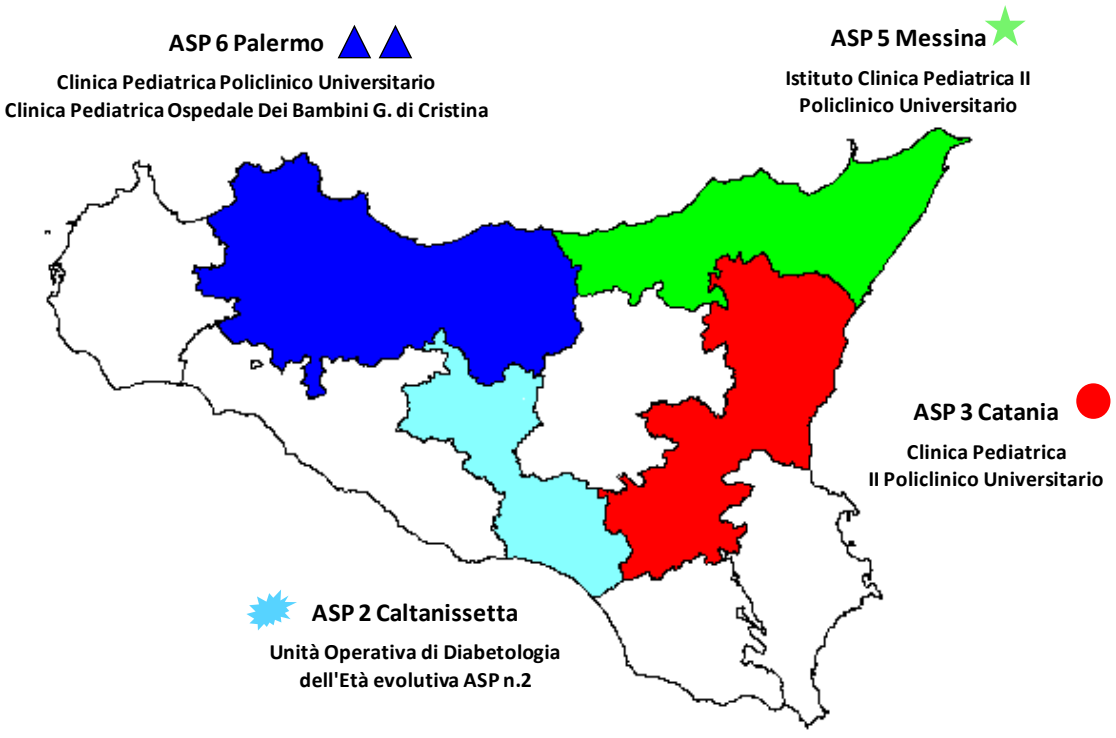


5.2.2.4 The context of Sicily Region

4.2.2.4.1. Diabetic pediatric centres in Sicily Region

Sicily, a southern Italian region with 9 Provinces, covers an area of 25.711 km2. Sicily has a resident population of 5.037.799 (update: 1st January 2011), 2.433.605 male and 2.604.640 female. Currently in Sicily there are 5 diabetic paediatric centres: 2 in Palermo (Pediatric Clinic University Hospital and Clinic Pediatric II Children's Hospital of Cristina G.), 1 in Catania (Pediatric Clinic II University Hospital), 1 in Caltanissetta (Unit of Diabetology Age evolutionary ASP 2) and finally 1 in Messina (Institute Pediatric Clinic II - University Hospital). Figure 1 shows the geographical location of the 5 paediatric diabetic centres.

Figure 1. Geographical location of the paediatric diabetic centres



5.2.2.4.2 Estimate of incidence and prevalence of type 1 diabetes for Sicily children and adolescents (age<18 year)

One study (Arpi M.L., 2002) has estimated the incidence of Type 1 diabetes mellitus (T1DM) in the district of Catania (eastern Sicily) in children under 15 yr of age over a ten-yr period (01/01/1989 - 31/12/1998) in relation to age, sex, monthly-seasonal variability, calendar yr and spatial clustering. The overall incidence rate was 12.38 per 100,000 during the period of the study.

Twenty-four percent of cases were 0-4 yr at diagnosis, 42% were 5-9 yr and 34% were 10-14 yr. More males (no. 148) than females (no.125) were newly diagnosed with a male/female ratio similar to the base population ratio in the range 0-14 yr and within age groups. The study revealed a non-random spatial distribution of T1DM incidence in children not accounted for by known demographic factors.

The estimated prevalence of diagnosed diabetes and treatment on the basis of specific rates by age and inferred on the basis of information provided by ISTAT (Italian Statistical Yearbook, year 2011) for Sicily is 5.7%, about 16% higher than the national average (4.9%)

For the present report the current prevalence and incidence of type 1 diabetes for children and adolescents (age<18 years) in Sicily Region have been estimated analyzing only the Regional Prescription Drug Database, Assistenza Farmaceutica Territoriale (AFT).

Considering the children and adolescents population of Sicily Region and the number of cases and new cases with type 1 diabetes the incidence rate and prevalence rate, resulting from AFT data base only, were estimated and reported in Table 1. For 2011 the incidence and prevalence rates of Type 1 diabetes in Sicily Region among children and adolescents are estimated at 36 per 100.000 inhabitants and 112 per 100.000 inhabitants, respectively.

Table 1. Number of cases, new cases, prevalence rates and incidence rates of children and adolescents with type 1 diabetes in Sicily region-2011

Year	Cases with type 1 diabetes (age<18 Year)	Sicily population (age<18 years)	New cases	Prevalence rate (age<18 year) *100 000	Incidence rate (age<18 year) *100 000
2011	1049	939667	335	112	36

5.2.2.4.3.Short-term and long-term complications for Sicily patients with type 1 diabetes

To identify patients with type 1 diabetes mellitus and either short-term or long-term complications the general method described in section 1.3.1 was modified as only AFT and SDO databases were used.

Short-term complications

The number of patients with type 1 diabetes, stratified by age, selected from Regional Prescription Drug Database (AFT) in the year 2011 is reported in Table 2.

Table 2. Number of patients with type 1 diabetes stratified by age (data source: Regional Prescription Drug Database AFT)

Year	Age	Patients with type 1 diabetes (N)	Patients with type 1 diabetes (%)
2011	<18	1049	2,6
	18-50	8238	20,7
	51-70	10954	27,5
	>70	19592	49,2
	ALL	39833	100,0

Figure 2 shows the percentage of short-term complications for children and adolescents (age<18 years) in the period 2008-2011 using 2011 prevalence as denominator. Ketoacidosis and uncontrolled diabetes were the most common complications for children and adolescents with a percentage respectively of 2.7% and 5,4% in the year 2011.

Figure 2. Short-term complications for children and adolescents (age<18 years) in the period 2008-2011.

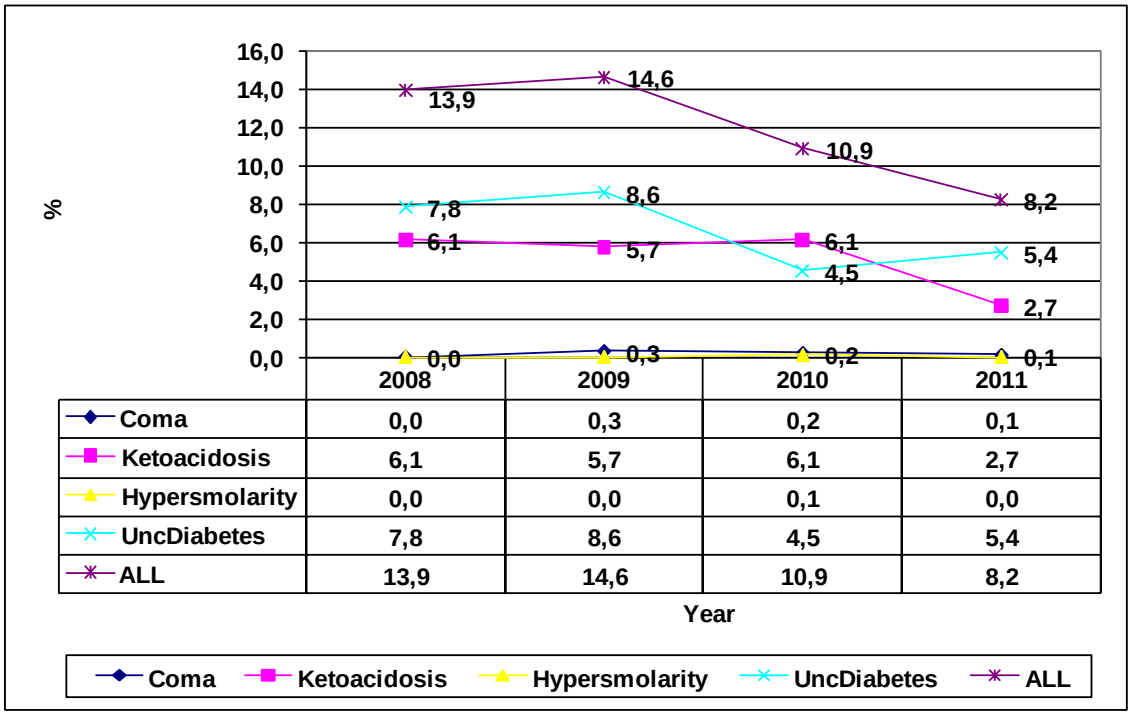
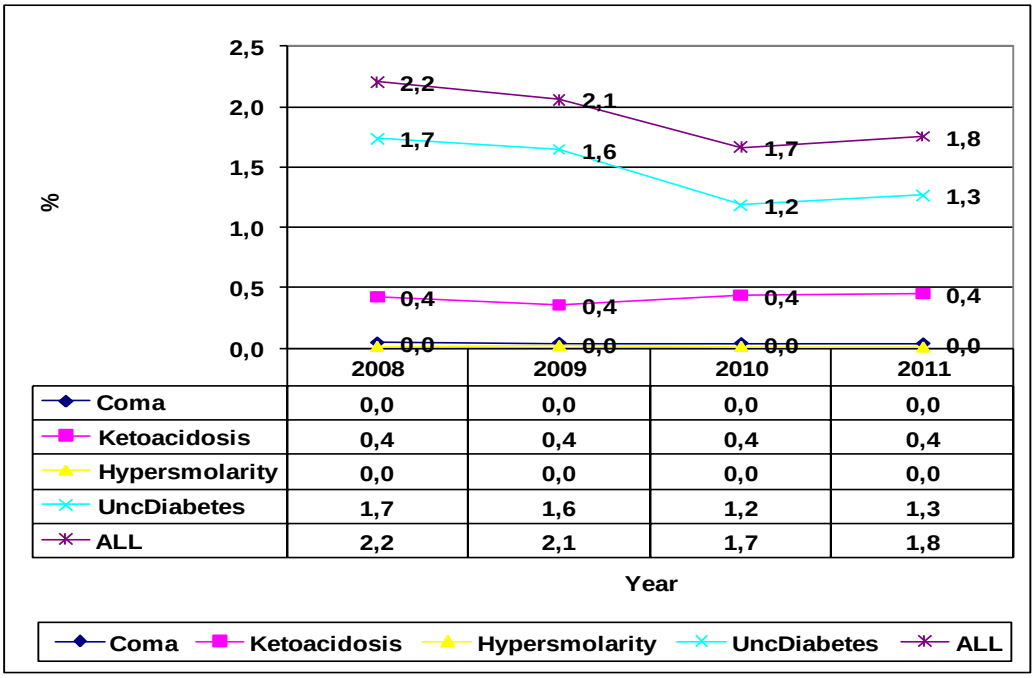


Figure 3 shows the percentage of short-term complications for adults (age>=18 years) in the period 2008-2011, using 2011 prevalence as denominator.

For this sub-population the short-term complications were less frequent than in children and adolescents.

Figure 3. Short-term complications for adults (age>=18 years) in the period 2008-2011



Long-term complications

Retinopathy requiring treatment, dialysis and amputation are long-term complications occurring mostly in the 51-70 years age group while kidney disease requiring treatment, stroke, myocardial infarction and peripheral revascularization are late long-term complications occurring mostly in the >70 years age group.

Figure 4 and Figure 5 show for the cohort of patients of 2006-11 prevalent cases and the prevalence rate of treated retinopathy (hospitalizations) over the period 2011. An overall prevalence rate of 4,8% was detected with a peak of prevalence of 6,7% in the over 70 years age group.

Figure 6 and Figure 7 show the prevalent cases and the prevalence rate of treated kidney disease (hospitalizations or outpatient procedures) over the period 2006-2011 for the cohort of patients of 2011. An overall prevalence rate of 8.5% was detected with a peak of prevalence of 10.6% in the class >70 years.

Figure 8 and Figure 9 show the prevalent cases and the prevalence rate of stroke (hospitalizations or outpatient procedures) over the period 2006-2011 for the cohort of patients of 2011. An overall prevalence rate of 8.2% was detected with a peak of prevalence of 12.4% in the class >70 years.

Figure 10 and Figure 11 show the prevalent cases and the prevalence rate of myocardial infarction (hospitalizations or outpatient procedures) over the period 2006-2011 for the cohort of patients of 2011. An overall prevalence rate of 2.0% was detected with a peak of prevalence of 2.5% in the class 51-70 years.

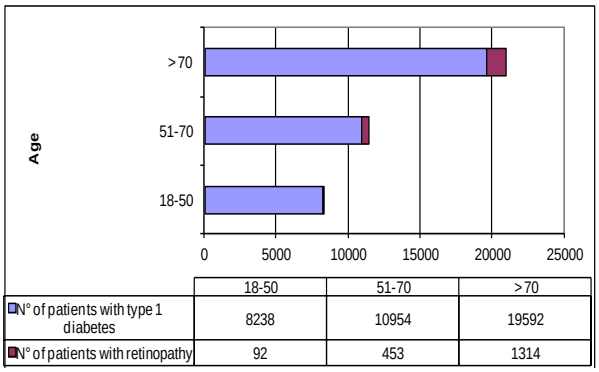
Figure 12 and Figure 13 show the prevalent cases and the prevalence rate of ischemic heart disease (hospitalizations or outpatient procedures) over the period 2006-2011 for the cohort of patients of 2011. An overall prevalence rate of 9.6% was detected with a peak of prevalence of 12.6% in the class >70 years.

Figure 14 and Figure 15 show prevalent cases and the prevalence rate of peripheral revascularization (hospitalizations or outpatient procedures) over the period 2006-2011 for the cohort of patients of 2011.

An overall prevalence rate of 5.5% was detected with a peak of prevalence of 7.0% in the class 51-70 years.

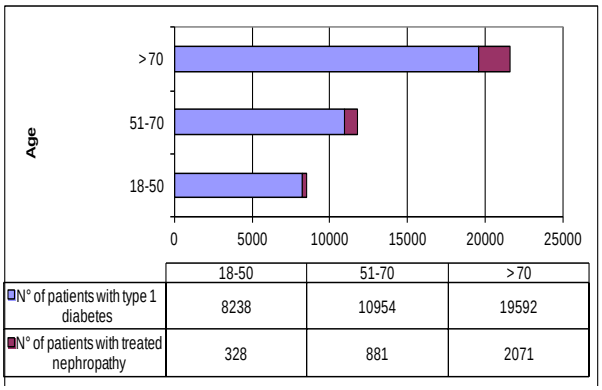
Figure 16 and Figure 17 show prevalent cases and the prevalence rate of amputation (hospitalizations or outpatient procedures) over the period 2006-2011 for the cohort of patients of 2011. An overall prevalence rate of 0.5% was detected with a peak of prevalence of 0.9% in the class 51-70 years.

Figure 4. **Number of patients treated for retinopathy -stratified by age**



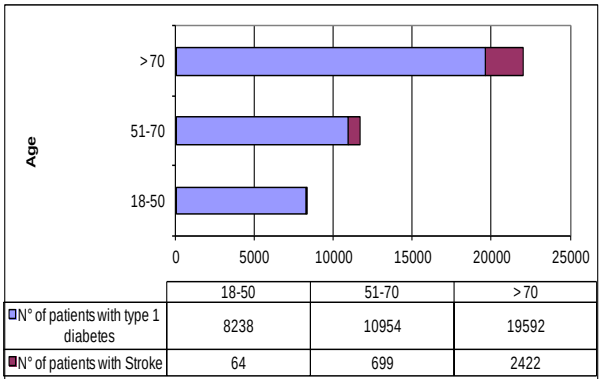
	18-50	51-70	>70
N° of patients with type 1 diabetes	8238	10954	19592
N° of patients with retinopathy	92	453	1314

Figure 6. Number of patients treated for kidney disease-stratified by age



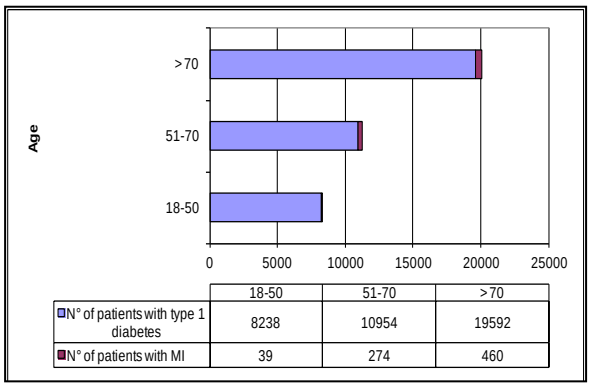
	18-50	51-70	>70
N° of patients with type 1 diabetes	8238	10954	19592
N° of patients with treated nephropathy	328	881	2071

Figure 8 . Number of patients with stroke -stratified by age



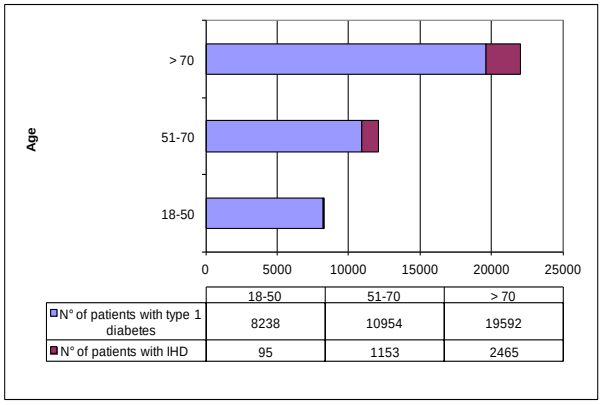
	18-50	51-70	>70
N° of patients with type 1 diabetes	8238	10954	19592
N° of patients with Stroke	64	699	2422

Figure 10. Number of patients with myocardial infarction-stratified by age



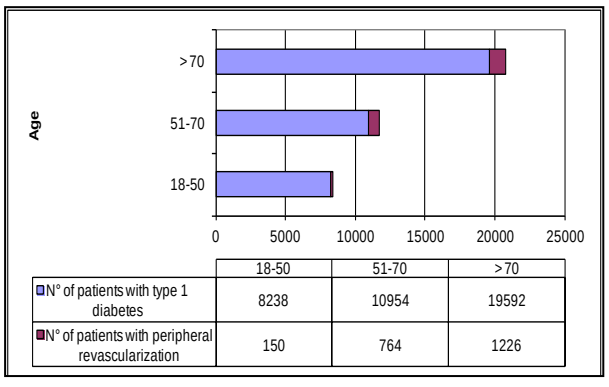
	18-50	51-70	> 70
N° of patients with type 1 diabetes	8238	10954	19592
N° of patients with MI	39	274	460

Figure 12. Number of patients with ischemic heart disease-stratified by age



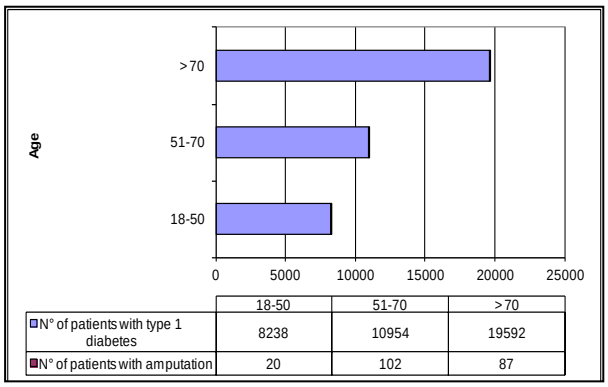
	18-50	51-70	> 70
N° of patients with type 1 diabetes	8238	10954	19592
N° of patients with IHD	95	1153	2465

Figure 14. Number of patients with peripheral revascularization-stratified by age



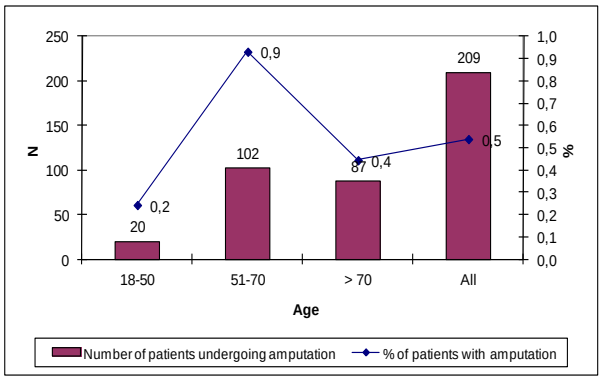
	18-50	51-70	> 70
N° of patients with type 1 diabetes	8238	10954	19592
N° of patients with peripheral revascularization	150	764	1226

Figure 16. Number of patients undergoing amputation -stratified by age



	18-50	51-70	>70
N° of patients with type 1 diabetes	8238	10954	19592
N° of patients with amputation	20	102	87

Figure 17. Prevalence rate of patients undergoing amputation-stratified by age



Conclusion on Sicily

The "target population" considered in our report for combined use of continuous subcutaneous insulin infusion (CSII) and continuous glucose monitor (CGM) devices (SAP-sensor augmented pump) are children and adolescents with type I diabetes mellitus: in 2011, in Sicily they were 1049. In the same year, 86 (8.2%) patients experienced short-term complications.

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6. PATIENTS VIEWS AND PREFERENCES

6.1 Background

Sensor Augmented Pump (SAP) is new therapy, based on the convergence of two technologies: continuous systems for insulin infusion (CSII) and real-time continuous glucose monitoring systems (CGMS). All those devices have common features, and similar psychosocial impacts and thus can be seen as belonging to a same device set/family. Common characteristics are:

- being external devices that a patient have to wear by insertion under the skin;
- being devices patients must learn to rely on in order to maintain and/or enhance his/her health.

Many advantages in flexibility of life style or, on the contrary, in problems patients can encounter (e.g. negative body image due to a device attached) with SAP are already experienced with CSII pump only.

6.2 Objectives

Our objectives were:

- to retrieve comparative studies on children, adolescents and/or their parents preferences and psychosocial outcomes related to the use of SAP in comparison to the MDI.
- to provide an outline of children, adolescents and/or their parents views about CSII versus MDI. so that advantages and disadvantages of therapies, based on wearing external devices could be properly described.

6.3 Methods

To outline the psychosocial dimension of technology's impact in the perspective of the Italian National Health System (NHS), context specific information about Italian patients' preferences should have been elicited. Because of time and resource constraints we could not collect primary data from our own context, so we had to rely on a systematic review of studies about SAP versus MDI in children and adolescent that had QoL as an outcome. Nontheless given the similarties between SAP and CSII in terms of psychosocial impact on patients, we also performed an overview of *HTA* reports and comparative studies on CSII versus MDI considering patients views in our target population.

We performed a:

- *Systematic review*[1] of the literature about SAP versus MDI with QoL as an outcome in our target population;
- *An overview of* HTA reports on CSII and/or CGMS that contained a chapter on children and adolescents views/preferences and of the studies on CSII and QoL in our population, selected from the dataset of publications for systematic review (for a detailed descriprion of the methods of the overview see below par. 4.3.2)

6.3.1 Systematic review of the literature for QoL with Sensor Augmented Pump versus Multiple Daily Injections

Methodology

A systematic review of the literature about QoL with SAP versus MDI in our target population was performed.

Data sources

Electronic databases

We searched were MEDLINE, EMBASE, PubMed, Cochrane Library, HTA databases– Centre for Review and Dissemination. See Appendix 1 for the detailed search strategy.

Web sites

We also searched on HTA agencies and Diabetes association's web sites to find reports or any grey literature on patients' views and QoL. List of consulted websites and date of latest consultation is at Appendix 2.

Selection criteria

Inclusion criteria

Inclusion criteria were applied to select those publications which compared Sensor Augmented Pump (SAP) with Multiple Daily Injections (MDI) in children and adolescents by

[1]This is a new systematic review based on a search strategy different from the one in chapter 3 performed by the Emilia Romagna working group for clinical effectiveness and safety. Different search strategies and inclusion criteria gives different results in terms of selected studies.

measuring Quality of Life (QoL) with standardised instruments or describing its impact on social/psychological life using other qualitative research techniques.

Study design: Qualitative or quantitative studies

Participants: Children and adolescents aged 0-18 with T1DM

Intervention: Sensor Augmented Pump

Comparison: Multiple Daily Injection

Outcomes: Quality of life, psychological and social effects, impact on social life

Exclusion criteria

Letters, opinions, posters and conference abstracts were excluded. Limitations in the search were language and time for publication. The search included literature from 2005 to 2011 in English and Italian. Time limits are due to the fact that before 2005 SAP was not widespread (Hoecks, 2005).

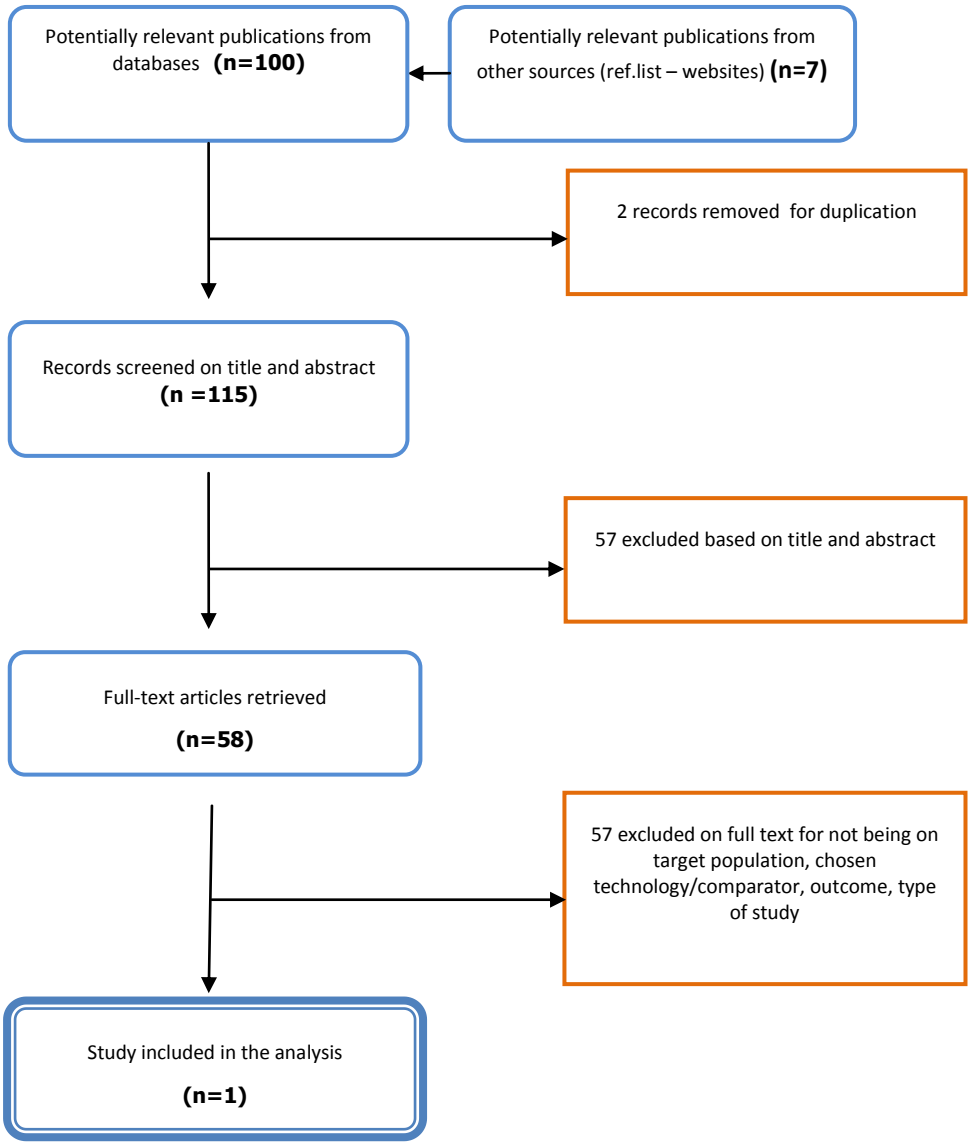
Analysis of the literature and data extraction

ProCite software was used to manage the references. One reviewer selected the studies to be included on the basis of title and abstract. Potentially relevant articles were selected for reading full text if quality of life and preferences, views, opinion of children and adolescent with T1DM were mentioned in abstract. When the abstract was not available or unclear full text was retrieved. Data extraction and tabulation was undertaken by one reviewer. A synthesis of each selected study by narrative review was provided.

Results

We retrieved 107 potentially relevant publications from electronic databases and other sources (web sites, see list in appendix) and 2 records were removed for duplication, 105 studies were screened on the basis of title and abstract. Fiftyeight (58) articles were retrived to read in full text and 1 was selected to be included, while the others were excluded for not being on target population, chosen technology/comparator, not delaing with QoL outcome, for being guidelines/mere opinion/author review (in Appendix 3 is the lsit of excluded studies and reasons for exclusion). See the flowchart for a graphic description of the selection process.

Flowchart



The study by Alemzadeh et al. 2007 is the only comparative study among our dataset that fit the inclusion criteria comparing MDI to CSII+CGMS in our target population and measured Quality of Life (QoL) alongside other clinical outcomes.

This is a before-after study conducted in a pediatric hospital in Wiscosin, (Milwaukee USA). Fourteen children (14), 8 girls and 6 boys, aged 2.2 -5.5 years were transitioned from flexible MDI to CSII. Continuous Glucose Monitoring System's sensors were used at baseline and every 3 months for 1 year on CSII. Data were collected 1 year before and 1 year after transition to CSII.

Eligible patients had to have recurrent episodes of moderate or severe hypoglycaemia and erratic blood glucose swings that did not resolve with insulin dose adjustments. Out of 19 patients who were initially screened, just 14 (74%) were selected for the CSII regimen. The reasons for exclusions were:

- 1. Inability to tolerate the insulin pump catheter placement (3 children).
- 2. Parents' difficulty with CSII operational tasks (2 children).

Children's main carers underwent a screening on their diabetes care skills and psychosocial characteristics to optimize compliance on CSII. Before initiation of CSII, the diabetes team evaluated each patient's ability to tolerate insulin pump catheter set placement and his or her parents' ability to operate CSII and perform insulin adjustments.

Quality of life was measured with the Preschool Children Quality of Life questionnaire (TAPQoL) The TAPQoL (Leiden Center for Child Health and Pediatrics, Leiden, The Netherlands) is a 43-item questionnaire with 12 scales covering physical, social, cognitive, and emotional functioningIt was used at baseline and at 1 year follow-up to assess the parent's perception of health-related quality of life (HRQoL) in each child. Although parents were both asked to complete the HRQoL measure, the mothers' perceptions of their children's HRQoL at baseline and 1 year follow-up were analysed using paired-samples t tests. Samples t tests were utilized to determine if there were significant differences between the 12 subscale scores at both baseline and 1 year follow-up. Paired-samples t tests were conducted to compare the parental reports of current study participants' HRQoL scores with a sample of chronically ill children. The majority of this comparison group had respiratory problems.

Authors' conclusions state that no significant differences were found at baseline and at 1 year follow-up scores for any of the subscales. Results show no improvement in QoL, although this is presented as a result in favor of the pump, as wearing this "complicated" technology would not make lifestyle and daily life worst. Results found no significant differences between the quality of life scores for the parental ratings of the present participants with a comparison group of chronically ill children on all of the subscales, except on appetite and lung problems (P=0.01), where the participants from the present study demonstrated higher quality of life scores at both baseline and 1 year follow-up than the comparison sample.

6.3.2 Overview of HTA reports and studies about children/parents and adolescents views on pump therapy

Objectives

This overview aims at finding Health Technology Assessement reports on simple CSII dealing with patients preferences. This would allow a better understanding of advantages/disadvantages in flexibility of life style (e.g. being able to eat out/having a negative body image due to a device attached) with a therapy that relies on "external devices" to manage the disease.

Method

We started from the dataset of literature already retrieved (see Appendix 1 for search strategy) and selected the HTA reports on CSII containing a chapter on patients views[2]. Those reports had been excluded in the systematic reviews as they were not on SAP versus MDI.

From the above dataset (see Appendix 1 for serach strategy and Appendix 3 for the list of excluded studies and reasons for exclusion) we also selected the studies that had been excluded as not being on SAP versus MDI, but that:

1. focused on our target population
2. were on simple pump (CSII) or on CGMS
3. considered QoL as an outcome
4. were published from 2007 to 2011[3].

Analysis of the literature

Our search identified two HTA reports which included a chapter on patients views: one by the Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS) and the other by the National Institute for Clinical Excellance (NICE). Both reports contain ad

[2]For this overview we did not perform an ad hoc search of HTA reports, but selected those that resulted from the systematic review (but were excluded as not being on SAP vs MDI). The series of HTA reports and guidelines selected for the Overview in chapter 3 is more extensive, both as it considers more languages (we just considered English and Italian literature) and it includes also guidelines. Among the identified publications of the overview at Ch. 3 the only two reports in English that deal with patient views are the ones form B. Coté et al. (2004) and from Cummins et al. (2010).

[3]We selected studies published from 2007 to 2011 as the systematic review by Cummins et al. included studies from 2005 to 2007 (see below description of Chapter 4 "Economics: CSII versus MDI").

hoc qualitative interviews/materials about pump therapy and a systematic review on Quality of Life of patients using CSII versus MDI measured with standardised instruments. A description of the qualitative interviews and material of both reports is reported below, while for the systematic review on QoL we describe the most recent report's results (NICE). This includes studies form 2005 to 2007. Starting from the latter date, we selected studies on CSII/CGMS QoL in children and adolescents published from 2007 to 2011 and provide a description of their main results.

- **Brigitte Côté and Carole St-Hilaire "Comparison of the insulin pump and multiple daily insulin injections in intensive therapy for type 1 diabetes" Report prepared for AETMIS, June 2005**

The report contains a systematic review of the literature on quality of life (as a paragraph of the overall systematic review) and a chapter on patients views (Chapter 6 "The patient perspective"). As mentioned above, we did not report results of AETMIS' systematic review as the NICE one is more updated.

n Chapter 6 authors describe results of the qualitative interviews which were purposely made by AETMIS reserchers to children/parents on pump therapy. AETMIS conducted a survey, which was answered, on a voluntary basis, by 11 people in a support group who were parents of children on pump therapy in the Quebec City. The questionnaire included closed-ended and open-ended questions of a qualitative nature about managing the disease with the pump instead on the previous therapy (MDI).

Authors underline that results show that main reasons leading patients to switch from MDI to pumps are substantially the same for adults and children. Besides clinical and medical reasons (e.g. improve the HbA1c level, reduce hypoglycemia, control long term complications etc), social and psychological reasons were :

- To have a better quality of life;
- To have greater flexibility in terms of schedule, diet and sports;
- Less stress for family members, an improvement in the couple's life.

Specific benefits of the pump for children are:

- More accurate insulin dosing (important in young children);
- Easier to control the blood glucose level during minor infections (a number of parents reporting a decrease in the number of hospital stays);
- Improved quality of life, not only for children, but for the entire family;
- Greater autonomy for the child with respect to him/her managing the disease.

Main drawbacks in children were: constant monitoring of the device, because of the risk of ketoacidosis and changing the cannula.

- **Cummins E. et al, Clinical Effectiveness and cost-effectiveness of CSII for diabetes: systematic review and economic evaluation, Health Technol Assessment 2010; 14 (11)**

The report's target population and disease is broader then ours as it is about both types of diabetes in adults, children and adolescents, but all data and information are broken down by age groups and type of diabetes. The report includes a chapter on patients (Chapter 5 "Patients perspectives"), and a focus on literature assessing Quality of Life with standardised instruments within Chapter 4 "Economics: CSII versus MDI". We synthesise their content below, focusing only on the articles and information related to our target population.

Chapter 5 "Patients perspectives"

In this chapter the authors describe:

- evidence on patients' preferences and views submitted by INPUT (English association of insulin pump users) and a based discussion group (Insulin Pumpers UK 2007);
- results from a previous report;
- new evidence on patients' preferences and views from interviews to parents of young children.

Cummins et al. highlight that perceived benefits prevail over negative aspects of CSII in parents' opinions as they are all parents of children using the pump. Further research would be needed to understand reasons for not using CSII from parents who do not use it or/and abandoned it. This selection bias (INPUT) does not affect validity of comments, but has implications on generalizability: they are successful pump users and are enthusiastic about it.

Evidence from INPUT and WEB based discussion

For the successful children and families who use CSII, QoL gains include the following:

- Being able to eat out;
- Go on excursion of uncertain duration (e.g. school trip);
- Do not force children to eat when they do not want;
- School routines are easier to manage, as e.g. some school cannot cope with lunchtime injections;

- No need of going to medical rooms to inject (suspending class activities);
- No need of going to eat before the others (risk of social exclusion);
- Children feel more in control;
- Improved mood and academic ability (post breakfast spike is said to reduce ability in some subjects, such as maths) in adolescents.

Qualitative interviews

Parents of children aged 5-8 years were interviewed to understand reasons which led them to switch from MDI to CSII. They were recruited through the INPUT group (see p.93-99 of the HTYA and Appendix 11 for a detailed description of the materials and methods). Eight out 10 had the costs of the pump paid by NHS, and just paid consumable.

In their opinion, benefits of the pump are:

- Improvement of family and child's flexibility in life style (e.g. diet, social and physical activity, school tours, and family's vacations etc.);
- Reduction of anxiety in parents and tensions within family;
- More acceptability of pumps at school among teachers who ususally have problems to manage daily injections with MDI therapies;
- Control of the child's mood.

Perceived challenges are related to:

- Problems in finding a clinical team able to manage the pump;
- Worry that the child can have problems in his/her body image with a pump always attached;
- Not enough support from patients associations;
- Considerable commitment was required to master the pump and that not all the parents are ready for this.

Chapter 4 "Economics: CSII versus MDI"

A paragraph of this chapter is dedicated to "*Patient preferences and quality of life*". A review of the evidence on patient quality of life with CSII versus MDI measured with standardised instruments is reported as an update of a previous report on the same topic by Colquitt et al. 2004 which – for our target population - had not identified any study.

Cummins et al. 2010 identified, from 2002-2007, 6 studies (out of 16) about CSII versus MDI involving children and adolescents with TD1 and measuring their QoL. Three were RCTs and 3 had a before/after design.

Authors' sonclusions are that three RCTs, one involving 8-14 years children and the others very young children under 5 years of age, show that there could be a slight enanchement in QoL with CSII versus MDI. There is no deterioration of it. More evidence is needed. Results from the three studies with a before/after design have a source of bias in that patients commenced CSII due to failure with their previous regime.

Weintrob et al. (2003). It is a "randomised cross over trial" involving a sample of 23 Israeli children aged 9-14 with a cross over period of 3.5 months after a 2 weeks run in period. The instrument used was Diabetes Treatment Satisfaction Questionnaire (DTSQ) and for more general Quality of Life they used DQoL-Y. DTSQ scores averaged 21.4 at baseline and 21.9 at the end of the MDI arm and 30.6 at the end of the CSII arm. No significant differences were recorded with DQoL-Y. At the end of the study patients were asked which regime they preferred and 70% said CSII for flexibility in lifestyle, avoidance pain of injections, and better glycaemic control or profiling. Those preferring MDI had concern for glycaemic control, overeating and weigh gains, shame at wearing the pump, too much self-monitoring.

Dimeglio et al. (2004). This is a RCT enrolling US children under 5 years age, with T1DM, reporting that CSII was well tolerated with 19/20 families opted to continue CSII after 6 months.

Fox et al. (2005). Six months RCT comparing CSII versus Mdi in 26 children, under 4 years. They were randomly assigned to continue to receive MDI or switching to CSII. Parental quality of life and perception of their kids QoL was assessed. Mothers on MDI group reported more distress on family life than CSII group, buy there were no more differences at 6 months. 19 out of 20 families in the CSII group continued with CSII therapy after 6 months.

Shehadeh et al. (2004) is a before and after study that briefly reports results on 15 Israeli children aged 1-6 years and with T1D. Treatment satisfaction and quality of life were measured through DTSQ and DQoL, for parents at baseline and at 4 months. Both significantly improved after 4 months.

McMahon et al. (2005). It is a before and after study. This means that patients has already shift to CSII from MDI, so results can have a strong source of bias. It prospectively followed 100 Australian children and adolescent, but QoL was measured among first 51, age < 10 years patients being switched to CSII with a modified DQoL questionnaire and the Self-Efficacy Score for *Diabetes Scale* SED scale. Within DQoL impact of diabetes score fell on average from 55.4 to 50.2. Worries and satisfaction showed no significant change. SED scale improved significantly from 159 to 174.

Juliosson et al (2006) this is a before/after study involving 31 children average age 14 years. QoL was measured with DQoL and generic health questionnaire-child form with 87-item CHQ-CF87 prior to starting and twice during 15 months of follow up. Differences were significant just in the family activities subscale, similarly DQoL improved but not significantly. Authors conclude that respondents may have an inmprovement in QoL, but for sure they di not have a deterioration.

- **Studies published from 2007 to 2011 on QoL with CSII versus MDI in our target population**

A systematic review on QoL studies with CSII versus MDI was identified (Bernard, 2007). Eight studies which had QoL as non clinical outcome were selected. 8. A description of the main results of each study is provided below.

Bernard et al. (2007) - Systematic review on QoL of CSII verusus MDI

Authors included studies from 1999-2005 reporting on participants with T1DM regardless of age and gender, good or poor glycemic control. It is about all ages, but studies were divided in 4 categories and for each category studies dedicated to adults and children/adolescents were highlighted and described. Seventeen (17) studies were selected from a 84 initially identified studies.

- Uncontrolled observational studies (7; 3 were pediatric/adolescents studies);
- Psychometric studies (2; 1 is on adults and the other seems to have a range age of 16-59);
- Controlled studies non randomized (3; 1 was on children/adolescents);
- Randomized controlled studies (5; 3 were on our target population).

Authors' conclusions about children/adolescents are that literature until 2005, is still limited, with conflicting, often with ambiguous results and many are the design/methodological flows. Of the 5 RCTs, 3 were with participants under 18 years and 2 of them found no quality of life benefits and 1 had mixed results. Authors suggest that more appropriate questionnaire to measure QoL in diabetic children population should be used to and that there a lack of validated measures for use in children.

Opipari-arrigan et al (2007) - *MDI vs CSII in Preschool children*

This is a randomized trial, lasting 12 months involving 16 children with a mean age 4.4 ±0.7 year (range 3.1-5.3 year). Originally 18 families were recruited, but 2 withdrew due to time reasons and other 2 families other did not complete the 1 year study.

Instruments used were Beck depression inventory (BDI) used to assess presence and intensity of parental symptoms and Brief symptoms inventory (BSI); Child Behavior Checklist

(CBCL) used to measure behavior problems and social competencies of children; Pediatric inventory for parents (PIP) measured frequency and difficulty of stress associated with caring for a child. Pediatric quality of life inventory (PedsQL) was used to assess health related QoL.

Results showed BDI, BSI and CBCL within normal limits at baseline and follow up (6 months); PIP showed that MDI children parents were more stressed. For DQoL a significant decrease of diabetes related worry in CSII group when compared to MDI parents was shown. Children on CSII do not seem to have increased problems related to wearing the pump. Parents of the CSII group reported a significant decrease in diabetes-related worry, while parents of the MDI group reported an increased frequency of stress associated with their child's medical care. Authors state that for young children with T1DM, CSII is associated with higher treatment satisfaction and improved quality of life.

Nuboer et al (2008) - *MDI vs CSII 4 to 16 years*

This is a before after study. This is stated by authors to be an "open, parallel, randomized controlled prospective comparative" study lasting 14 months. It was completed by 38 patients aged 4–16 years following a 3.5-months run-in phase.

Pediatric Quality of life Inventory (PedsQL 4.0, Dutch version) was taken from all parents and from children older than 5 years (37 out of 39). Disease impact scores were obtained from parents only, using a modified Diabetes Quality of Life Questionnaire (DQOL) (last 4 impact questions designed for children were cut). A single psychologist interviewed parents and scored every 3.5 months. Data showed significant improvement in PedsQL and impact scores after pump treatment.

Data show that quality of life and impact of disease scores are improved by pump treatment in comparison to regular treatment with four daily insulin injections. PedsQL scores obtained from children and parents improved and impact of disease scores obtained from parents decreased significantly.

Skoseberg et al (2008) - *MDI vs CSII in population 7- 17 years*

This investigation was a multicenter study with nine participating pediatric departments in Sweden. The study was stated to be a "randomized, open study". One group received CSII and the other group received MDI treatment. Seventy-two children/adolescents (7–17 year of age) were enrolled and stratified by gender and puberty (prepuberty and puberty).

Approximately half of the patients were treated with MDI and the other half received CSII. Patients were followed for 24 months with clinical visits at the entry of the study and after 1, 6, 12, and 24 months. During these visits the patients/parents answered the Diabetes Treatment Satisfaction Questionnaire (DTSQ) designed to assess satisfaction with diabetes treatment regardless of the type of treatment. It consists of eight questions that are answered on a 7-point scale (range 0–6). Six items contribute to the treatment satisfaction score, and two items assess perceived frequency of hyperglycemia and hypoglycemia. Higher scores on the satisfaction scale indicate greater satisfaction. Higher scores on the hyperglycemia and hypoglycemia items indicate greater problems.

Treatment satisfaction was found to be significantly higher in the CSII group compared with the MDI group after 1 month of treatment and continued to be higher throughout the study (Fig. 2). This difference was more pronounced after every subsequent study visit (except between 6 and 12 months). After 1 month of treatment, the satisfaction score for the CSII group was 31.5±1.4 and 28.4±1.8 for the MDI group, p=0.01. At 24 months, the scores were 33.1 ±0.9 and 27.5±2.0, respectively, p=0.001.

Muller-Godeffroy et al. (2009) - *MDI vs CSII population 8-16 years*

This is a multi-centre prospective pre/post-study with children (53 girls, 64 boys, age 10.5 ± 3.7 years, mean ± sd) and main carer from 18 German diabetic centres.

Twenty-five children aged 8–11 years and 63 adolescents aged 12–16 years and their parents, plus 29 parents of children aged 4–7 years completed standardized questionnaires on generic and diabetes-specific quality of life (QoL), generic parenting stress, mealtime behavior, fear of hypoglycemia and family conflict immediately before and 6 months after transition to CSII.

Patient-reported outcomes were assessed by standardized questionnaires: KIDSCREEN10-Index, (KINDLR); Health-related quality of life (HRQOL); Generic as well as diabetes-specific QoL was assessed. Patients 8 years and older completed the KIDSCREEN-10 Index and the diabetes-specific module (KINDL-DM) of theKINDL-R. Parents of younger children aged 4–7 years proxy-reported on their child's QoL, using the KINDL-R and KINDL-DM.

Diabetes-specific QoL of children transitioned to CSII increased significantly in all age groups, with moderate to large effect sizes (children aged 4–7 years: Cohen's effect size d = 1.3; 8–11 years: d = 0.9, adolescents 12– 16 years: d = 0.6). Parents reported reduced

frequency ($P < 0.01$, $d = 0.4–0.7$) and difficulty ($P < 0.01$, $d = 0.3–0.6$) of overall parenting stress and decreased worries about hypoglycaemia ($P < 0.01$, $d = 0.4–0.6$). Parents of younger children (4–7 years) reported reduced problems with nutrition management (frequency: $P < 0.001$, $d = 1.1$; difficulty: $P < 0.05$, $d = 0.7$). Authors conclude that CSII may have substantial psychosocial benefits.

Hilliard et al (2009) - *MDI vs CSII 8-18 years population*

This is a before/after study aimed at understanding QoL with pump and psychosocial factors that helps in the successful use of CSII.

Fifty-three (53) parent–child dyads completed questionnaires on four occasions prior to and following the transition from MDI to CSII. Questionnaire assessed QoL, family environment, depressive and anxiety symptoms, and medical and demographic information. The Diabetes Quality of Life for Youths scale measured child-report of health-related QoL with 53-items: scores from the three subscales (Impact, Worries, and Satisfaction) and a Total QoL sum score were used.

Elements of children's QoL significantly improved after the transition and improvement was predicted by psychosocial, medical, and demographic characteristics. Results also indicates that individual and contextual factors may play a role in QoL as children transition to the insulin pump (this may give information for candidacy for transition to the pump). In unconditional models (i.e., models with no Level-2 predictors of change trajectories), two scales of the health related QoL measure (Satisfaction and Impact) improved from prior to the transition to insulin pump therapy through 12 months after the transition. There was no main effect change of the trajectories of Total QoL or the Worries subscale.

Pankowska et al. (2010) - *MDI vs CSII in >7 year population*

This is RCT. After a 3-week HI MDI run-in involving 61 children aged no more than 7 years, they were randomized to IAsp MDI or HI MDI for 26 weeks. Authors' aim was to compare basal–bolus multiple daily injection (MDI) therapy with mealtime insulin aspart (IAsp) or human insulin (HI) (both with basal NPH insulin), or of continuous subcutaneous infusion (CSII) with IAsp. Beside clinical outcomes, treatment satisfaction of in preschool age children with type 1 diabetes mellitus was also measured.

Caregiver treatment satisfaction was evaluated using a World Health Organization questionnaire with 7-point scale answers based on the World Health Organization Diabetes Treatment Satisfaction Questionnaire (DTSQ), with modifications to address the caregivers rather than children. It had eight questions with 7-point scale answers. Parents were given the questionnaire at the beginning and end of treatment.

After 26 weeks of treatment with IAsp CSII, IAsp MDI, or HI MDI, all metabolic control parameters remained unchanged and equivalent. Caregiver treatment satisfaction was higher

in parents who chose IAsp CSII pump therapy. IAsp CSII and IAsp MDI demonstrated a significant increase in treatment satisfaction during the trial, but the increase in mean treatment satisfaction total score was significantly greater for CSII compared to the IAsp and HI MDI groups and significantly greater for IAsp MDI compared with HI MDI. However both IAsp, injected or administrated continuously by pump, and HI MDI are safe and well tolerated.

Authors state that their study has limitations in that allocation to MDI groups was determined by numerical randomization, but allocation to CSII was based on parent choice. Consequently, the results regarding caregiver satisfaction in the CSII group could be due to the fact that parents were very motivated in using CSII, nonetheless this selection reflects the type of families which would be referred to CSII in actual daily practice. Diabetes' duration was different between the groups. Although not compared statistically, the CSII group had on average a longer duration of diabetes compared with the injection groups.

Wu et al. (2010) - *MDI versus CSII in adolescents*

Adolescents and their parents completed questionnaires assessing quality of life and parenting stress. Stress Index for Parents of Adolescents Parenting stress was assessed with the Stress Index for Parents of Adolescents (SIPA). The SIPA measures the amount of stress experienced by parents and contains 112 items rated on a 5-point Likert-type scale. It has been standardized for use with parents of adolescents aged 11–19. The Diabetes Quality of Life measure (DQoL) was modified for use with adolescents. It assesses satisfaction, impact, worry about treatment and worry about social issues. Metabolic and psychosocial outcomes did not differ significantly between adolescents using pump therapy and adolescents using MDI. So does parenting stress.

OOi et al. (2011) *MDI versus CSII*

This was a retrospective cohort study involving 22 patients with Type 1 Diabetes started on insulin pump therapy between april 2004 and december 2009. Eighteen (18) patients were enrolled and all of them were initially on multiple daily injections of long and short acting insulin. Eight questions submitted with a face to face interview, either before and after the clinic visit. 15 out of 18 patients interviewed.

6.4 Conclusions

There is no reliable evidence about better, equal or worst quality of life with SAP (CSII+CGMS) versus MDI therapies in our target population. In the systematic review only one study could be selected (Almadazeh 2007) fulfilling our selection criteria, but it has indeed several limitations that we describe below.

It is uncertain if we can define the use of CSII+CGMS used at baseline and every three months as sensor augmented pump therapy. In the text the comparator is almost always referred to as "CSII" by the authors. In the abstract and conclusion they always name the device as "CSII". Besides this in the text a detailed description on the use on CGMS is provided. Parents had two days training about glucose sensor placement, calibration of the sensors etc. They had to perform at least four self-monitoring of blood glucose per day and enter this values into the CGMS monitor to obtain correlation coefficient between SMBG and the CGMS values.

The before-after design is weak, the sample of patients is very small and purposely selected so that children's carers had optimal diabetes care skills and the right psychosocial features to improve compliance on CSII. The target population is a subgroup (pre school children) of our 0-18 years population. Conclusions could be drawn from this study they would only be imputed to this subgroup. Again this subgroup - very young children with type 1 DM - has very specific problems connected to diabetes daily management and glycemic control e.g. physical activity is not predictable, frequent viral infections, limited communications skills.

Besides the weak design, the study has also other sources of bias. Of the 19 patients who were initially screened, 5 (26%) were not selected, reasons for exclusions being inability to tolerate the pump and parents' difficulty with CSII operational tasks. The group of selected patients is thus particularly capable and motivated in the use of the pump. It is not stated if the pump has been purchased by the parents or given for free by the hospital. This may imply that the socio-economic status of families included is high as they can buy the pump by themselves. Last, the study has been financed by Novordik and Medtronic, which are pumps producers.

As concerns to CSII versus MDI, in the report by Cummins authors included comparative studies from 2005 to 2007 that considered QoL as an outcome and measured it with standardized instruments. Authors state that more evidence is needed, although CSII regime does not seem to deteriorate QoL. The comparative studies from 2007 to 2011 that we selected to complete the overview of the evidence on CSII versus MDI, have weak designs and many limitations, but may show that some aspects of quality of life among pump users improve significantly when compared with MDI patients. Stronger designs and studies that differentiate among different group of ages (preschool children, children 6-11 and adolescnts) are needed. These group may indeed have different QoL results in terms of satisfaction, worry, impact of treatment and those differences should be accounted for in future studies.

The qualitative interviews and materials reported by the HTA report by Coté et al (2004) and Cummins et al (2010) show that in a subgroup of paediatics patients (preschool children and children 6-10) the use of the pump can have a positive impact on QoL in terms of life style and management of the diasese when the principal carer is absent (e.g. at school).

Comparative context-specific clinical studies are needed to confirm this, which comes from qualitative interviews with parents of children who already use the pump in other context (that is Uk and Quebec/Canada).

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7.COSTING AND ECONOMIC EVALUATION

Systematic review of economic studies

Objectives

We decided to carry out a systematic review of economic evaluations comparing the costs and outcomes of SAP with MDI in the hope of informing and populating a possible economic model

Literature search

We carried out a search of the literature on the following databases: MEDLINE, EMBASE, Cochrane Library (including see below). Details on the search strategy are provided at Appendix 1.

We also consulted the following databases:

- EconLit
- INAHTA
- CINAHL
- Health Technology Assessment Database (HTA Database - Centre for Reviews and Dissemination CRD);
- Database of Abstracts of Reviews of Effects (DARE - Centre for Reviews and Dissemination).

  Current Controlled Trials (www.controlledtrials.com - con link ad altri databases) e

  National Research Register (www.update-software.com/National/nrr-frame.html).

  Inclusion criteria

We decided to include all economic evaluations based on all types of economic analysis (Cost-effectiveness Analysis - CEA, Cost Utility Analysis - CUA, Cost-consequence analysis - CCA; Cost Minimisation Analysis - CMA) comparing the use of SAP and MDI in people aged up to 18, published in English, Italian, French or Spanish from 1 January 2005 to 1 March 2012.

Study selection and Data extraction

We used ProCite programme (version 5 for MS Windows) to manage the references to the studies. The selection of the studies to be included followed these steps:

1. exclusion on the basis of title and abstract;
2. full text retrieving of the potentially iteresting studies;
3. reading of the selected articles and application of the inclusion criteria.

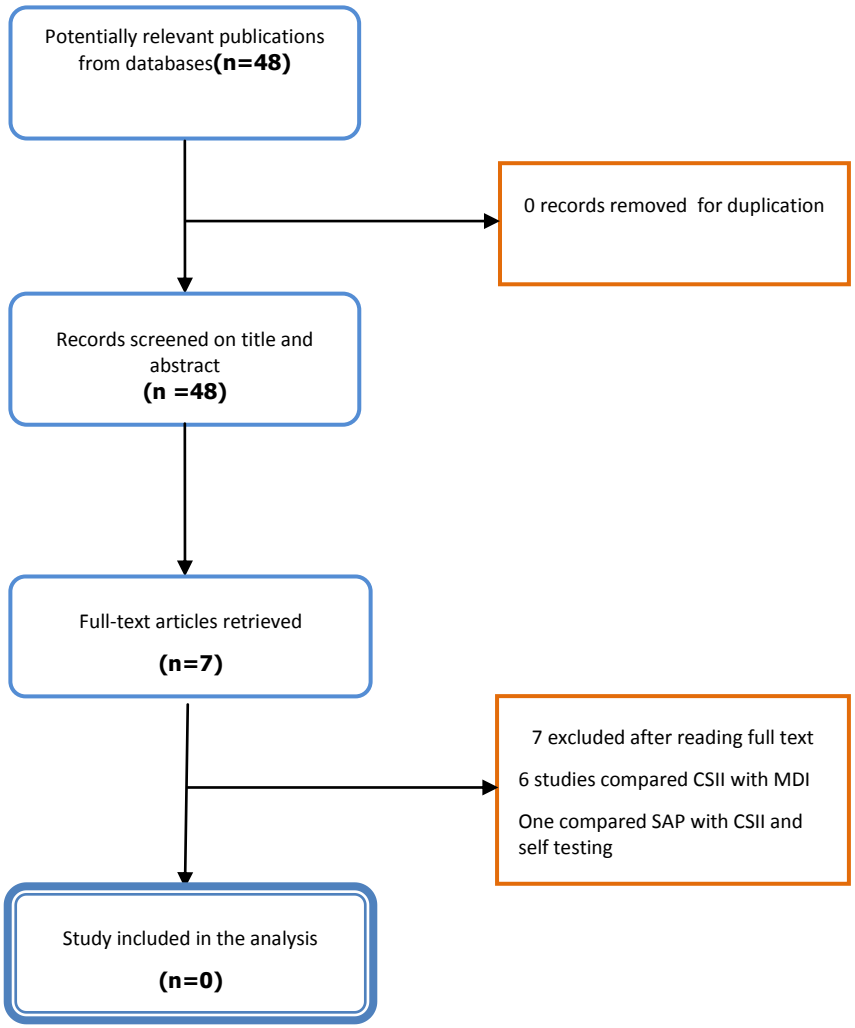
It was our intention to extract data from the selected using a standardised extraction sheet is double and assess Methodological quality using the checklist for economic evaluations of health programmes [Drummond 1997].

Results

We identified 48 records of studies possibly meeting our inclusion criteria. After reading titles and abstracts we retrieved the complete text of 7 papers.

Six of the seven papers compared various aspects of CSII and MDI. One (Rubin 2009) compared SAP with CSII. No studies fulfilled our inclusion criteria

The list of the seven excluded studies is at Appendix 2.



Discussion

We were disappointed at our inability to identify economic evaluation with comparisons relevant to our review. However, given the relative novelty of SAP and its potential developments we were not surprised. It is important in the future that such evaluations be carried out especially with evaluation designs which incorporate QoL elements for recipients of SAP (i.e. CUA).

Survey on costs and use of the device in the participating regions

Objective

To collect information on:

- Diffusion of Sensor Augmented Pump in the Region and Provinces participating in the project;
- Direct and indirect costs related to the Sensor Augmented Pump and the Multiple Daily Injections therapies.

Methods

Each regional representative identified the pediatric diabetic centers in their Region. A letter from the Agenas Director presenting the survey was sent to all the identified centers with a brief questionnaire aimed at ascertaining use, or not, of the SAP. Each Region and province centers with SAP were identified and a detailed questionnaire on costs was sent to them (see Appendix 17).

Results

Collected data and information were about number of children and adolescents treated with SAP or MDI in year 2011, health personnel and hours involved in the various steps of each therapy, type and price of the device. Twentysix (26) centers delivering SAP were identified in the participating regions and provinces. Fourteen centers sent their questionnaire back to the regional representatives (see table 1). We had a 50% answering rate.

Centers involved in the survey

Tab. 1 Number of involved centers and number of responding centers

REGIONS	NO of centers with SAP	NO of respondents to SAP survey
EMILIA ROMAGNA	**7**	**4**
LAZIO	**4**	**3**
LOMBARDIA	**9**	**0**
TOSCANA	**2**	**2**
TRENTO	**1**	**1**
SICILIA	**3**	**3**

We based our analysis on the results from 11 questionnaires, as three of the responding centres gave unclear and incomplete answers to this question.

NO. of patients broken down by age		
< 5 years	**5-13 years**	**13-18 years**
342	1559	1606

NO. Of patients per age range broken down by type of therapy					
MDI <5 yrs	MDI 5_13 yrs	MDI 14_18 yrs	SAP <5yrs	SAP 5-13 yrs	SAP 14-18 yrs
201*	1015*	922*	22	64	75

*two centers did not state the number of patients treated with MDI

NO. Of patients per age range who tried the SAP therapy		
< 5 years	5-13 years	13-18 years
10	46	60

NO. Of patients per age range who maintained the SAP therapy		
< 5 years	5-13 years	13-18 years
11	42	55

Human resources and SAP

We asked centers about the number of health personnel and hours per human resource spent in one month for treating 1 patient during the *trial period*. Procedure was divided into three steps: training for patient/parents about using SAP, set up of the device and follow up. Three categories of health personnel – physicians, nurses, dieticians - were identified, plus the technician sent by the Industry who, in some cases was reported to be actively involved in the training. The average time for trial period was 2 months (1 center did not respond). Minimum time 1 month, maximum 3 months.

Average number of PHYSICIANS and hours/month for training/set up and Follow up

Training	
Avarage NO. of physicians	Avarage No. of hours per month/patient
1,3	6,6
Set up	
Avarage NO. of physicians	Avarage No. of hours per month/patient
1,3	4,2
Follow up	
Avarage NO. of physicians	Avarage No. of hours per month/patient
1,5	5,0

Average number NURSES and hours/month for training/set up and Follow up

Training	
Avarage NO. of nurses	Avarage No. of hours per month/patient
0,7	2,0
Set up	
Avarage NO. of nurses	Avarage No. of hours per month/patient
0,7	1,6
Follow up	
Avarage NO. of nurses	Avarage No. of hours per month/patient
0,8	1,3

Average number DIETicians and hours/month for training/set up and Follow up

Training	
Avarage NO. of dietarians	Avarage No. of hours per month/patient
0,9	3,3
Set up	
Avarage NO. of dietarians	Avarage No. of hours per month/patient
0,6	1,0
Follow up	
Avarage NO. of dietarians	Avarage No. of hours per month/patient
0,8	1,6

Average number TECHNICIANS and hours/month for training/set up and follow up

Training	
Avarage NO. of technicians*	Avarage No. of hours per month/patient
0,8	5,1
9 out of 11 centres stated to involve Producer's technicians in this process	
Set up	
Avarage NO. of technicians	Avarage No. of hours per month/patient
0,9	2,8
Follow up	
Avarage NO. of technicians	Avarage No. of hours per month/patient
0,6	1,3

Time spent to follow up patients once they pass to SAP therapy after the trial period are reported in table below. Time is intended for 3 months of therapy. Twelve centers responded to this question in a complete manner.

Follow up	
Avarage NO. of physicians	Avarage No. of hours per month/patient
1,4 (range 1-3)	7,7

Follow up	
Avarage NO. of nurses*	Avarage No. of hours per month/patient
1,8 (range 1-2)	2,9

*Nurses are involved in just 8 out of 12 responding centers

Follow up	
Avarage NO. of dietarians*	Avarage No. of hours per month/patient
1	2,6

*All but one center (11/12) involved dietarians in the follow up.

Human resources and MDI

Four centers gave incomplete answers, so tables are based on 10 questionnaires.

Average number of PHYSICIANS and hours/3 monthsfor Training and Follow up

Training	
Avarage NO. of physicians	Avarage No. of hours
1,4 (1-3)	3,5
Follow up	
Avarage NO. Of physicians	Avarage No. of hours
2,2 (1-4)	1,6

Information on the device

All the providers stated that the device was free for the trial period and the consumables as well. Only 8 centers reported information on the price of the device. This was an average of **3912,5** Euros, ranging from a maximum of 6500 to a minimum of 3600. Warranty was 4 years (average).

Below is the list of the type of devices the centers declared to use.

- Medtronic VEO e animasvibe
- Medtronicguardianreal time
- Medtronic e Animas (movi)
- Roche e Movi
- Paradigm VEO Medtronic Italia
- Animasmedtronic e Roche
- Medtronic
- Medtronic VEO
- Paradigm e ParadigmVeomedtronic

- Paradigmreal time – Medipress
- paradigmreal time medtronic
- Medtronic/Roche
- Veomedtronic
- Paradigm e Paradigmveomedtronic

Conclusion

Although partial our data show that the device has limited spread and use as yet in the participating Italian regions. However, we have no reason to believe that the situation may be any different in the other regions of Italy. The potential of SAP for a painless and relatively effortless good glycaemic control is recognized. Possible factors limiting its use are novelty, limited specialized facilities and "personality fit" in adolescents, a most difficult age group to manage. We have collected sufficient data for the Italian SSN to start thinking about carrying out an economic evaluation privileging QoL aspects given the very delicate nature of acceptance by adolescents of such potentially bulky and distinguishing equipment as the components of the SAP devices. Such an evaluation should also aim to identify potential age groups or personality types which are more likely to make best use of such expensive but important devices.

9. DISCUSSION AND FINAL RECOMMENDATION

The analysis of the evidence included in the systematic review on effectiveness and safety of SAP versus MDI shows that the use of this technology as a more effective and safe alternative to MDI has not yet been demonstrated. There is the need to generate evidence with a reliable design and a appropriate number of diabeticspatients included to answer the study question. One point to bear in mind is that different age groups in the range 0-18 year population have different clinical and psychosocial features and could have very different clinical outcomes. From an economic point of view data on costs show that SAP is a very expensive investment. To justify such an investment compared to the existing well-tried MDI more data is needed, especially on the impact of the new technique on QoL of DM1 sufferers.

There is no definitive evidence of any enhancements of quality of life using SAP versus MDI. We were able to retrieve one study only measuring this outcome with a standardized instrument, but it has several limitations that prevents us from drawing any conclusions on QoL. However, qualitative interviews (see HTA reports by AETMIS and NICE - Coté B et al. 2005 and Cummins, 2010) have shown that parents of children using CSII (not SAP) are satisfied with it and would continue to use it due to greater life style flexibility for them and their children.

The strapping on the body of slim but still bulky equipment and its maintenance is both a demanding and aesthetically onerous task, especially in the elder children and adolescent age group. In younger age groups it is likely that considerable parental input would be necessary to ensure compliance. Utimately acceptability of the device will determine its effectiveness. Data to identify which kind of patient in the age group 0-18 is most likely to benefit from such an expensive investment will also have to be generated.

Clearer guidelines for the appropriate use of SAP should be produced and the evidence base on the use of these expensive and potentially important devices should be developed.

The following questions should be answered by empirical studies:

- What are the effects of SAP compared to other forms of T1DM management?
- How acceptable is SAP to T1DM patients and their families?
- Which category of patents with T1DM are most likely to benefit from SAP?

10. FUNDING

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Agenas takes the sole responsibility for the finalform and content of this HTA report. The views expressed herein do not necessarily represent the views of the ItalianMinistry of Health or any regional government.

11. COMPETING INTERESTS DECLARATION

Authors declare that they will not receive either benefits or harms for the publication of this report.

Dr. Lorenzo Lenzi participated to two Congresses sponsored by the producers and does not have any other conflict of iterests. None of the remaining authors have or have held share, consultacies or personal relationships with any of the producers of the devices assessed in this document.

Glossary and abbreviations

Closed-loop system: it consists of three components: a real-time continuous glucose monitoring device (CGM, see below) to measure glucose concentration, a titrating algorithm to determine the amount of insulin to be delivered and an insulin pump delivering computed insulin doses. Closed-loop systems could deliver insulin according to real-time changes in glucose levels. Generally speaking, one can distinguish between "fully-closed loop" and "semi-closed loop" systems. In a "fully-closed loop system" insulin is delivered in a fully automated fashion without information about the time or size of the meal or, for example, exercise: insulin delivery is based solely on the evaluation of glucose excursions measured. On the other hand, "semi-closed-loop" systems are informed about a meal and its size and may generate advice on insulin delivery, which is released by the patient (open loop mode).

Continuous subcutaneous insulin infusion (CSII): continuous administration of insulin under the skin by a cannula connected to an insulin pump. This is also called insulin pump therapy.

Continuous glucose monitoring (CGM) or Continuous glucose monitoring systems (CGMS): it measures interstitial fluid glucose levels to provide semi-continuous information about glucose levels throughout the day, the direction, magnitude, duration, frequency and causes of fluctuations in blood glucose levels. Generally.

Continuous Glucose Monitoring devices or systems can be discriminated in systems that measure the glucose concentration during a certain time span: the information is stored in a monitor and can be downloaded later (the Holter-type) and real time systems that continuously provide the actual glucose concentration on a display. The continuous glucose monitoring system essentially comprises of a needle (containing a glucose-dependent enzyme generating glucose-dependent electrical currents) which has to be inserted into subcutaneous fat (also non-invasive systems exist that aim to measure the glucose concentration in exudate that is triggered by iontophoresis), a transmitter connected to the needle (translating and relaying data by infrared or wi-fi technology) and a separate receiver that displays the glucose profile. Calibrating the continuous glucose monitoring system with a number of self-monitoring of blood glucose measurements is necessary. Those systems can be used continuously or intermittently (e.g. a couple of days per month or in intervals of three days. With real-time continuous glucose monitoring systems, glucose thresholds can be set with an alarm going off with glucose levels outside the target area and thresholds can also be set using rates of change.

Hyperglycaemia: condition characterised by too high a level of glucose (sugar) in the blood, for example in cases when diabetes is out of control. It occurs when the body does not have enough insulin to turn glucose into energy, and/or store it, or the insulin present in the body is not used up.

Hypoglycaemia: abnormally low concentration of glucose in the blood, which can cause muscular weakness and inco-ordination, mental confusion and sweating. If severe it may lead to hypoglycaemic coma. Hypoglycaemia most commonly occurs in diabetes mellitus as a consequence of relative insulin excess from insulin injection or insulin secretagogue therapy, associated with insufficient intake of carbohydrate, excess energy expenditure, and/or other blood glucose-lowering agents, such as alcohol. It is treated by administration of glucose or glucagon.

Multiple daily injections (MDI): an intensified form of insulin regimen based on a combination of one or two injections of long-acting (basal) insulin, with injections of short-acting insulin at mealtimes.

Self-monitoring blood glucose (SMBG): it is the conventional method to self-assess glucose concentrations in the blood; it is achieved by finger-capillary blood sample, where the blood glucose is usually measured employing a small handheld device - a blood glucose meter. SBGM provides a value of the blood glucose at the moment when the blood is sampled. Although this method has been found to provide an accurate estimate of the glucose level, marked fluctuations in blood glucose can be missed hampering optimal glycaemic control. In addition, intensified blood glucose self-monitoring requires a number of finger punctures per day ($\geq$ 3) to assess the glucose concentration.

Sensor augmented insulin pump therapy (SAP): is a convergence of two technologies, the CSII and real-time continuous interstitial blood glucose monitoring (CBGM).

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease, characterized by absolute insulin deficiency resulting from immuno-mediated destruction of insulin-producing β-cells in the pancreatic islets of Langherans. The etiology of the disease is unclear, although a genetic component is evident.

Interstitial Fluid Sensor (ISF) device can be inserted under the skin for up to three days and monitors glucose levels.

List of abbreviations	
AP	Artificial Pancreas
BMI	Body Mass Index
CSII	Continuous Subcutaneous Insulin Infusion
CGMS	Continuous Glucose Monitoring System
DCCT	Diabetes Control and Complications Trial
HbA1c	glycated haemoglobin
HTA	Health Technology Assessment
IIT	Intensive InsulinTherapy
MAGE	Mean amplitude of glycaemic excursions
MDI	Multiple Daily Injections
QOL	Quality of Life
RCT	Randomized Controlled Trial
SMBG	Self-Monitoring of Blood Glucose
SR	Systematic Review
T1D	Type 1 Diabetes Mellitus
T2D	Type 1 Diabetes Mellitus
SDO	Scheda di Dimissione Ospedaliera
AFT	Assistenza farmaceutica Territoriale
DRG	Diagnosis Related Group

Appendices

APPENDIX 1

Producers involvement

Several sources were consulted (from march to July 2012) to identify producers/distributors of SAPs, including "Health Comparison Systems" database by ECRI, articles and publications on web site Diabetes Association (http://professional.diabetes.org, last access 18.09.2012) and the results of the survey described in Chapter 5. The identified producers/distributors were contacted following the indication suggested on the producer's official web site. Four, on five producers identified, answered by mail and established a personal contact, but only two provided support and technical information, one producer did not submit any response. Three SAPs producers were included in our study: Animas, Medtronic and Roche.

They were asked to provide information about the following topics:

- Description of the technology and material from which it is possible to understand the functioning of the device (Datasheet and technical information);
- Studies or articles that compare SAP with MDI in terms of:
  - Health outcomes:
  - Analysis and economic models;
  - Qualitative studies and / or quantities that indicate the data / information on the quality of life of patients (0-18 years) / relatives;
  - Studies related to equipment and procedures safety (eg, incident analysis and case studies).

Suppliers contacted	Way to establish contact	Established Contact	Support and technical information provided
Animas	by mail	Yes	No
Insulet Corp.	by mail	Yes	No
Medtronic	by mail	Yes	Yes
Roche	by mail	Yes	Yes
Sooil	by mail	No	No

APPENDIX 2

Detailed description of the technologies

- **Animas SAP system**

Animas system includes the CSII Animas® Vibe™ (produced by Animas Corporation) and the CGM Dexcom G4™ (produced by Dexcom and distributed by Animas).

Animas® Vibe™ is a CSII and it needs to confirm and calibrate (twice a day) the reading with a fingerstick test. Dexcom G4™ is a CGM and is made up of three components: sensor, transmitter and receiver. Dexcom G4™ sensor is introduced underneath the skin of the patient through a small needle, approved for a maximum of 7 continuous days of use. The glucose reading takes place every 5 minutes. Data about glucose levels are transmitted to the insulin pump by Dexcom G4™. Data are received by the pump that displays the last glucose level value, maximum and minimum values and the overall trend of the last 1, 3, 6, 12, and 24 hours. Alarms for high and low levels are customizable by the patients, which is therefore able to set personal thresholds. In addition, a rate of change alarm and a non-adjustable alarm set at 3.1 mmol/L to prevent hypoglycemic accidents are present.

Insulin doses can be delivered in both basal and bolus modality. Basal administration of insulin ranges from 0,025 U/hr to 25,0 U/hr. Bolus ranges from 0,05 U to 35,0 U [http://multivu.prnewswire.com/mnr/animas/49461/docs/49461-Animas_Vibe_Fact_Sheet_new.pdf, last access on 16.07.2012].

Animas SAP system includes also a software named Diasend witch allows the transmission of data to a personal computer in order to store all the measures of glucose concentration taken.

Technical information here reported have been collected through the internet, browsing the official Animas Vibe™ webpage, Medical Device Repertory of Italian Ministry of Health and other specialized websites as American and European Diabetes Association.

- **Medtronic SAP system**

The Paradigm® Veo™ (554/754) (produced by Medtronic) includes in a single device CSII and CGM for the management of diabetes. Paradigm® Veo™ 554 differs from 754 only in the reservoirs capacity the first of 1,8 ml and 3 ml the latter.

Paradigm® Veo™ is composed of:

- MiniLink™ transmitter: a small device that is connected to the Enlite® glucose sensor and continuously measures glucose levels in the body. When connected to the sensor that is inserted in the body, the transmitter automatically initializes the sensor and begins to periodically send glucose data to the Paradigm® Veo™ insulin pump via wireless using a radio signal;
- Enlite® glucose sensor: measures the glucose levels in interstitial fluid through a needle placed under the skin. Paradigm® Veo™ receives and displays glucose values provided by the sensor and delivers insulin present in the reservoirs located inside the pump;
- The infusion set and cannula can suit different shapes, sizes, and preferences;
- CareLink® USB, inserted into a pc allows data downloading from pump and report view in various formats. CareLink® is an online software program stored on the Medtronic server. [Corriveau 2008].
- The insertion of the Enlite® glucose sensor in an appropriate body area is the first step in using the device. Then the sensor is connected to the Minilink™ transmitter who wirelessly sends signals to the Paradigm® Veo™. Medtronic Paradigm® Veo™ displays continuous glucose values and stores this data so that it can be analysed to track patterns and improve diabetes management.
- Paradigm® Veo™ incorporates a bolus calculator called Bolus Wizard® for setting or suggesting the bolus amount. It is possible to select various bolus infusion:
- Normal bolus: an insulin bolus is immediately delivered (programmable with variables increments from 0,025 to 75 U).
- Dual-wave bolus delivers a combination of an instant normal bolus and a next square wave bolus; the amount of square wave bolus is delivered uniformly in a programmable time.
- The square wave bolus delivers insulin uniformly over a prolonged period of time, between 30 minutes and 8 hours. This type of bolus may be used for the delivery of insulin for the management of a prolonged meal.

Paradigm® Veo™ is equipped with a network of checks and security systems and if detects an unusual condition as to be careful, emits a beep or a vibration intermittently indicating the event.

It's possible to customize the alarm settings to help patients to optimize their glycaemic control and

to set predictive alerts 5, 10, 15, 20, 25 or 30 minutes before reaching a high or low glucose limit, allowing to take early action. The risk of hypo-or hyperglycaemia is minimised thanks to additional protection with alerts whenever patient are crossing the high or low glucose limit, [Bode 2004, Garg 2006]. In addition, Medtronic Paradigm® Veo™ is equipped with Low Glucose Suspend (LGS) function that suspends the infusion when patient doesn't respond to the warning for some reason.

Paradigm® Veo™ is provided with alarms system related, for example, to: low battery, reservoir almost empty, calibration error, no dispensing (see Main technical details of SAPs table for details). It is possible to select two types of alert for alarms, special conditions and programming: a vibrate (silent) alert, or an audible beep alert. There are three beep types: long, medium and short tones. Medtronic Paradigm® Veo™ is able to storage and show the history of alarms, errors or warning.

The main screen displays the time and the icons for the indication of the charge of the reservoirs and batteries and activation of the special features of the insulin pump. It allows graphics mode for viewing glucose trends over time.

It's also possible to use a radio frequency (RF) remote control for programming the bolus and the suspension at distance.

The calibration of the sensor is a necessary procedure to real-time conversion of the electrical measurements in blood glucose levels.

For the calibration of the sensor it is necessary to control the blood glucose using a traditional glucometer and then enter the values in the Paradigm® Veo™ control unit.

For best accuracy of the sensor it is recommended to perform the calibration three or four times a day. Using the "calibration timer" it is possible to set a timer that alerts the need for calibration. The infusion set should be replaced every 2-3 days.

Technical information and datasheets were provided by Medtronic.

- **Roche Diagnostics SAP**

Roche Diagnostics SAP system includes Accu-Chek® Combo – CSII and glucose meter - (produced by Roche) and DexCom Seven® Plus – CGM - (produced by DexCom and distribuited by Roche).

Accu-Chek® Combo consists of a pump for continuous subcutaneous administration of insulin (Accu-Chek® Spirit Combo) and a glucose meter (Accu-Chek® Aviva Combo) integrating bolus advice, data management, data analysis, reminder functions and remote control of the

pump. Accu-Chek® Spirit Combo and Accu-Chek® Aviva Combo bi-directionally interact via Bluetooth.

Accu-Chek® Spirit Combo insulin pump has 5 programmable basal rates that can be personalized. The device can infuse four types of boluses: rapid bolus and standard bolus for immediate delivery, extended bolus for a delivery over a programmed period of time, multiwave bolus which combines fast delivery with delivery over a programmed period of time (see Main technical details of SAPs table for details). The pump is controlled by two microprocessors: master processor and supervisor processor. When a defect or problem occurs in the master processor, it is detected by the supervisor processor. The insulin is delivered from the cartridge through the infusion set tubing and cannula or needle into subcutaneous tissue. The adapter that connects the cartridge to the infusion set must be changed with at least every 10th cartridge change.

Accu-Chek® Aviva Combo blood glucose meter is able to determine the values of glucose in the blood and allows to remotely manage the insulin pump and also has an electronic diary that can process graphs, bolus calculator and set different reminders. It allows immediate display of glucose values and their temporal dynamics and assists in the detection of episodes of hyperglycemia and hypoglycemia. The system allows to view the past trends, future trends of blood glucose and the speed with which the blood sugar may increase or decrease. Data can be reported in graphical and tabular format for the last 7, 14, 30, 60 or 90 days. Bolus calculator has an algorithm focused on the control of blood glucose level for a calculation of the bolus tailored to each patient. All bolus recommended by the instrument are determined by current glucose values in relation to the target, influenced by the contribution of carbohydrates and the assessment of insulin boluses delivered in previous injections.

The DexCom Seven® Plus is a CGM made up of three components: sensor, transmitter and receiver. The sensor is indicated for detecting trends and patterns of glucose levels in adults. The sensor uses the electro-chemical glucose oxidase and continuously detects the concentration of glucose in interstitial fluid (ISF). It is placed under the skin via a needle and a safety device prevents the needle from accidentally falling out. The DexCom Seven® Plus sensor is approved for use up to 7 days and ensures an accuracy equal to 95.9% according to the grid of Clarke, with a total delay (lag time) between the blood glucose readings of the interstitial fluid and the reference values of venous blood measured by the laboratory (YSI) amounting to 8-11 minutes [Zisser 2009, Bailey 2009]. DexCom Seven® Plus could be used to monitor glucose in real time visualization or in blind. The transmitter connected to the sensor sends, via wireless, glucose readings every 5 minutes to the receiver with a communication range from 1.50 m. When connected to the sensor, the transmitter is fully waterproof and can be immersed in water for 30 minutes up to 1 meter deep. It has an integrated battery of silver oxide which does not need to be recharged. The receiver stores

the values and the information up to 30 days. DexCom Seven® Plus needs calibration with strips every 12 hours to ensure the performance of the device.

Technical information and datasheets were provided by Roche.

Main technical details of SAPs

	Animas Corp.	Medtronic	Roche Diagnostics
Device/model	Animas® Vibe™ (CSII) and Dexcom G4™ (CGM)	Paradigm® Veo™ 554/754 (includes CSII and CGM in a single device)	Accu-Chek® Combo: • Accu-Chek® spirit Combo (insulin pump CSII) • Accu-Check® Aviva Combo (glucose meter and remote control insulin pump) DexCom Seven® Plus (CGM)
Connection mode	Transmitter and sensor are connect wirelessly.	Paradigm® Veo™ and Enlite® glucose sensor are connect wirelessly.	Accu-Chek® spirit Combo and Accu-Check® Aviva Combo are connected via Bluetooth. Sensor and transmitter of the DexCom Seven® Plus are connect wirelessly. Accu-Chek® Combo and DexCom Seven® Plus are not connected.
Programs	4 adjustable programs for basal rate (12 different basal rate each in the 24-hour period): • Weekend • Weekdays • Exercise • Other		5 programs for basal rate: • Each profile can be divided into 24 different hourly basal rates. Adjustable in increments of: • 0.01 U (up to 1.00 U); • 0.05 U (up to 10.0 U); • 0.1 U (up to 25.0 U); The hourly minimum basal rate is 0.05 U with supply up to 0.0025 units of insulin every 3 minutes.
Infusion mode	Basal rate Bolus rate: • Normal bolus • Audio bolus (it allows to use the pump without looking at the screen display) • ezCarb bolus (it allows to calculate the bolus according to the quantity of Carbs eaten) • ezBG (it allows to calculate the bolus according to the current value of BG) • Combo bolus (used to split the bolus into a normal and extended bolus, for prolonged carbs absorption)	Bolus: normal bolus, dual-wave bolus and square wave bolus	Infuse 4 types of boluses: • **Rapid** bolus for immediate delivery; • **Standard** bolus for immediate delivery is adjustable in fixed increments of 0.1 U; • **Extended** bolus dispenses during a predetermined period with increments of 0.1 units and the duration of the bolus can be programmed intervals from 15 minutes up to 12 hours; • **Multiwave** combines the immediate with delivery during a predetermined period of time adjustable in intervals of 15 minutes (from 15 minutes up to 12 hours) with increase of 0.1U

	Animas Corp.	Medtronic	Roche Diagnostics
Alarms	Warnings: • Suspend • No cartridge detected, deliveries disabled • Low battery • Low cartridge • Exceeds max bolus • Exceed max TDD • Exceed max 2-hour delivery • Exceed max basal • Delivery cancelled due to low cartridge • No prime no delivery • Bolus delivery canceled Alarms: • Occlusion • Empty cartridge • Replace battery • Call service • Auto-off	• Hypo- and hyperglycaemia • Variation's rate • Predictive alarms • maximum delivery • empty reservoir • Battery Out Limit Alarm • Bolus Stopped Alarm • Button Error Alarm • Check Settings Alarm • E (Alarm) Explaination • Empty Reservoir Alarm, • Fail Batt Test Alarm • Finish Loading Alarm • Is Priming Complete? • Alarm, Low Glucose Alarm • Max Delivery Alarm • Max Fill Reached Alarm, Motor Error Alarm • No Delivery Alarm • No Reservoir Alarm • Off No Power Alarm • Reset Alarm • Weak Battery Alarm	• Glucose level excursions • Pump occlusions • Empty cartridge • Low Battery • Auto off • End timers micro (only for the reserve pump) • Mechanical failure • Electronic failure • Power failure • Cartridge error • Empty set • Transfer failed • Language error • Hyperglycemia • Hypoglycemia • Rapid growth or rapid decline of blood glucose
Automatic suspend of glucose infusion		Low glucose suspend (LGS), suspends the infusion when patient doesn't respond to the warning for some reason	
Alerts	• Active basal program empty • Temp basal minimum rate • Suspend • Low BG • High BG • Clear program basal segments • Basal program display change • Basal delivery suspended	• SilenceAuto Alert, • Off Alert, • Bad Sensor Alert, • bad Transmitter Alert, Change Sensor Alert, • Charge Transmtr Alert, • Cal Error Alert, • Fall Rate Alert, • High Predicted Alert, • High Sg Alert, High Xxx Mg/Dl (Xxx = Sg Measurement) Alert - (or mmol/L), • Lost Sensor Alert, • Low Battery Alert, • Low Predicted Alert, • Low Reservoir Alert, • Low Sg Alert, • Low Transmtr Alert, • Meter Bg By Xx:xx Alert, • Meter Bg Now Alert, • Rise Rate Alert, • Sensor End Alert, • Sensor Error Alert, • Weak Signal Alert	• Low cartridge • Low battery • Check time and date • Call toll free number • Temporary basal rate cancelled • Temporary basal rate terminated • Bolus cancelled • End function (this setting is specific for each country and may not be visible on the pump)
Accessories	• Carry pouch	• CareLink therapy management software • Remote control • Glucometer	
Disposables parts	Cartridges and infusion for single use only	Cartridges and infusion for single use only	

APPENDIX 3

OVERVIEW SEARCH STRATEGY

Continuous subcutaneous insulin pumps

The Cochrane Library

1. Infusion Pumps[mesh descriptors]
2. "Continuous Subcutaneous Insulin Infusion":ti,ab,kw
3. csii: :ti,ab,kw
4. “Insulin Infusion Systems” [MeSH descriptor]
5. "insulin infusion" NEAR/2 (pump* or device* or system*:ti,ab,kw
6. 1/5 OR

PUBMED

1. "continuous subcutaneous insulin infusion"[Title/Abstract]
2. "Infusion Pumps"[Mesh]
3. "infusion pump"[Title/Abstract]
4. "infusion pumps"[Title/Abstract]
5. "insulin infusion"[Title/Abstract]
6. "insulin infusion device"[Title/Abstract]
7. "insulin infusion devices"[Title/Abstract]
8. "insulin infusion pump"[Title/Abstract]
9. "insulin infusion system"[Title/Abstract]
10. "insulin infusion systems"[Title/Abstract]
11. "insulin infusions"[Title/Abstract]
12. "Insulin/administration and dosage"[Mesh]
13. 1/12 OR
14. "diabetes mellitus"[Title/Abstract]
15. "Diabetes Mellitus"[Mesh]
16. 14 OR 15
17. 13 AND 16
18. cochrane database syst rev"[TA]
19. search"[Title/Abstract]
20. "meta analysis"[Publication Type]
21. "meta analysis"[Title/Abstract]
22. "medline"[Title/Abstract]
23. "PubMed"[Title/Abstract]
24. "systematic"[Title/Abstract]
25. 18/25 OR
26. "review"[Text Word]
27. "meta analysis"[Publication Type]
28. 26 OR 27
29. 25 AND 28
30. 29 AND 17

Continuous blood glucose monitoring (CBGM) system

The Cochrane Library

1. “Blood Glucose Self-Monitoring” [MeSH descriptor]
2. glucometer or GlucoWatch or Medronic or guardian or glucosemeter) or "blood glucose" NEAR/2 (monitor*: or sensor):ti
3. 1 OR 2

PUBMED

1. "blood glucose self analyses"[Title/Abstract]
2. "blood glucose self measurement"[Title/Abstract]
3. "blood glucose self monitoring"[Title/Abstract]
4. "Blood Glucose Self-Monitoring"[Mesh]
5. "blood glucose meter"[Title/Abstract]
6. "blood glucose monitoring"[Title/Abstract]
7. "blood glucose measurement"[Title/Abstract]
8. "blood glucose measurements"[Title/Abstract]
9. "blood glucose measures"[Title/Abstract]
10. "blood glucose analyser"[Title/Abstract]
11. "blood glucose analysis"[Title/Abstract]
12. "Blood Glucose/analysis"[Mesh]
13. glucometer*[ti/ab]
14. 1/14 OR
15. cochrane database syst rev"[TA]
16. search"[Title/Abstract]
17. "meta analysis"[Publication Type]
18. "meta analysis"[Title/Abstract]
19. "medline"[Title/Abstract]
20. "PubMed"[Title/Abstract]
21. "systematic"[Title/Abstract]
22. 15/21 OR
23. "review"[Text Word]
24. "meta analysis"[Publication Type]
25. 23 OR 24
26. 25 AND 22
27. 26 AND 14

APPENDIX 4

Tables synthetising selected literarture for CSII and CGMS

Table 1. Summary of HTA reports and HS assessing the CSII therapy in children and/or adolescents with T1DM.

Reference	AETS 2000[1]	STEER 2002[2]	AETMIS 2005[3]	HSAC 2008[4]	NICE 2010[5]
Literature search	1990-2000	Until November 2001	January 2002 – July 2004	January 2002 - August 2007 inclusive	2002 - June 2007
Inclusion criteria and outcomes	Studies on pregnant women and children/adolescents with T1DM treated with CSSI pumps or peritoneal pumps in comparison to MDI Outcomes: HbA1c, insulin dose, hypoglycaemic events, body weight increase, QOL	Studies including patients with type 1 diabetes testing clinical effects of CSII in comparison to MDI Outcomes: HbA1c, ketoacidosis	RCT, cohort and case-series (≥10 weeks), in English, French, Spanish, Italian, German comparing CSII versus MDI in patients with type 1 DM (excluded studies on pregnant women, newly diagnosed T1DM, T2DM); hand-searching, national incident report databases (from USA, GB and Canada), users' and professionals' perspective Outcomes: HbA1c, users' and health professionals' preferences	RCTs on efficacy and safety testing CSII versus optimal MDI (at least three injections/day) for almost 10 weeks in type 1 and 2 DM, economic studies Outcomes: HbA1c, Insulin dose, hypoglycaemic events, ketoacidosis	RCTs comparing - T1DM: CSII versus MDI with the newer insulin analogues - TDM2: CSII versus MDI with a duration > 12 weeks Observational studies, studies on cost-effectiveness and QOL were also included; analysis of users' perspectives (through INPUT's members) was carried out Outcomes: HbA1c, QOL, hypoglycaemic events, ketoacidosis
Studies included	48 included studies (no details on study design) 2 out of 48 on adolescent and/or children	1 systematic review and 1 RCT (including also adults)	2 meta-analyses, 4 economic studies, 21 primary studies on children/adolescents (5 RCTs , 16 observational), 13 primary studies on adults (3 RCTs, 10 observational studies)	11 RCTs, 3 out of 11 on children and/or adolescents with type 1 diabetes (CSII versus MDI)	7 RCTs and 28 observational studies on children and/or adolescents with type 1 diabetes

Conclusions	• no differences between CSII and MDI in terms of efficacy and safety • indication for CSII pumps instead of MDI appears to be related more to patients' preferences and characteristics • some Authors suggest using pumps during pregnancy or in patients with uncontrolled DM through MDI	• good evidence that intensified treatment is superior to conventional treatment, • limited evidence that CSII improves glucose control but increases the risk of ketoacidosis compared with MDI • no evidence to compare CSII and MDI for chronic diabetic complications	• MDI with NPH insulin still the standard treatment; • for selected adult and paediatric patients with inadequate glycemic control (HbA1c level ≥ 8.5%), CSII may be associated with improvement of HbA1c		based on the totality of evidence, using observational studies to supplement the limited data from randomised trials against best MDI, CSII provides some advantages over MDI in type 1 diabetes.
Recommendations	Public reimbursement of CSII should be restricted to patients who respond to specific selection criteria the most important being to be compliant with an intensive insulin therapy from 6 to 12 months before CSII initiation.		• the preferred therapeutic approach to type 1 diabetes in both adults and children should be based on intensive therapy with MDI therapy • CSII should be recognized in Québec as a treatment modality that might be indicated for a limited, selected group of type 1 diabetics (various selection criteria based on expert opinions are cited in this report); • setting up criteria to identify possible candidates to CSII		NB they are given in another NICE document (TA guidance 151):[9] […] CSII therapy is recommended as a treatment option for • adults and children ≥ 12 years with type 1 DM provided that attempts to achieve target (HbA1c) levels with MDIs result in the person experiencing disabling hypoglycaemia. […] or HbA1c levels have remained high (≥ 8.5%) on MDI therapy despite a high level of care. • children ≤ 12 years with type 1 DM provided that MDI therapy is considered to be impractical or inappropriate, and children on insulin pumps would be expected to undergo a trial of MDI therapy between the ages of 12 and 18 years. […] CSII therapy is not recommended for the treatment of people with type 2 DM.

Table 2. Guideline recommendations on CSII

Year	Producer	Type of Institution	Country	Title	Target population and condition	Recommendations/statements on CSII
2004	NICE	Governmental	UK	Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults	Children, young people, and adults with type 1 diabetes	Continuous subcutaneous insulin infusion (or insulin pump therapy) is recommended as an option for people with type 1 diabetes provided that: • multiple-dose insulin therapy (including, where appropriate, the use of insulin glargine) has failed; and • those receiving the treatment have the commitment and competence to use the therapy effectively. Continuous subcutaneous insulin infusion therapy should be initiated only by a trained specialist team, [...] All individuals beginning continuous subcutaneous insulin infusion therapy should be provided with specific training in its use. [...] Established users of continuous subcutaneous insulin infusion therapy should have their insulin management reviewed by their specialist team [...]
2007	International Diabetes Center	Provider/Health trust	USA	Type 1 diabetes. In: Prevention, detection and treatment of diabetes in adults.	Children, adolescents, and adults with suspected or documented T1DM	Treatment Options: Insulin Stage (Mixed or Basal/Bolus) or Insulin Pump synchronized with food plan and exercise program […].
2007	Welsh Assembly Government	Governmental	Wales	Designed for the Management of Type 1 Diabetes in Children and Young People in Wales	Type 1 diabetes in children and young people	Pump regimens should only be used under the supervision of a centre with experienced staff trained in their use.
2008	NICE	Governmental	UK	Diabetes in pregnancy. Management of diabetes and its complications from pre-conception to the postnatal period. NICE Clinical guideline 63	Pregnant women with either type 1 or gestational diabetes mellitus	During pregnancy, women with insulin-treated diabetes should be offered continuous subcutaneous insulin infusion (CSII or insulin pump therapy) if adequate glycaemic control is not obtained by multiple daily injections of insulin without significant disabling hypoglycaemia.

Year	Producer	Type of Institution	Country	Title	Target population and condition	Recommendations/statements on CSII
2008	NICE	Governmental	UK	Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus. NICE Clinical guideline151	Children, young people, and adults with type 1 and type 2 diabetes mellitus	CSII therapy is recommended as a treatment option for adults and children 12 years and older with T1DM provided that: • attempts to achieve target haemoglobin A1c (HbA1c) levels with multiple daily injections (MDIs) result in the person experiencing disabling hypoglycaemia [...] or • HbA1c levels have remained high (that is, at 8.5% or above) on MDI therapy [...] despite a high level of care. CSII therapy is recommended as a treatment option for children younger than 12 years with type 1 diabetes mellitus provided that: • MDI therapy is considered to be impractical or inappropriate, and • children on insulin pumps would be expected to undergo a trial of MDI therapy between the ages of 12 and 18 years. It is recommended that CSII therapy be initiated only by a trained specialist team, [...]. Following initiation in adults and children 12 years and older, CSII therapy should only be continued if it results in a sustained improvement in glycaemic control, evidenced by a fall in HbA1c levels, or a sustained decrease in the rate of hypoglycaemic episodes [...]. CSII therapy is not recommended for the treatment of people with type 2 diabetes mellitus.
2008	Canadian Diabetes Association	Scientific society	Canada	Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada	Patients with either type 1 or type 2 diabetes mellitus	To achieve glycemic targets in adults with type 1 diabetes, multiple daily insulin injections (prandial [bolus] and basal insulin) or the use of CSII as part of an intensive diabetes management regimen is the treatment of choice. Insulin aspart or insulin lispro should be used when CSII is used in adults with type 1 diabetes. Insulin therapy should be assessed at each clinical encounter to ensure it still enables the **child** to meet A1C targets, minimizes the risk of hypoglycemia and allows flexibility in carbohydrate intake, daily schedule and activities. This assessment should include consideration of: • Increased frequency of injections • Change in the type of basal (long-acting analogue) and/or prandial (rapid-acting analogue) insulin. • Change to CSII therapy

Year	Producer	Type of Institution	Country	Title	Target population and condition	Recommendations/statements on CSII
2010	SIGN	Governmental	Scotland	Management of diabetes	Patients with either type 1 or type 2 diabetes mellitus	CSII therapy is associated with modest improvements in glycaemic control and should be considered for patients unable to achieve their glycaemic targets. CSII therapy should be considered in patients who experience recurring episodes of severe hypoglycaemia.
09-10	Associazione medici Diabetologi e Società Italiana di Diabetologia	Scientific society	Italy	Standard italiani per la cura del diabete mellito 2009-2010	Patients with either type 1 or type 2 diabetes mellitus	In soggetti selezionati che, malgrado un regime basal-bolus ottimale, presentino scarso controllo glicemico e/o ipoglicemie ricorrenti, può essere considerata l'indicazione all'uso del microinfusore da parte di un team esperto nel suo utilizzo. In soggetti [pediatrici] selezionati che, malgrado un regime basal-bolus ottimale, presentino scarso controllo glicemico, marcata instabilità metabolica con ipoglicemie ricorrenti, insulino-resistenza o ridotto fabbisogno insulinico, può essere considerata l'indicazione all'uso del microinfusore. [CSII experienced team could consider pumps use on patients with low glycemic control and/or frequent hypoglycaemic episodes (despite good basal-bolus regimen). CSII could be considered in paediatric patients with low glycemic control, high metabolic instability with frequent hypoglycaemic episodes, insulin-resistant or with low insulin need.]
2010	VA/DoD	Governmental	USA	Clinical practice guideline for the management of diabetes mellitus	Patients with either type 1 or type 2 diabetes mellitus	CSII therapy should only be initiated and managed by an endocrinologist/diabetes team with expertise in insulin pump therapy. CSII therapy should only be considered in patients who have either documented type 1 diabetes [...] or be insulin deficient with a need for intensive insulin therapy to maintain glycemic control and are not able to maintain it using multiple daily injections (MDI) therapy. This may include patients with: a. Poor glycemic control [...] despite an optimized regimen using MDI in conjunction with lifestyle modification. b. Marked dawn phenomenon (fasting AM hyperglycemia) not controlled using NPH at bedtime, glargine or detemir. c. Recurrent nocturnal hypoglycemia despite optimized regimen using

Year	Producer	Type of Institution	Country	Title	Target population and condition	Recommendations/statements on CSII
						glargine or detemir. d. Circumstances of employment or physical activity, for example shift work, in which MDI regimens have been unable to maintain glycemic control. Patients using CSII should have: a. Demonstrated willingness and ability to play an active role in diabetes self-management to include frequent self-monitoring of blood glucose (SMBG), and to have frequent contact with their healthcare team. b. Completed a comprehensive diabetes education program. The use of CSII over MDI regimens is not recommended in most patients with type 2 diabetes.
2011	American Association of Clinical Endocrinologists (AACE)	Scientific society	USA	American Association of Clinical Endocrinologists medical guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan	Patients with either type 1 or type 2 diabetes mellitus	CSII is useful in motivated and DM-educated patients with T1DM and in certain insulinopenic patients with T2DM who are unable to achieve optimal glycemic control with MDI. Thorough education and periodic reevaluation of CSII users, as well as CSII expertise of the prescribing physician, is necessary to ensure patient safety. Sensor-augmented CSII should be considered in patients in whom it is deemed appropriate.
2011	American Diabetes Association (ADA)	Association	USA	American Diabetes Association (ADA). Standards of medical care in diabetes.	Patients with either type 1 or type 2 diabetes mellitus	[…] recommended therapy for type 1 diabetes consists of the following components: 1) use of multiple dose insulin injections […] or CSII therapy;
2011	Wisconsin Diabetes Prevention and Control Program	Governmental	USA	Wisconsin Diabetes Prevention and Control Program	Patients with either type 1 or type 2 diabetes mellitus	Candidates for pump therapy include people with type 1 diabetes, type 2 diabetes, and gestational diabetes who are motivated to achieve optimal control. People wishing to use an insulin pump must be willing to invest time and energy into learning a new insulin delivery approach and be able to fulfill follow-up responsibilities. Insulin pump therapy augmented by use of a continuous glucose monitor has been shown to improve glycemic control in people with type 1 diabetes.

Table 3. Summary of HTA reports and HS assessing the CGM in children and/or adolescents with T1DM.

Reference	AETSA 2005	AZNHSN 2006	CTAF 2009	AIAQS 2010a	AIAQS 2010b	OHTAS 2011	WS HTA 2011
Literature search	N/A	until 15th March 2006	from 2003 to January 2009	from 2006 to July 2010	until October 2009	from January 1, 2002 to September 15, 2010	until July 2010
Inclusion criteria	N/A	N/A	N/A	• Study: GL, SR, RCT (o CT) y quasi-experimental studies; • Population: adults and/or paediatric pop. • Intervention: use of real time CGM with or without CSII; • Technology: CGMRT (Medtronic, DexCom, Freestyle navigator, GloucoDay); • Comparator: SMGC; • Outcomes: HbA_{1c} level; frequency or duration of hypo- or hyperglycaemia; safety, acceptability and HRQoL.	• Study: GL, SR, RCT (o CT) y quasi-experimental studies; • Population: adults and/or paediatric pop. and/or gestational DM. • Intervention: CGM Medtronic-minimed (retrospective or real time, with or without CSII); • Comparator: SMGC; • Language: Spanish, English and French; • Outcomes: HbA_{1c} level; frequency or duration of hypo- or hyperglycaemia; safety, acceptability and HRQoL.	• English language • Randomized controlled trials (N>30 patients) • Adults or paediatric patients with insulin dependent diabetes (type 1 or 2 or gestational) • Studies comparing CGM plus SMBG versus SMBG alone	• Patients: Persons ≤ 18 years old with insulin-requiring diabetes mellitus. • Intervention: SMBG or currently available FDA approved rt-CGM. • Comparators: Comparisons of different frequency of SMBG; standard care; SMBG versus CGM; SMBG as a stand-alone intervention versus SMBG as part of a package including education, feedback, and support. • Outcomes: Achieving/maintaining A1C targets, hospitalization, hypo-hyperglycemia, diabetic ketoacidosis, microvascular and macrovascular complications, effect on medication or nutritional management, QoL, mortality, safety, costs and long term benefits.

Reference	AETSA 2005	AZNHSN 2006	CTAF 2009	AIAQS 2010a	AIAQS 2010b	OHTAS 2011	WS HTA 2011
Studies included	Overall, 11 6 paediatric pop.	Overall, 13 4 paediatric pop.	Overall, 22 studies: 11 RCT 11 observational stud. Paediatric pop., 7: 3 RCT 4 observational stud. Mixed pop.: 2 RCT	Overall, 16: 2 paediatric pop. 7 mixed pop.	Overall, 15: 2 meta-analysis 13 studies Paediatric* pop., 8: 2 meta-analysis 6 studies * one MA and 1 study include mixed-pop.	Two moderate quality studies have been included, both on mixed paediatric-adults population (data on paediatric sub-population alone are not reported)	Overall, 43 studies but only four RCTs and seven observational studies deal with CGM efficacy and effectiveness.

Reference	AETSA 2005	AZNHSN 2006	CTAF 2009	AIAQS 2010a	AIAQS 2010b	OHTAS 2011	WS HTA 2011
Conclusions	• CGMS and SMBG have good correlation (Pearson's coefficient over 0.80); • correlation is higher for hyperglycaemic episodes, but frequency and duration of hypoglycaemic episodes appear overestimated. • Sensitivity and specificity were found to be acceptable but with high rate of false positive. • Contradictory results have been found about glycaemic control; • higher quality studies didn't find significant difference on the improvement of HbA1c. neither improvements in quality of life nor in fear of hypoglycaemic episodes have been found.	• Evidence from RCTs, though somewhat contradictory and limited by small and select patient groups, indicates some effectiveness in glycaemic control and increased safety due to greater awareness of glycaemic variation but these devices are less accurate, particularly during hypoglycaemic episodes and can cause minor skin reactions, and do not improve diabetes related quality of life, compared with SMBG. • CGM is useful as an adjunct to conventional SMBG in selected patients with difficulties in maintaining glycaemic control. At this stage, CGM will not replace conventional SMBG	• The three RCT (all small, ranging from 27-36 participants) didn't find any difference in glycaemic control for the intervention group (CGM users) compared with the control group. • the largest RCT to date found conclusive benefit only for adults 25 years and older. • […] there is little evidence that use of a CGM device confers an ultimate health benefit as measured by HbA1C as a marker of overall glycemic control. It may be that for children and adolescents this is in large part due to difficulty with device adherence and not with the device itself. • […] evidence has not yet shown conclusive benefit for children, adolescents, and even young	• use of CGMSRT requires some additional conditions such as frequent use of the sensor or a combination with a CSII to be considered of some efficacy	• the limited evidence available, both in improving metabolic control and in reducing the frequency of hypo- and hyperglycemias with the retrospective Medtronic-Minimed CGMS does not allow to make conclusions about its effectiveness.	Exists moderate quality evidence that CGM + SMBG: 1. is not more effective than self monitoring of blood glucose (SMBG) alone in the reduction of HbA1c using insulin infusion pumps for Type 1 diabetes; 2. is not more effective than SMBG alone in the reduction of hypoglycemic or severe hypoglycemic events using insulin infusion pumps for Type 1 diabetes. No studies on cost-effectiveness were found	• It is not clear from the evidence available what specific role these devices [CGM] might play in patients 18 years old or younger, nor which individuals may most benefit from this technology. • It is not clear to what extent improvement in overall glycemic control within CGM groups is clinically meaningful or how it may affect other long-term health outcomes. The short follow-up period applied by current trials to date precludes any conclusions on long-term benefits of CGM.

Reference	AETSA 2005	AZNHSN 2006	CTAF 2009	AIAQS 2010a	AIAQS 2010b	OHTAS 2011	WS HTA 2011
Recommendations	N/A	N/A	• continuous glucose monitoring devices do not meet CTAF criteria for safety, effectiveness and improvement in health outcomes for the management of diabetes mellitus in children, adolescents and pregnant women.	N/A	• Considering the available evidence, the CGMS in real time should be restricted to the following potential candidates: DM1 Adults patients with a lack of glycaemic control treated with an intensive insulin therapy including a 3 months review.	N/A	N/A

Table 4. Guideline recommendations on CGMS

Year	Producer	Type of Institution	Country	Title	Target population and condition	Recommendations/statements on CGMS
2004	NICE	Governmental	UK	Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults	Children, young people, and adults with type 1 diabetes	Children and young people with type 1 diabetes who have persistent problems with hypoglycaemia unawareness or repeated hypoglycaemia or hyperglycaemia should be offered continuous glucose monitoring systems. Continuous glucose monitoring systems have a role in the assessment of glucose profiles in adults with consistent glucose control problems on insulin therapy, notably: • repeated hyper- or hypoglycaemia at the same time of day • hypoglycaemia unawareness, unresponsive to conventional insulin dose adjustment.
2007	International Diabetes Center	Provider/health trust	USA	Type 1 diabetes. In: Prevention, detection and treatment of diabetes in	Children, adolescents, and adults with suspected or	Consider supplementing [SMBG] with continuous glucose monitoring (CGM).

Year	Producer	Type of Institution	Country	Title	Target population and condition	Recommendations/statements on CGMS
				adults.	documented T1DM	
2008	Canadian Diabetes Association	Scientific society	Canada	Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada	Patients with either type 1 or type 2 diabetes mellitus	The scarcity of data (including accuracy data) presently available precludes making definitive recommendations regarding the role of real-time CGMS in diabetes management. However, given its rapidly increasing use, it is incumbent upon healthcare providers involved in the management of people with diabetes (particularly type 1 diabetes) to be aware of this technology.
2010	SIGN	Governmental	Scotland	Management of diabetes	Patients with either type 1 or type 2 diabetes mellitus	CGM systems are generally only considered for use by patients who experience particular difficulties in maintaining normal glucose levels or who have been transferred to CSII therapy. The evidence on the value of CGM in people with type 1 diabetes is conflicting. CGM should not be used routinely in people with diabetes.
09-10	Associazione medici Diabetologi e Società Italiana di Diabetologia	Scientific society	Italy	Standard italiani per la cura del diabete mellito 2009-2010	Patients with either type 1 or type 2 diabetes mellitus	Il monitoraggio glicemico continuo (CGM) nei diabetici di età superiore ai 25 anni in terapia insulinica intensiva è uno strumento utile per ridurre l'HbA1c. Il CGM può essere di utilità nel ridurre l'HbA1c in diabetici tipo 1 in altre classi di età, in particolare nei bambini e comunque nei soggetti che dimostrano una buona aderenza all'utilizzo continuativo dello strumento. Il CGM può contribuire a ridurre le ipoglicemie e può essere utile nel trattamento di soggetti proni all'ipoglicemica o con sindrome da ipoglicemia inavvertita. [CGM in people older than 25 years subject to intensive insulin therapy is a useful tool to reduce HbA1c.

Year	Producer	Type of Institution	Country	Title	Target population and condition	Recommendations/statements on CGMS
						CGM could be useful in people younger than 25, particularly in child and in people compliant with its continuative use. CGM could contributes to hypoglycaemic episodes reduction and could be of some utility in treatment of patients prone to hypoglycaemia or with unperceived hypoglycaemia syndrome].
2011	American Association of Clinical Endocrinologists (AACE)	Scientific society	USA	American Association of Clinical Endocrinologists medical guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan	Patients with either type 1 or type 2 diabetes mellitus	Although still early in its development, continuous glucose monitoring (CGM) can be useful for many patients to improve A1C levels and reduce hypoglycemia
2011	American Diabetes Association (ADA)	Association	USA	American Diabetes Association (ADA). Standards of medical care in diabetes.	Patients with either type 1 or type 2 diabetes mellitus	Continuous glucose monitoring (CGM) in conjunction with intensive insulin regimens can be a useful tool to lower A1C in selected adults (age 25 years) with type 1 diabetes. Although the evidence for A1Clowering is less strong in children, teens, and younger adults, CGM may be helpful in these groups. Success correlates with adherence to ongoing use of the device. CGM may be a supplemental tool to SMBG in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes.
2011	Wisconsin Diabetes Prevention and Control Program	Governmental	USA	Wisconsin Diabetes Prevention and Control Program	Patients with either type 1 or type 2 diabetes mellitus	CGM is not intended to be a replacement for finger stick testing. A CGM reading should never be used to determine treatment.

APPENDIX 5

Search strategies for published studies

The Cochrane Library

1. “Blood Glucose Self-Monitoring” [MeSH descript]
2. glucometer OR GlucoWatch OR Medronic OR guardian OR glucosemeter OR "blood glucose" NEAR/2 (monit*: sens):ti
3. **1/2 OR**
4. Infusion Pumps[mesh descripts]
5. "Continuous Subcutaneous Insulin Infusion":ti,ab,kw
6. csii: :ti,ab,kw
7. “Insulin Infusion Systems” [MeSH descriptor]
8. "insulin infusion" NEAR/2 (pump* device* system*:ti,ab,kw
9. **4/8 OR**
10. Diabetes Mellitus, Type 1[MeSH descriptor]
11. Diabetic Ketoacidosis [MeSH descriptor]
12. Hypoglycemia [MeSH descript]
13. "type 1" NEAR/3 "diabetes mellitus" :ti,ab,kw
14. Diabetic Ketoacidosis":ti,ab,kw (hypoglicemya):ti,ab,kw
15. **10 /15 OR**
16. **(3 OR 9) AND 15**
17. 16 from 2005 to 2012

PUBMED

1. “blood glucose self analyses"[Title/Abstract]
2. "blood glucose self measurement"[Title/Abstract]
3. "blood glucose self monitoring"[Title/Abstract]
4. "Blood Glucose Self-Moniting"[Mesh]
5. "blood glucose meter"[Title/Abstract]
6. "blood glucose monitoring"[Title/Abstract]
7. "blood glucose measurement"[Title/Abstract]
8. "blood glucose measurements"[Title/Abstract]
9. "blood glucose measures"[Title/Abstract]
10. "blood glucose analysis"[Title/Abstract]
11. glucometer*[title/abstract]
12. glucowatch
13. medtronic guardian
14. "Continuous Subcutaneous Insulin Infusion"
15. "insulin infusion"[Title/Abstract]
16. "insulin infusion device"[Title/Abstract]
17. "insulin infusion devices"[Title/Abstract]
18. "insulin infusion pump"[Title/Abstract]
19. "insulin infusion system"[Title/Abstract]
20. "insulin infusion systems"[Title/Abstract]
21. "insulin infusions"[Title/Abstract]
22. "infusion pump"[Title/Abstract]

23. "infusion pumps"[Title/Abstract]
24. "continuous subcutaneous insulin infusion"[Title/Abstract]
25. "Infusion Pumps"[Mesh])
26. "integrated system"[title/abstract]
27. "integrated systems"[title/abstract]
28. **1/27 OR**
29. "Diabetes Mellitus, Type 1"[Mesh]
30. "Diabetic Ketoacidosis"[Mesh]
31. "Hypoglycemia"[Mesh:noexp]
32. "type 1 diabetes mellitus"[Title/Abstract]
33. "Diabetic Ketoacidosis"[title/abstract]
34. "Hypoglycemia"[title/abstract]
35. **29/34 OR**
36. **28 AND 35**

Limits: Humans, English, French, Italian, Spanish, Systematic Reviews, Publication Date from 2009 to 2012

37. Clinical Trials as Topic"[Mesh]
38. Randomly[title/abstract] trial[title]
39. RANDOMIZED[title/abstract]
40. placebo[title/abstract]
41. "controlled clinical trial"[Publication Type]
42. **37/41 OR**
43. **36 AND 42**

Limits: Humans, English, French, Italian, Spanish, Publication Date from 2010 to 2012

Embase

1. 'insulin infusion'/exp
2. 'insulin infusion'/syn
3. glucometer:ab,ti OR glucowatch:ab,ti OR 'glucosemeter':ab,ti OR 'glucose meter':ab,ti
4. 'blood glucose monitoring'/exp
5. **1/4 OR**
6. 'insulin dependent diabetes mellitus'/exp
7. 'insulin dependent diabetes mellitus'/exp
8. diabetic ketoacidosis'/exp
9. 'insulin hypoglycemia'/exp
10. **6/9 OR**
11. 'clinical trial'/exp OR 'comparative study'/exp OR 'randomization'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'placebo'/exp OR 'prospective study'/exp
12. (clinical OR control OR comparative OR placebo OR prospective OR random*) NEAR/3 trial* OR stud*:ab,ti
13. random* NEAR/4 allocat* OR assign* OR basis OR order*:ab,ti
14. single OR double NEAR/4 blind OR mask.:ab,ti
15. cross:ab,ti AND over:ab,ti OR crossover:ab,ti
16. **11/15 OR**
17. 10 AND 16

Limits: article; article in press; english, french, italian, spanish, humans, embase; Publication Date from 2010 to 2012

18. meta:ab,ti AND analy*:ab,ti OR 'meta analysis':ab,ti
19. 19. (review OR search) NEAR/6 literature OR 'medical database' OR 'medical databases' OR medline OR pubmed OR embase OR cochrane OR cinhal OR psychinfo OR psychlit OR healthstar OR biosis OR systematic:ab,ti
20. 'health technology assessment':ab,ti OR hta:ab,ti
21. 'literature'/exp OR 'biomedical technology assessment'/exp
22. 18/21
23. 10 AND 22

Limits: article; article in press; english, french, italian, spanish, humans, embase; Publication Date from 2010 to 2012

APPENDIX 6

Search strategies for ongoing studies

"insulin pump" OR "Insulin Infusion" OR "Blood Glucose Self-Monitoring" OR " Insulin Infusion Systems"

conditions: diabetes type 1

APPENDIX 7

Characteristics of included studies

Bergenstal 2010

N. patients	Patients' characteristics	Follow-up, weeks	Outcomes	SAP	MDI + SGBM	Difference (95%CI)	P-*value*
485 • 82 children (age: 7-12) • 74 adolescents (age: 13-18) • 329 adults (age: >18)	• Age, years [mean (SD)]: adults: SAP: 41.9 (12.3), MDI: 40.6 (12.0) adolescents: SAP: 14.5 (1.4), MDI: 15.2 (1.8) children: SAP: 9.4 (1.7), MDI: 10.1 (1.7) • Male patients (%): adults: SAP: 57, MDI: 57 adolescents: SAP and MDI: 51 children: SAP: 65, MDI: 54 • DM1 duration, years [mean	52	• difference in HbA1c at 52 weeks VS baseline, % [mean (SD)]	all patients: - 0.8 (0.8)	all patients: - 0.2 (0.9)	-0.6 (-0.7 to -0.4)	<0.001
				adults: -1.0 (0.7)	adults: - 0.4 (0.8)	-0.6 (-0.8 to -0.4)	<0.001
				children and adolescents: - 0.4 (0.9)	children and adolescents: +0.2 (1.0)	-0.5 (-0.8 to -0.2)	<0.001
			• patients reaching target HbA1c (adults:<7%; adolescents: <7.5%, children: <8%), % [mean (SD)]	all patients: 27%	all patients:10 %	NR	<0.001
				adults: 34%	adults: 12%	NR	<0.001
				children and adolescents: 44%	children and adolescents: 20%	NR	<0.005
			• patients reaching target HbA1c (adults:<7%; adolescents: <7.5%, children: <8%) at least once by month 6, number (%)	children: 38/43 (88%)	children: 20/39 (51%)	NR	NR
				adolescents: 20/35 (57%)	adolescents: 5/39 (13%)	NR	NR

	(SD)] adults: SAP: 20.2 (12.2), MDI: 20.2 (11.7) adolescents: SAP: 5.8 (3.5), MDI: 6.7 (4.2) children: SAP: 3.8 (2.4), MDI: 4.2 (2.6) • baseline HbA1c, % [mean (SD)]: adults (all): 8.3 (0.5) adolescents: SAP: 8.3 (0.5), MDI: 8.4 (0.5) children: SAP: 8.2 (0.6), MDI: 8.2 (0.5) • history of blood glucose testing ≥ 4 times daily in the previous 30 days Exclusion criteria - insulin pump use during the previous 3 years,	• weight gain at 52 weeks, kg [mean]	all patients: +2.4	all patients: +1.8	NR	0.19
		• change in BMI from the baseline, kg/m^2 [mean (SD)]	adolescents: +1.31 (0.26)	adolescents: +0.44 (0.26)	NR	0.043
			children: +1.07 (0.19)	children: +1.24 (0.29)	NR	0.519
		• severe hypoglycaemia, no. events	all patients: 32	all patients: 27	NR	0.58
			adults: 25	adults: 23	NR	0.53
			children and adolescents: 7	children and adolescents: 4	NR	0.53
		• severe hypoglycaemia, rate per 100 person-year	all patients: 13.31	all patients: 13.48	NR	0.84
			adults: 15.31	adults: 17.62	NR	0.66
			children and adolescents: 8.98	children and adolescents: 4.95	NR	0.35
		• diabetic ketoacidosis, no. of events	all patients: 3	all patients: 2	NR	0.38
			adults: 2	adults: 0	NR	NA
			children and adolescents: 1	children and adolescents: 2	NR	0.49
		• diabetic ketoacidosis, rate per 100 person-yr	all patients: 0.01	all patients: <0.01	NR	0.60
			adults: 0.01	adults: 0	NR	NA
			children and adolescents: 0.02	children and adolescents: 0.02	NR	0.20

to be continued

- history of at least 2 severe hypoglycemic events in the previous 12 months, - use of a pharmacologic noninsulin treatment for diabetes during the previous 3 months, - pregnancy or intention to become pregnant	• AUC for hypoglycemia (< 50 mg/dl), at 56 weeks [mean (SD)]	all patients: 0.02 (0.05)	all patients: 0.02 (0.08)	NR	0.25
		adults: 0.02 (0.04)	adults: 0.03 (0.09)	NR	0.16
		children and adolescents: 0.02 (0.07)	children and adolescents: 0.01 (0.05)	NR	0.64
	• AUC for hyperglycemia (>180 mg/dl), at 56 weeks [mean (SD)]	all patients: 20.36 (15.73)	all patients: 32.23 (23.41)	NR	<0.001
		adults: 16.06 (12.84)	adults: 26.01 (19.52)	NR	<0.001
		adolescents: 27.88 (16.85)	adolescents: 46.65 (31.84)	NR	0.002
		children: 32.04 (17.75)	children: 44.05 (18.40)	NR	0.012
	• hospital admissions for cellulitis related to insertion-site infections (N)	2	0		
	• death from sudden cardiac event	0	1		

NR = not reported

NA = not applicable

Hermanides 2011

N. patients	Patients' characteristics	Follow-up, weeks	Outcomes	SAP	MDI + SGBM	Difference (95%CI)	P-*value*
83	• Age, years [mean (SD)]: SAP: 37.3 (11.9), MDI: 37.3 (10.7) • DM1 duration, years [mean (SD)] SAP: 16.9 (10.7), MDI: 21.0 (9.4) • baseline HbA1c, % [mean (SD)] despite treatment with MDI: SAP: 8.47 (0.94), MDI: 8.64 (0.86) • Total daily insulin dose at baseline, units [mean (SD)]: SAP54.2 (21), MDI: 53.9 (14.0) • Patients experiencing severe hypoglycaemia in the last 12 month before randomization [n (%)]: SAP: 6 (13.6), MDI: 3 (7.7) Exclusion criteria - hearing problems or impaired vision that might hinder recognition of alarms; - substance abuse other than	26	• HbA1c reduction at 26 weeks VS baseline, %[mean (SD)]	-1.23 (1.01)	-0.13 (0.56)	-1.10 (-1.47 to -0.73)	< 0.001
			• HbA1c reduction at 26 weeks between groups, % [mean (SD)]	7.23 (0.65)	8.46 (1.04)	1.23 (0.83-1.63)	< 0.001
			• total daily insulin dose, units at 26 weeks, UI [mean (SD)]	46.7 (16.5)	57.8 (18.1)	-11.0 (-16.1 to -5.9)	< 0.001
			• time spent in hyperglycemia (>11.1 mmol/L), % [mean (SD]	21.6 (12.2)	38.2 (21.5)	16.5 (7.8-25.2)	< 0.001
			• time in hypoglycemia (< 4.0 mmol/L), % [mean (SD]	2.7 (3.4)	2.5 (3.6)	0.2 (-1.4 to 1.9)	0.79
			• number of hyperglycemia episodes/day [mean (SD)]	2.1 (0.8)	2.2 (0.7)	0.2 (-0.2 to 0.5)	0.30
			• number of hypoglycemia episodes/day [mean (SD)]	0.7 (0.7)	0.6 (0.7)	0.1 (-0.2 to 0.5)	0.40
			• total number of episodes of severe hypoglycaemia (%)	4 (9%)	1 (3%)	NR	0.21
			• total number of patients reaching HbA1c < 7%	34%	0%	NR	<0.001
			Patient-reported outcomes [mean (SD)]				
			• Problem Areas In Diabetes scale	21.0 (19.3)	23.7 (19.4)	2.7 (-7.9 to 13.4)	0.61
			• Hypoglycaemia Fear Survey	24.1 (20.2)	20.3 (16.9)	3.9 (-5.7 to 13.4)	0.42
			• Diabetes treatment satisfaction questionnaire	32.4 (3.5)	23.8 (6.2)	8.6 (6.2-11.0)	<0.001
			• Perceived	2.4	3.9	1.5 (1.0-	<0.00

to be continued

nicotine; - abdominal skin abnormalities that might hinder subcutaneous insertion; - current treatment for any psychiatric disorder other than depression; - treatment with CSII in the 6 months prior to study entry; - pregnancy, heart failure, cancer or kidney disease; - concomitant participation in another therapeutic study.	frequency of hyperglycaemia	(1.2)	(1.2)	2.1)	1
	• Perceived frequency of hypoglycaemia	2.4 (1.2)	2.2 (1.3)	0.2 (-0.4 to 0.8)	0.51
	• SF-36	No statistically significant difference between groups at 26 weeks in any of the 8 domains			

NR = not reported

NA = not applicable

Bergenstal 2010

Methods	Parallell, multicenter open-label RCT
Participants	INCLUSION CRITERIA: aged between 7 and 70 years, MDI for at least 3 months, HbA1c between 7.4 and 9.5%, under care for at least 6 months, access to a computer at home, history of SMBG average 4 times a day or more for the previous 30 days EXCLUSION CRITERIA:Use of insulin pump therapywithin previous 3 years, history of at least two severe hypoglycaemic events in the year before enrolment, use of pharmacologic non-insulin treatment for diabetes during the previous 3 months, pregnancy or intention to become pregnant DURATION OF INTERVENTION: 12 months CHARACTERISTICS OF PARTICIPANTS: 485 patients, 329 adults and 156 children SEX: 274 males and 211 females AGE (mean age (SD)): Adults: 41.9 (12.3) in the CGM group and 40.6 (12.0) in the control group. Children: 11.7 (3.0) in the CGM group and 12.7 (3.1) in the control group ETHNIC GROUPS: 14 Hispanic, 443 white, 28 other DURATION OF DISEASE (mean years (SD)): Adults: 20.2 (12.2) in the CGM group and 20.2 (11.7) in the control group. Children: 4.7 (3.1) in the CGM group and 5.4 (3.7) in the control group BASELINE HbA1c (%): Adults: 8.3 (0.5) in the CGM group and 8.3 (0.6) in the control group. Children: 8.3 (0.5) in the CGM group and 8.3 (0.5) in the control group COUNTRY: United States and Canada SETTING: outpatients TREATMENT BEFORE STUDY: MDI with SMBG
Interventions	• sensor-augmented pump therapy (SAP): CSII+CBGM (MiniMed Paradigm REAL-Time System, Medtronic): 166 adults, 78 children • MDI+SMBG (finger sticks)+blinded CBGM*: 163 adults, 78 children for 12 months. *In the control group, a device for continuous glucose monitoring that collected but did not display data was used. All patients used a diabetes-management software (CareLink Therapy management System for Diabetes-Clinical, Medtronic) All patients wore a CGMS and CGM studies were carried out at baseline, 6 and 12 months.
Outcomes	PRIMARY: change from baseline in the HbA1c level at 1 year SECONDARY: severe hypoglycaemic events (episodes requiring assistance and confirmed by documentation of blood glucose value < 50 mg/dl)

	OTHER: % of patients reaching Hb1Ac % < 7% OTHER: weight gain (kg)
Notes	Primary analysis: on "the intention-to-treat population, defined as patients who underwent at least one measurement of glycated hemoglobin after randomization, with the last observation carried forward for the imputation of missing data."

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were randomly assigned to receive either sensor-augmented pump therapy (pump therapy) or a regimen of multiple daily injections (injection therapy) with the use of a block design, stratified according to age group: adults (19 to 70 years of age) or children (7 to 18 years of age)." Comment: randomization in blocks, stratified according to age group: adults (19-70 years) or children (7-18 years)
Allocation concealment (selection bias)	Unclear risk	"Patients were randomly assigned to receive either sensor-augmented pump therapy (pump therapy) or a regimen of multiple daily injections (injection therapy) with the use of a block design, stratified according to age group: adults (19 to 70 years of age) or children (7 to 18 years of age)." Comment: Authors do not provide information on allocation concealment
Blinding of participants and personnel (performance bias)	Unclear risk	The study was open.
Blinding of outcome assessment (detection bias)	Low risk	The study was open but one can be assured that, given the objective nature of the study outcomes, the risk of bias is low
Incomplete outcome data (attrition bias)	Low risk	Drop-out rate: Intervention: 9%, control: 12%; all drop-outs and withdrawal explained
Selective reporting (reporting bias)	Low risk	All the outcomes cited in the protocol are analysed and results are reported; weight was not included as an outcome in the protocol
Other bias	Unclear risk	Amendments to the original protocol: • "the eligibility cutoff level for glycate emoglobin was lowered from 7.5% to 7.4%, • the exclusion criteria were changed from no previous use of insulin-pump therapy to no such use within the previous 3 years, • the sample size was increased from 336 patients at 25 centers to 552 patients at 30 centers,

		• results on the Hypoglycemia Fear Survey were moved from a secondary end point to a tertiary end point, • the Telemetered Glucose-Monitoring System (Medtronic) was replaced with the MiniLink transmitter (Medtronic), • three visits during the 5 weeks after randomization were removed from the schedule for the injection-therapy group"
Authors' conflicts of interest	High risk	Several authors received consulting fees, honoraria and grant support from Medtronic
Influence of the sponsor	High risk	• "Data management and statistical analyses were conducted by Parexel International, an independent clinical research organization, which transferred all data to the sponsor, Medtronic • Novo Nordisk supplied all insulin aspart used in the study, and LifeScan, Bayer Healthcare, and Becton Dickinson supplied blood glucose meters." • All authors had access to the data, wrote the first draft of the manuscript with editorial assistance from representatives of the sponsor, subsequently revised the manuscript, and made the decision to submit the manuscript for publication. All authors vouch for the accuracy and completeness of the data and analyses. The STAR 3 steeringcommittee was responsible for the study design and methods."

Hermanides 2011

Methods	Multicenter, parallell, open-label RCT
Participants	INCLUSION CRITERIA: aged 18–65 years, diagnosed with Type 1 diabetes at least 1 year prior to study participation, currently treated with optimized multiple daily injections, but having anHbA1c ‡ 8.2% (‡ 66 mmol / mol) at screening, despite repeated attempts to improve this by re-education, including the availability of insulin pump therapy. Patients treated with human insulin could also be included if analogues had been tried in the past EXCLUSION CRITERIA:hearing problems or impaired vision that might hinder recognition of alarms; substance abuse other than nicotine; abdominal skin abnormalities that might hinder subcutaneous insertion; current treatment for any psychiatric disorder other than depression; treatment with continuous subcutaneous insulin infusion in the 6 months prior to study entry; pregnancy, heart failure, cancer or kidney disease; participation in another therapeutic study. DURATION OF FOLLOW-UP: 26 weeks CHARACTERISTICS OF PARTICIPANTS: 83 adult patients (43 SAP group and 35 MDI group) SEX: 43 males and 40 females AGE (mean age (SD)): SAP group: 39.3 (11.9), Control group: 37.3 (10.7) ETHNIC GROUPS: n.a. DURATION OF DISEASE (mean years (SD)): SAP group: 16.9 (10.7), Control group: 21.0 (9.4) BASELINE HbA1c (%) (mean, [SD]): SAP group: 8.47 (0.94), Control group: 8.64

	(0.86) COUNTRY: Europe SETTING: outpatients TREATMENT BEFORE STUDY: MDI with SMBG
Interventions	• sensor-augmented insulin pump (SAP): CSII + CBGM (MiniMed Paradigm REAL-Time System, Medtronic): 44 patients • MDI + SMBG (finger sticks at least 3 times/day) + blinded CBGM (for 6 days before the 13- and 26-week visits): 39 patients for 26 weeks
Outcomes	PRIMARY: change from baseline in the HbA1c level at 26 weeks between groups SECONDARY: change from 13 weeks in the HbA1c at 26 weeks SECONDARY: % time in hyperglycemia (>11.1 mmol/L) SECONDARY: % time in hypoglycemia (< 4.0 mmol/L) SECONDARY: number of hyperglycemia events/day SECONDARY: number of hypoglycemia events/day SECONDARY: sensor use: average h/week and % of sensor usage during the whole trial (only for patients randomised to SAP) SECONDARY: % of patients reaching Hb1Ac % < 7% SECONDARY: contact time with study personnel SECONDARY: number of self-mesuraments of blood glucose per 3 weeks SECONDARY: total daily insulin dose/patient OTHER: difference between groups in QOL measured with several questionnaires: SF-36 version 2, Diabetes Treatment Satisfaction Questionnaire, 13-item worry subscale of the Hypoglycaemia fear Survey.
Notes	The primary outcome was the difference in % of HbA1c at 26 weeks versus baseline for each group and not the difference between groups in % of HbA1c at 26 weeks.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was stratified per centre in computer-generated sequences unknown to the investigator.
Allocation concealment	Low risk	Via a secured Internet database (Oracle Corporation, Redwood City, CA,

(selection bias)		USA), the investigators performed the randomization.
Blinding of participants and personnel (performance bias)	Unclear risk	The study was open.
Blinding of outcome assessment (detection bias)	Unclear risk	Not specified if assessors were blinded or not but the clinical outcomes were objectively mesurable thus less prone to be afected by detection bias
Incomplete outcome data (attrition bias)	Low risk	Only 5/83 randomised patients did not complete the trial; reasons given
Selective reporting (reporting bias)	Low risk	The results of all the outcomes were reported
Other bias	Unclear risk	
Authors' conflicts of interest	High risk	Three authors received fees from Medtronic.
Influence of the sponsor	Unclear risk	"This trial was financially supported by Medtronic International Trading Srl. This was an investigator-initiated trial. The funding source had an advising role in trial design details and drafting of the report and was only involved in the collection of the sensor data. The funding source had no role in the conduct of the analyses, interpretation of the data or in the decision to approve publication."

APPENDIX 8

Characteristics of excluded studies (Ch.4.2)

Alemzadeh 2005

Alemzadeh R, Palma-Sisto P, Parton EA, Holzum MK. Continuous Subcutaneous Insulin Infusion and Multiple Dose of Insulin Regimen Display Similar Patterns of Blood Glucose Excursions in Pediatric Type 1 Diabetes. Diabetes Technol Ther 2005;7(4):587-96.

Allemann 2009

Allemann S, Houriet C, Diem P, Stettler C. Self-monitoring of blood glucose in non-insulin treated patients with type 2 diabetes: a systematic review and meta-analysis. Curr Med Res Opin. 2009;25(1473-4877 (Electronic), 0300-7995 (Linking), 12):2903-13.

Augstein 2007

Augstein P, Vogt L, Kohnert KD, Freyse EJ, Heinke P, Salzsieder E. Outpatient assessment of Karlsburg Diabetes Management System-based decision support. Diabetes Care 2007;30(7):1704-8.

Barnard 2007

Barnard KD, Lloyd CE, Skinner TC. Systematic literature review: quality of life associated with insulin pump use in Type 1 diabetes. Diabet Med 2007;24(6):607-17.

Barrio 2010

Barrio Castellanos R, Garcia Cuartero B, Gomez Gila A, Gonzalez Casado I, Hermoso Lopez F, Luzuriaga Tomas C, et al. [Consensus document on continuous subcutaneous insulin infusion (CSII) treatment in paediatrics with type I diabetes]. An Pediatr.(Barc.) 2010;72(1695-9531 (Electronic), 1695-4033 (Linking), 5):352-4.

Battelino 2011

Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes Care 2011;34(1935-5548 (Electronic), 0149-5992 (Linking), 4):795-800.

Bergenstal 2011

Bergenstal RM, Tamborlane WV, Ahmann A, Buse JB, Dailey G, Davis SN, et al. Sensor-augmented pump therapy for A1C reduction (STAR 3) study: results from the 6-month continuation phase. Diabetes Care 34:2403–2405, 2011 2011;34:2403-05.

Berndt-Zipfel 2011

Berndt-Zipfel C, Köthe L, Nawrodt B, Mraz B, Patzelt-Bath A, Nauck MA. Glycaemic rises after waking up in response to an alarm clock in type 1-diabetic patients analysed with continuous glucose monitoring (GlucoDay® S). Exp Clin Endocrinol Diabetes 2011;119(1):56-8.

Bode 2005

Bode BW, Steed RD, Schleusener DS, Strange P. Switch to multiple daily injections with insulin glargine and insulin lispro from continuous subcutaneous insulin infusion with insulin

lispro: a randomized, open-label study using a continuous glucose monitoring system. Endocr Pract 2005;11(3):157-64.

Bragd 2010

Bragd J, Von Dobeln A, Lins PE, Adamson U, Bergstrom J, Oskarsson P. Basal insulin substitution with glargine or continuous subcutaneous insulin infusion in adult type 1 diabetes patients-a randomized controlled trial. Diabetes Technology and Therapeutics 2010;12(1557-8593 (Electronic), 1520-9156 (Linking), 9):689-93.

Buckingham 2010

Buckingham B, Chase HP, Dassau E, Cobry E, Clinton P, Gage V, et al. Prevention of nocturnal hypoglycemia using predictive alarm algorithms and insulin pump suspension. Diabetes Care 2010;33(5):1013-7.

Buse 2011

Buse JB, Dailey G, Ahmann AA, Bergenstal RM, Green JB, Peoples T, Tanenberg RJ, Yang Q. Baseline predictors of A1C reduction in adults using sensor-augmented pump therapy or multiple daily injection therapy: the STAR 3 experience. Diabetes Technol Ther 2011;13(6):601-6.

Cameron 2011

Cameron F, Bequette BW, Wilson DM, Buckingham BA, Lee H, Niemeyer G. A closed-loop artificial pancreas based on risk management. J Diabetes Sci Technol 2011;5(2):368-379.

Castle 2010

Castle JR, Engle JM, El Youssef J, Massoud RG, Ward WK. Factors influencing the effectiveness of glucagon for preventing hypoglycemia. J Diabetes Sci Technol 2010;4(6):1305-1310.

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Chase HP, Horner B, McFann K, Yetzer H, Gaston J, Banion C, et al. The use of insulin pumps with meal bolus alarms in children with type 1 diabetes to improve glycemic control. Diabetes Care 2006;29(5):1012-5.

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Chimenti EM, de la Morena LH, Vaquero PM, Saez-de-ibarra L, Dominguez MG, Sanchez LFP. Assessing glycaemic variability with continuous glucose monitoring system before and after continuous subcutaneous insulin infusion in people with Type 1 diabetes. Diabetes Research and Clinical Practice 2010;90(3):e57-9.

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Cobry E, Chase HP, Burdick P, McFann K, Yetzer H, Scrimgeour L. Use of CoZmonitor in youth with type 1 diabetes. Pediatric Diabetes 2008;9:148–151.

Conget 2011

Conget I, Battelino T, Giménez M, Gough H, Castañeda J, Bolinder J; SWITCH Study Group. The SWITCH study (sensing with insulin pump therapy to control HbA(1c)): design and methods of a randomized controlled crossover trial on sensor-augmented insulin pump

efficacy in type 1 diabetes suboptimally controlled with pump therapy. Diabetes Technol Ther 2011;13(1):49-54.

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Danne T, Kordonouri O, Holder M, Haberland H, Golembowski S, Remus K, Bläsig S, Wadien T, Zierow S, Hartmann R, Thomas A. Prevention of hypoglycemia by using low glucose suspend function in sensor-augmented pump therapy. Diabetes Technol Ther 2011;13(11):1129-34.

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Davis SN, Horton ES, Battelino T, Rubin RR, Schulman KA, Tamborlane WV. STAR 3 randomized controlled trial to compare sensor-augmented insulin pump therapy with multiple daily injections in the treatment of type 1 diabetes: research design, methods, and baseline characteristics of enrolled subjects. Diabetes Technol Ther 2010;12(4):249-55.

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Farrar Diane, Tuffnell Derek J, West Jane. Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes. Cochrane Database of Systematic Reviews 2007.

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Fatourechi MM, Kudva YC, Murad MH, Elamin MB, Tabini CC, Montori VM. Clinical review: Hypoglycemia with intensive insulin therapy: a systematic review and meta-analyses of randomized trials of continuous subcutaneous insulin infusion versus multiple daily injections. J Clin Endocrinol Metab 2009;94(3):729-40.

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Garg SK, Voelmle MK, Beatson CR, Miller HA, Crew LB, Freson BJ, et al. Use of continuous glucose monitoring in subjects with type 1 diabetes on multiple daily injections versus continuous subcutaneous insulin infusion therapy: A prospective 6-month study. Diabetes Care 2011;34(3):574-9.

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Hartemann A, Bourron O. Insulin pump and continuous glucose monitoring: Is it really "the best treatment" for all patients. Med Mal Metab 2011;Med Mal Metab(5):303-307.

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Petrovski G, Dimitrovski C, Bogoev M, Milenkovic T, Ahmeti I, Bitovska I. Is there a difference in pregnancy and glycemic outcome in patients with type 1 diabetes on insulin pump with constant or intermittent glucose monitoring? A pilot study. Diabetes Technol Ther 2011;13(11):1109-13.

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Ongoing studies

NCT01454700

Unpublished data only [ClinicalTrials.gov:]

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Characteristics of excluded studies (Ch.4.2)

Alemzadeh 2005

Reason for exclusion	Study design: case-control study

Allemann 2009

Reason for exclusion	Type of partecipants: patients with DM2

Augstein 2007

Reason for exclusion	Type of comparison: • MDI+CBGM/Karlsburg Diabetes Management System–Based Decision Support versus • MDI+CBGM Included patients with either DM1 or DM2 (only pooled data available) Excluded patients on CSII pump

Barnard 2007

Reason for exclusion	Type of comparison: • MDI+SBGM versus • CSII+SBGM (systematic review)

Barrio 2010

Reason for exclusion	Study design: consensus statement

Battelino 2011

Reason for exclusion	Type of comparison: • MDI/CSII+CGMS versus • MDI/CSII+SMBG with finger-sticks

Bergenstal 2011

Reason for exclusion	Non-randomised 6-month additional follow-up of STAR-3

Berndt-Zipfel 2011

Reason for exclusion	Study design: observational study Duration: 3 nights

Bode 2005

Reason for exclusion	Type of comparison: • CSII versus • MDI + CBGM Duration: 7 days

Bragd 2010

Reason for exclusion	Type of comparison: • CSII+CBGM versus • insulin glargine+CSII+CBGM

Buckingham 2010

Reason for exclusion	Study design: observational study Duration: one day

Buse 2011

Reason for exclusion	Analysis of baseline prognostic factors for a good response to SAP (publication of STAR-3 study)

Cameron 2011

Reason for exclusion	Type of study: Development of a new algorithm for CBGM

Castle 2010

Reason for exclusion	Study design: Phase II, non-randomised study

Chase 2006

Reason for exclusion	Type of comparison: • CSII with alarm system+SBGM with finger-sticks versus • CSII+SBGM with finger-sticks

Chimenti 2010

Reason for exclusion	Study design: observational study

Churchill 2009

Reason for exclusion	Type of comparison: • CSII versus • MDI (systematic review)

Cobry 2008

Reason for exclusion	Type of comparison • CSII+integrated CBGM versus • CSII+stand alone CBGM

Conget 2011

Reason for exclusion	Study design: protocol of the SWITCH Study

Cote 2005

Reason for exclusion	Study design: HTA report Type of comparison: CSII versus MDI

Cummins 2010

Reason for exclusion	Type of comparison: • CSII versus • MDI (HTA report)

Danne 2011

Reason for exclusion	Type of comparison: • SAP with a "low glucose suspend (LGS) function" versus • SAP

Davis 2010

Reason for exclusion	Protocol of the STAR-3 study

El-Khatib 2010

Reason for exclusion	Study design: Phase I, non-randomised study Duration: 27 hours Note: perhaps interesting as a future technology (bihormonal closed-loop artificial pancreas)

Elleri 2011

Reason for exclusion	Study design: narrative review

Farmer 2005

Reason for exclusion	Type of intervention: telemedicine (systematic review)

Farrar 2007

Reason for exclusion	Type of comparison: CSII vs MDI (systematic review)

Fatourechi 2009

Reason for exclusion	Type of comparison: • CSII versus • MDI (systematic review)

Gandhi 2011

Reason for exclusion	Impossible to retrieve the full-text article.

Garg 2011

Reason for exclusion	Sudy design: non-randomized study Type of comparison: • CSII + SBGM with finger-sticks (+CBGM) versus • MDI + SBGM with finger-sticks (+CBGM)

Golicki 2008

Reason for exclusion	Type of comparison: • retrospective CBGM + SMBG versus • SMBG (systematic review)

Hartemann 2011

Reason for exclusion	Study design: non-randomised study

Haupt 2005

Reason for exclusion	Type of comparison: • portable combined insulin doser + BG monitor (integrated system) versus • insulin pen + BG monitor (non-integrated system)

Hirsch 2008

Reason for exclusion	Type of comparison: • Sensor-augmented insulin pump (SAP: CSII+RT-CBGM) versus • CSII+SMBG

Hoeks 2011

Reason for exclusion	Type of comparison: • CBGM versus • SBGM (systematic review)

Hovorka 2010

Reason for exclusion	Type of comparison: • CSII+CGM versus • CSII Duration: overnight

Hovorka 2011

Reason for exclusion	Type of comparison: • Closed-loop CSII+CBGM versus • CSII Closed-loop: sensor measurements of glucose were fed into a computer algorithm, which advised on insulin pump infusion rates at 15 minute intervals Duration: overnight

Jeitler 2008

Reason for exclusion	Type of comparison: • CSII versus • MDI (systematic review; primary studies' abstracts examined to retrieve data on our comparison, no data fund)

Jenkins 2010

Reason for exclusion	Type of comparison: • CSII+RT-CBGM with algorithm versus • CSII+RT-CBGM Phase 1 was an open 16-week multicenter randomized controlled trial; Group A received CSII/RT-CGM with the algorithm, and Group B received CSII/RT-CGM without algorithm. Phase 2 was the 16–32-week follow-up study; Group A returned to usual care (CSII without RT-CGM), and Group B was provided with algorithm at 16 weeks.

Jenkins 2011

Reason for exclusion	Duplicate of Jenkins 2010

Jones 2005

Reason for exclusion	Study design: observational study

Keenan 2010

Reason for exclusion	Type of comparison: • SAP versus • (CSII+standard SMBG with finger-sticks). STAR-1 study.

Kerr 2010

Reason for exclusion	Narrative review

Klonoff 2011

Reason for exclusion	Study design: guideline

Kordonouri 2010

Reason for exclusion	Type of comparison: • CSII+CGBM versus • CSII+standard SMBG with finger-sticks ONSET Study

Kordonouri 2012

Reason for exclusion	Study design: long-term follow-up of the ONSET study (that was excluded because of the type of comparison: CSII+CGBM versus CSII+standard SMBG with finger-sticks, see Kordonouri 2010)

Kovatchev 2010

Reason for exclusion	Study design: editorial

Kovatchev 2011

Reason for exclusion	Study design: editorial to Hovorka 2011

Ladyzynski 2007

Reason for exclusion	Type of comparison: • MDI+CGM versus • MDI+CGM with telecare

Langendam 2012

Reason for exclusion	Systematic review including the two presently available RCTs comparing SAP versus MDI+SBGM that Authors decided to analyse in details (see STAR-3, Hermanides 2011)

Li 2010

Reason for exclusion	Impossible to retrieve full-text article.

Lin 2011

Reason for exclusion	Study design: observational study.

Logtenberg 2009

Reason for exclusion	Type of comparison: • CIPII+open RT-CBGM versus • CIPII+blinded RT-CBGM CIPII = continuous intra-peritoneal insulin infusion Duration: 6 days

Misso 2010

Reason for exclusion	Type of comparison: • CSII versus • MDI (systematic review)

Monami 2010

Reason for exclusion	Type of comparison: • CSII versus • MDI (systematic review)

Mukhopadhyay 2007

Reason for exclusion	Type of comparison: • CSII versus • MDI (systematic review, pregnant women)

Murphy 2011

Reason for exclusion	Study design: observational study

Petrovski 2011

Reason for exclusion	Type of comparison: • CSII + constant (24h/day) versus • CSII + intermittent (12h/day) CGBM. Pregnant women with type 1 DM.

Peyrot 2009

Reason for exclusion	Type of comparison: • CSII+RT-CBGM a adjunct to SMBG versus • MDI+SMBG (in both arms all insulin adjustments were made based on SMBG results)

Pickup 2008

Reason for exclusion	Type of comparison: • CSII versus • MDI (systematic review)

Pickup 2011

Reason for exclusion	Type of comparison: • real time CBGM versus • SMBG (systematic review)

Raccah 2009

Reason for exclusion	Type of comparison: • CSII+SBGM+RT-CGM versus • CSII+SBGM

Radermecker 2010

Reason for exclusion	Type of comparison: • CSII+SMBG+CBGM versus • CSII+SMBG

Renard 2010

Reason for exclusion	Number of patients: <10 Type of comparison: CIPII+CBGM versus CIPII Duration: 2 days

Rigla 2008

Reason for exclusion	Type of comparison: • CSII+RT-CBGM+SBGM with finger-sticks+telemedicine versus • CSII+SBGM with finger-sticks

Rubin 2012

Reason for exclusion	Impossible to retrieve the full-text article

Russell-Minda 2009

Reason for exclusion	Type of comparison • all types of self-monitoring devices and technologies (SMBG devices, blood pressure devices, heart rate monitors, pedometers or accelerometers, wireless data technologies, devices that use Web-enabled technologies, and global information systems) versus • no use of self-monitoring devices and technology (systematic review)

Scaramuzza 2011

Reason for exclusion	Study design: observational study

Shalitin 2011

Reason for exclusion	Study design: narrative review

St John 2010

Reason for exclusion	Type of comparison: no studies on the comparison of interest (systematic review)

Thrailkill 2011

Reason for exclusion	Type of comparison: • CSII+standard SBGM with finger-sticks versus • MDI+standard SBGM with finger-sticks

Torres 2011

Reason for exclusion	Type of study: consensus statement

Toscos 2012

Reason for exclusion	Type of comparison: • conventional care (MDI or CSII) + SBGM (with fingersticks) versus • conventional care (MDI or CSII) + SBGM (with fingersticks) + Automated Diabetes management System (AMDS) ADMS consists of GlucoMON and GlucoDYNAMIX that are wireless technologies that work together to provide automated BGM data retrieval, analysis and reporting. GlucoMON is a sort of dock station for the glucometer whilst GlucoDYNAMIX provides two features 1. “real-time alerts,” notification by text message to cell phones or e-mail of the last BG result immediately after the docking of the glucometer to theGlucoMON device, and 2. “trend analysis reports,” a daily e-mail to parents including the system generated 21-day BG log attached as a PDF document

Tsukamoto 2011

Reason for exclusion	Patients: critically ill patients

Wadien 2010

Reason for exclusion	Study design: case studies.

Wojciechowski 2011

Reason for exclusion	Type of comparison: no studies on the comparison of interest (systematic review)

Yatabe 2011

Reason for exclusion	Study design: observational Setting: ICU

Yates 2006

Reason for exclusion	Type of comparison: • MDI or CSII + SBGM (with fingersticks) versus • MDI or CSII + SBGM (with fingersticks) + CBGM

Zucchini 2011

Reason for exclusion	Type of comparison: • CSII+CGM versus • MDI+CGM Duration: 3 days

APPENDIX 9

Characteristics of ongoing studies (Ch.3.2)

NCT01454700

Study name	Effect of CSII and CGM on Progression of Late Diabetic Complications
Methods	open label RCT
Participants	Inclusion Criteria: - 18-75 years of age, - Type 1 diabetes according to WHO criteria, - Urin albumine > 100 mg/g (albumine/creatinine ratio), - HbA1c > 7.5 < 11.0%, - No change in RAAS blocking treatment at least 4 weeks prior to screening. Exclusion Criteria: - Kidney disease other that diabetic nephropathy, - Recurrence of severe hypoglycaemia or hypoglycaemia unawareness as judged by the investigator, - Proliferative retinopathy or macular edema treated with photocoagulation, Use of insulin pump within 12 months, - Acute myocardial infarction within 3 months, - Severe arteriosclerosis as judged by the investigator, - Heart failure (NYHA class 3 or 4), - Abuse of alcohol or drugs, - Any cancer diagnosis unless in remission at least 5 years prior to screening, - Participation in other intervention studies, - Pregnant or lactating women, - Any other disease, condition or type of treatment which - as judged by the investigator - render the patient ineligible to participate in the study.
Interventions	• Experimental: insulin pump therapy (CSII) plus continuous glucose monitoring (CGM) • Comparator: Multiple daily insulin injections (MDI) + SMBG for 12 months
Outcomes	Primary • difference in change in urine albumine excretion from baseline to end of study (12 months). Urine albumin excretion is evaluated at screening, at entry, after 1,3,6,9, and 12 months.

	Secondary • difference in change of HbA1c from baseline to 12 months • difference in change in standard monitored blood glucose (SMBG) measurement 4-point glucose profiles • difference in change of 24-hour blood pressure • difference in change of glomerular filtration rate (GFR) • difference in the occurence or progression of retinopathy • difference in change of cardiovascular biomarkers of inflammation, lipid metabolism and NT-proBNP • difference in endothelial cell dysfunction • difference in carotid intima media thickness (CIMT)
Starting date	December 2011
Contact information	Contact: Steen Andersen, MD, DMSc, +45 3075-7056, stan@steno.dk Contact: Signe Rosenlund, MD, +45 3079-8832, svr@steno.dk
Notes	Location country: Denmark Collaborator: Medtronic

APPENDIX 10

Description of interventions (Ch.4.2)

Study ID	Intervention (CSII and CGM types)	Control
STAR-3	MiniMed Paradigm REAL-Time System (Medtronic)	MDI + SMBG
Hermanides 2011	MiniMed Paradigm REAL-Time System (Medtronic)	MDI + SMBG

APPENDIX 11

Selected codes of complications (Ch. 5.)

Short-term complications

Coma

Data sources: Hospital Discharge database (SDO)

ICD9-CM diagnosis codes	Description
250.31	Diabetes with other coma
250.33	Diabetes with other coma
In any diagnosis field	

Ketoacidosis

Data sources: Hospital Discharge database (SDO)

ICD9-CM diagnosis codes	Description
250.11	Diabetes with ketoacidosis
250.13	Diabetes with ketoacidosis
In any diagnosis field	

Hypersmolarity

Data sources: Hospital Discharge database (SDO)

ICD9-CM diagnosis codes	Description
250.21	Diabetes with hyperosmolarity
250.23	Diabetes with hyperosmolarity
In any diagnosis field	

Uncontrolled diabetes

Data sources: Hospital Discharge database (SDO)

ICD9-CM diagnosis codes	Description
250.03	Uncontrolled diabetes
In any diagnosis field	

Long-term complications

Ischemic heart disease

Data sources: Hospital Discharge database (SDO)

ICD9-CM diagnosis codes	ICD9-CM Procedure codes	Description
410		Acute myocardial infarction-any episode of care
411		Other acute and subacute forms of ischemic heart disease
412		Old myocardial infarction
413		Angina pectoris
414		Other forms of chronic ischemic heart disease
In any diagnosis field		
	36.0	Percutaneous coronary artery angioplasty (PTCA)
	36.1	Bypass anastomosis for heart revascularization
	36.2	Heart revascularization arterial implant
	36.3	Other heart revascularization
	36.9	Operations vessels heart
	Main procedure selected by DRG-Grouper	

Myocardial infaction

Data sources: Hospital Discharge database (SDO)

ICD9-CM diagnosis codes	Description
410._1	Acute myocardial infarction initial episode of care
In any diagnosis field	

Kidney disease

Data sources: Hospital Discharge database (SDO) and Outpatient Database (ASA)

ICD9-CM diagnosis codes	ICD9-CM Procedures codes	Description
Data sources: SDO		
250.4_		Diabetes with renal manifestations
581.81		Nephrotic syndrome in diseases classified elsewhere
584._		Acute kidney failure
585		Chronic kidney disease
586		Renal failure, unspecified
595.0		Acute cystitis
595.2		Other chronic cystitis
596.54		Neurogenic bladder NOS
791.0		Proteinuria
V56		Treatment related to dialysis
In any diagnosis field		
	38.95	Venous catheterization renal dialysis

	39.27	Arteriovenostomy renal dialysis
	39.42	Revision arteriovenous shunt renal dialysis
	39.95	Hemodialysis
	54.93	Creation of cutaneoperitoneal fistula
	54.98	Peritoneal dialysis
	Only main procedure	
Data sources:ASA		
	39.95.1	Emodialisi in acetato o in bicarbonato
	39.95.2	Emodialisi in acetato o in bicarbonato, ad assistenza limitata
	39.95.3	Emodialisi in acetato o in bicarbonato, domiciliare
	39.95.4	Emodialisi in bicarbonato e membrane molto biocompatibili
	39.95.5	Emodiafiltrazione
	39.95.6	Emodiafiltrazione ad assistenza limitata
	39.95.7	Altra emodiafiltrazione
	39.95.8	Emofiltrazione
	39.95.9	Emodialisi- Emofiltrazione
	38.95	Cateterismo venoso per dialisi renale
	39.99.1	Valz ricircolo fistola arterovenosa
	54.93	Creazione fistola cutaneoperitoneale
	54.98.1	Dialisi peritoneale automatizzata (CCPD)
	54.98.2	Dialisi peritoneale continua (CAPD)

Retinopathy

Data sources: Hospital Discharge database (SDO) and Outpatient Database (ASA)

ICD9-CM diagnosis codes	ICD9-CM Procedures codes	**DRG**	Description
	14.23;14.24:14.25		Retinal lesion photocoagulation
	14.33;14.34;14.35		Repair retinal tear photocoagulation
	14.41		Air retinal detachment sclera buckling implant
	14.53;14.54;14.55		Repair retinal detachment
	14.59		Other repair for retinal detachment
	14.73;14.74		Vitrectomy
	13._		Cristalline repair
	Main procedure selected by DRG-Grouper		
		039	Intervention on Crystalline
Data sources:ASA			
	14.33		Riparazione lacer. retina con fotocoagulazione (xenon)
	14.34		Riparazione lacer. retina con fotocoagulazione (argon)
	13.41.01		Facoemulsionamento ed aspirazione di cataratta

Stroke

Data sources: Hospital Discharge database (SDO)

ICD9-CM diagnosis codes	ICD9-CM Procedures codes	Description
430		Subarachnoid hemorrhage
431		Intracerebral hemorrhage
432._		Unspecified intracranial hemorrhage
433._		Occlusion and stenosis of precerebral artery
434._		Occlusion and stenosis of cerebral artery
435._		Transient cerebral ischemias
436		Acute, but ill-defined, cerebrovascular disease
437._		Other vascular cerebral disease
438._		Late effects of cerebrovascular disease
784.3		Aphasia
In any diagnosis field		
	38.11	Endarterectomy intracranial vessels
	38.12	Endarterectomy vessels head neck
	Main procedure selected by DRG-Grouper	

Peripheral revascularization

Data sources: Hospital Discharge database (SDO)

ICD9-CM diagnosis codes	ICD9-CM Procedures codes	Description
440.2_		Atherosclerosis of native arteries of the extremities
250.7_		Diabetes with peripheral circulatory disorders
In any diagnosis field		
	38.18	Endarterectomy lower limb arteries
	39.25	Aortailiacfemoral bypass
	39.29	Peripheral vascular shunt bypass
	39.50	Angioplasty or atherectomy of other non-coronary vessel(s)
	Main procedure selected by DRG-Grouper	
	MPR 39.50 with 39.90	Angioplasty or atherectomy of other non-coronary vessel(s) with Insertion of non-drug-eluting peripheral vessel stent(s)
	MPR 39.50 with 88.48	Angioplasty or atherectomy of other non-coronary vessel(s) with Arteriography of femoral and other lower extremity arteries

Amputation

Data sources: Hospital Discharge database (SDO)

ICD9-CM diagnosis codes	ICD9-CM Procedures codes	Description
	84.10	Lower limb amputation not otherwise specified
	84.11	Toe amputation
	84.12	Amputation through foot
	84.13	Ankle disarticulation
	84.14	Ankle amputation through malleoli tibia fibula
	84.15	Below knee Amputation
	84.16	Knee disarticulation
	84.17	Above Knee amputation
	84.18	Hip disarticulation
	84.19	Abdomino-pelvic amputation
Excluded DRG: 213,408,442,443 Excluded diagnosis 170.7, 170.8,895._,896._897._		

APPENDIX 12

Search Strategy (Ch. 6)

MEDLINE	Diabetes Mellitus, Type 1"[Mesh] OR "Insulin/administration and dosage"[Mesh]	AND	CSII OR “Infusion System, Insulin” [All Fields] OR “Infusion Systems, Insulin” ” [All Fields] OR “Insulin Infusion System” ” [All Fields] OR “System, Insulin Infusion” ” [All Fields] OR “Systems, Insulin Infusion” ” [All Fields] OR “Continuous subcutaneous” ” [All Fields] OR Sensor augmented pump” [All Fields] OR SAP	AND	"Patient Compliance"[Mesh] OR "Patient Participation"[Mesh] OR "Patient Preference"[Mesh] OR "Patient Satisfaction"[Mesh] OR "Quality of Life"[Mesh] OR "Patient Acceptance of Health Care"[Mesh] OR "Adaptation, Psychological"[Mesh] OR “patient compliance” [Title/Abstract] OR “Patient Participation” [Title/Abstract] OR “Patient Preference” [Title/Abstract] OR "Patient Satisfaction"[Title/Abstract] OR “Quality of Life"[Title/Abstract] OR “Patient Acceptance” [Title/Abstract]

Limits: All Child: 0-18 years, Newborn: birth-1 month, Infant: 1-23 months, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years, Publication Date from 2005/01/01 to 2012

Narrow Strategy

MEDLINE	Diabetes Mellitus, Type 1"[Mesh] OR "Insulin/administration and dosage"[Mesh]	AND	CSII OR “Infusion System, Insulin” [All Fields] OR “Infusion Systems, Insulin”	AND	(continuous blood glucose monitoring) [Title/Abstract] OR (continuous glucose monitoring) [Title/Abstract] OR CGM	AND	"Patient Compliance"[Mesh] OR "Patient Participation"[Mesh] OR "Patient Preference"[Mesh] OR "Patient Satisfaction"[Mesh] AND "Quality of Life"[Mesh] OR "Patient Acceptance of Health Care"[Mesh] OR	3 results

			” [All Fields] OR “Insulin Infusion System ” ” [All Fields] OR “Syste m, Insulin Infusion ” ” [All Fields] OR “Syste ms, Insulin Infusion ” ” [All Fields] OR “Contin uous subcuta neous” ” [All Fields] OR Sensor augmen ted pump” [All Fields] OR SAP		[Title/Abstr act] OR SMBG [Title/Abstr act] OR (Sensor augmented) [Title/Abstr act] OR SAP [Title/Abstr act]		"Adaptation, Psychological"[Mesh] OR “patient compliance” [Title/Abstract] OR “Patient Participation” [Title/Abstract] OR “Patient Preference” [Title/Abstract] OR "Patient Satisfaction"[Titl e/Abstract] OR “Quality of Life"[Title/Abstra ct] OR “Patient Acceptance” [Title/Abstract]	
Limits: All Child: 0-18 years, Newborn: birth-1 month, Infant: 1-23 months, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years, Publication Date from 2005/01/01 to 2012								

Embase	"Diabetes Mellitus, Type 1"/syn OR "Diabetes Mellitus, Type 1"/exp OR "Insulin/administration and dosage"	AND	CSII/syn OR CSII/exp OR "Continuous subcutaneous"/syn OR "Continuous subcutaneous"/exp AND "Insulin Infusion System"	AND	"continuous blood glucose monitoring" : ab:ti OR "continuous glucose monitoring" : ab:ti OR CGM: ab:ti OR SMBG: ab:ti OR "Sensor augmented" : ab:ti OR SAP: ab:ti	AND	"Patient Compliance" : ab:ti OR "Patient Participation" : ab:ti OR "Patient Preference" : ab:ti OR "Patient Satisfaction" : ab:ti OR "Quality of Life": ab:ti OR "Patient Acceptance of Health Care" : ab:ti OR "Patient Adaptation": ab:ti

"Diabetes Mellitus, Type 1” ti,ab,kw OR "Diabetes Mellitus, Type 1”/” ti,ab,kw OR "Insulin/administration and dosage"” ti,ab,kw	AND	CSII OR “Infusion System, Insulin” ti,ab,kw OR “Infusion Systems, Insulin” ti,ab,kw OR “Insulin Infusion System” ” ti,ab,kw OR “System, Insulin Infusion” ” ti,ab,kw OR “Systems, Insulin Infusion” ti,ab,kw OR “Continuous subcutaneous” ti,ab,kw OR Sensor augmented pump” ti,ab,kw OR SAP	AND	"Patient Compliance" : ti,ab,kw OR "Patient Participation" : ti,ab,kw OR "Patient Preference" : ti,ab,kw OR "Patient Satisfaction" : ti,ab,kw OR "Quality of Life": ti,ab,kw OR "Patient Acceptance of Health Care” : ti,ab,kw OR "Patient Adaptation": ti,ab,kw

APPENDIX 13

Consulted websites (Ch.6.)

National Institute for Health and Clinical Excellence NICE	www.nice.org.uk	28th January 2012
Patient.co.uk	Patient.co.uk	4th March 2012
Diabetes.org.uk	Diabetes.org.uk	4th March 2012
Progetto Diabete /	www.progettodiabete.org	4th March 2012
U.S. Centre for Disease Control CDC	www.cdc.gov	4th March 2012
American Diabetes Association	www.diabetes.org	4th March 2012
All citizens associations included in the web site of Partecipasalute	www.partecipasalute.it/cms_2/assodiabete	5th March 2012
Agency for Healthcare Research and Quality (AHRQ)	www.ahrq.gov	29th January 2012
Alberta Heritage Foundation for Medical Research	www.aihealthsolutions.ca	30th January 2012
Australian Safety and Efficacy Register of New Interventional Procedures	www.surgeons.org/for-health-professionals/audits-and-surgical-research/asernip-s/	5th March 2012
Bandolier. /	www.medicine.ox.ac.uk/bandolier	5th – March 2012

Technologies in Health (CADTH: Catalan Agency for Health Technology Assessment (CAHTA) /	www.gencat.cat/salut/depsan/units/aatrm/html/en/Du8/index.html	5th March 2012
Centre for Reviews and Dissemination, University of York	www.york.ac.uk/inst/crd/	5th March 2012
L. Hayes, Inc.	http://hayesinternational.com/	5th March 2012
Health Canada	www.hc-sc.gc.ca	5th March 2012
Health Services/Technology Assessment Text National Library of Medicine	text.nlm.nih.gov/	5th March 2012
Institute for Clinical Evaluative Sciences. Canada	www.ices.on.ca/	5th March 2012
Institute for Healthcare Improvement.	www.ihi.org	5th March 2012
International Network of Agencies for Health Technology Assessment (INAHTA)	www.inahta.org/	5th March 2012
Medical Services Advisory Committee (MSAC):	www.msac.gov.au	3rd March marzo 2012
National Centre for Biotechnology Information (NCBI).	www.ncbi.nlm.nih.gov/	3rd 2012

National Coordinating Centre for Health Technology Assessment (NCCHTA) National Horizon Scanning Centre	www.hta.ac.uk	3rd March 2012

APPENDIX 14

List of excluded studies and reasons for exclusions (Ch.6.)

Excluded for not being on target population

Aberle, I. and others. March 2009. Psychological aspects in continuous subcutaneous insulin infusion: a retrospective study. J Psychol 143, no. 2: 147-60.

Boyle, M. E. December 2008. Optimizing the treatment of type 2 diabetes using current and future insulin technologies. Medsurg Nurs 17, no. 6: 383-90.

Delea, T. E. and others. October 2007. Consequences and costs of noncompliance with iron chelation therapy in patients with transfusion-dependent thalassemia: a literature review. Transfusion 47, no. 10: 1919-29.

Fisher, L. K. and M. Halvorson. January 2006-28 February 2006. Future developments in insulin pump therapy progression from continuous subcutaneous insulin infusion to a sensor-pump system. Diabetes Educ 32, no. 1 Suppl: 47S-52S.???

Franciosi, M. and others. January 2010. Correlates of quality of life in adults with type 1 diabetes treated with continuous subcutaneous insulin injection. Nutr Metab Cardiovasc Dis 20, no. 1: 7-14.

Garg, S. and others. November 2010. Clinical experience with insulin glargine in type 1 diabetes. Diabetes Technol Ther 12, no. 11: 835-46.

Minicucci, W. J. March 2008. [Insulin pump therapy in patients with type 1 diabetes]. Arq Bras Endocrinol Metabol 52, no. 2: 340-8.

Ritholz M. D. and others. March 2007. Perceptions of psychosocial factors and the insulin pump. Diabetes Care 30, no. 3: 549-54.

Rodrigues I. A. and others. July 2005. Indications and efficacy of continuous subcutaneous insulin infusion (CSII) therapy in Type 1 diabetes mellitus: a clinical audit in a specialist service. Diabet Med 22, no. 7: 842-9.

Rubin R. and M. Peyrot. November 2009. Treatment satisfaction and quality of life for an integrated continuous , glucose monitoring/insulin pump system compared to self-monitoring plus an insulin pump. J Diabetes Sci Technol 3, no. 6: 1402-10.

Sane, T. and others. 2005. [Insulin pump in the treatment of adult age diabetes]. Duodecim 121, no. 8: 839-45.

Shapira, G. and others. July 2010. Bolus guide: a novel insulin bolus dosing decision support tool based on selection of carbohydrate ranges. J Diabetes Sci Technol 4, no. 4: 893-902.

van Bon, A. C. and others. July 2011. Future acceptance of an artificial pancreas in adults with type 1 diabetes. Diabetes Technol Ther 13, no. 7: 731-6

Seereiner, S. and others. January 2010. Attitudes towards insulin pump therapy among adolescents and young people. Diabetes Technol Ther 12, no. 1: 89-94.

Excluded for not reporting data/not including QoL as an outcome

The accuracy of the Guardian RT continuous glucose monitor in children with type 1 diabetes. August 2008. Diabetes Technol Ther 10, no. 4: 266-72.

Babar, G. S. and others. March 2009. Factors associated with adherence to continuous subcutaneous insulin infusion in pediatric diabetes. Diabetes Technol Ther 11, no. 3: 131-7.

Bonfanti, R. and others. 2010. Insulin pump therapy versus multiple injections in young children with diabetes: Comparison of long-term efficacy. Pediatr. Diabetes 11: 100.

Buckingham, B. and others. October 2007. Continuous glucose monitoring in children with type 1 diabetes. J Pediatr 151, no. 4: 388-93, 393.e1-2

Buckingham, B. and others. April 2008. Use of the DirecNet Applied Treatment Algorithm (DATA) for diabetes management with a real-time continuous glucose monitor (the FreeStyle Navigator). Pediatr Diabetes 9, no. 2: 142-7.

Chobot, A. P. and others. 2007. [Treatment of type 1 diabetes mellitus revealed below 7 years of age in the Diabetes Center of Silesia, Poland]. Pediatr Endocrinol Diabetes Metab 13, no. 2: 75-8.

Hirsch, I. B. and others. October 2008. Sensor-augmented insulin pump therapy: results of the first randomized treat-to-target study. Diabetes Technol Ther 10, no. 5: 377-83.

Hofer, S. E. and others. March 2010. Discontinuation of insulin pump treatment in children, adolescents, and young adults. A multicenter analysis based on the DPV database in Germany and Austria. Pediatr Diabetes 11, no. 2: 116-21.

Lange, K. and others. October 2007. Prerequisites for age-appropriate education in type 1 diabetes: a model programme for paediatric diabetes education in Germany. Pediatr Diabetes 8 Suppl 6: 63-71.

Lombardo, F. and others. 2005. Compliance and administration methods in management of type 1 diabetes. Acta Biomed 76 Suppl 3: 66-9.

O'Connell, M. A., S. Donath, and F. J. Cameron. September 2011. Poor adherence to integral daily tasks limits the efficacy of CSII in youth. Pediatr Diabetes 12, no. 6: 556-9..

Weinzimer, S. A. and others. August 2006. Emerging evidence for the use of insulin pump therapy in infants, toddlers, and preschool-aged children with type 1 diabetes. Pediatr Diabetes 7 Suppl 4: 15-9.

Wiebe, D. J. and others. November 2010. Parental involvement buffers associations between pump duration and metabolic control among adolescents with type 1 diabetes. J Pediatr Psychol 35, no. 10: 1152-60.

Wood, J. R. and others. November 2006. Durability of insulin pump use in pediatric patients with type 1 diabetes. Diabetes Care 29, no. 11: 2355-60.

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Olinder, A. L., A. Kernell, and B. Smide. April 2009. Missed bolus doses: devastating for metabolic control in CSII-treated adolescents with type 1 diabetes. Pediatr Diabetes 10, no. 2: 142-8.

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APPENDIX 15

Search Strategy (Ch.7.)

MEDLINE 1

"Diabetes Mellitus, Type 1"[Mesh] OR "Diabetes Mellitus" [Title/Abstract]	AND	CSII [Title/Abstract] OR "Insulin infusion systems"[Mesh] OR "Continuous subcutaneous"[Title/Abstract] OR Infusion pumps "[Mesh]	AND	"multiple daily injections" [Title/Abstract] OR MDI [Title/Abstract] OR "Injections"[Mesh] OR "Multiple insulin injection" [Title/Abstract]	AND	"Costs and Cost Analysis"[Mesh] OR "Economics"[Mesh] OR "Cost Allocation"[Mesh] OR "Cost-Benefit Analysis"[Mesh] OR "Cost of Illness"[Mesh] OR "Cost Control"[Mesh] OR "Cost Savings"[Mesh] OR "Health Care Costs"[Mesh] OR "Direct Service Costs"[Mesh] OR "Hospital Costs"[Mesh]) OR Cost-effectiveness [Title/Abstract] OR Cost-utility [Title/Abstract] OR Cost – effectiveness [Title/Abstract] OR Cost – utility [Title/Abstract] OR Cost*[Title/Abstract]

MEDLINE 2

“Diabetes Mellitus, Type 1"[Mesh] OR “Diabetes Mellitus” [Title/Abstract]	AND	(CSII [Title/Abstract] OR “Insulin infusion systems"[Mesh] OR “Continuous subcutaneous”[Title/Abstract] OR Infusion pumps "[Mesh] AND “continuous blood glucose monitoring” [Title/Abstract] OR “continuous glucose monitoring” [Title/Abstract] OR CGM [Title/Abstract]) OR (“Sensor augmented pump” [Title/Abstract] OR SAP [Title/Abstract] OR Insulin Pump [Title/Abstract])	AND	“multiple daily injections” [Title/Abstract] OR MDI [Title/Abstract] OR "Injections"[Mesh] OR “Multiple insulin injection” [Title/Abstract]	AND	"Costs and Cost Analysis"[Mesh] OR "Economics"[Mesh] OR "Cost Allocation"[Mesh] OR "Cost-Benefit Analysis"[Mesh] OR "Cost of Illness"[Mesh] OR "Cost Control"[Mesh] OR "Cost Savings"[Mesh] OR "Health Care Costs"[Mesh] OR "Direct Service Costs"[Mesh] OR "Hospital Costs"[Mesh]) OR Cost-effectiveness [Title/Abstract] OR Cost-utility [Title/Abstract] OR Cost – effectiveness [Title/Abstract] OR Cost – utility [Title/Abstract] OR Cost*[Title/Abstract]

EMBASE 1

“Diabetes Mellitus, Type 1"/exp OR “Diabetes Mellitus, Type 1"/syn OR ’insulin dependent diabetes mellitus’/exp	AND	CSII :ab,ti OR “Insulin Infusion”/ :ab,ti OR “Insulin pump” :ab,ti OR “Continuous subcutaneous”/:ab,ti	AND	“multiple daily injections”/ :ab,ti OR MDI/ :ab,ti OR Injection*/ :ab,ti	AND	"Costs and Cost Analysis/:ab,ti OR "Economics”/:ab,ti OR "Cost Allocation”/:ab,ti OR "Cost-Benefit/:ab,ti OR "Cost Control"/:ab,ti OR "Cost Saving"/:ab,ti OR Cost*/:ab,ti OR “Cost-effectiveness”/:ab,ti OR “Cost-utility”/:ab,ti OR

EMBASE 2

“Diabetes Mellitus, Type 1"/exp OR “Diabetes Mellitus, Type 1"/syn OR ’insulin dependent diabetes mellitus’/exp	AND	CSII :ab,ti OR “Insulin Infusion”/ :ab,ti OR “Insulin pump” :ab,ti OR “Continuous subcutaneous”/:ab,ti AND “Continuous monitor system” :ab,ti OR “Sensor Augmented Pump”/ :ab,ti OR SAP/:ab,ti	AND	“multiple daily injections”/ :ab,ti OR MDI/ :ab,ti OR Injection*/ :ab,ti	AND	"Costs and Cost Analysis/:ab,ti OR "Economics”/:ab,ti OR "Cost Allocation”/:ab,ti OR "Cost-Benefit/:ab,ti OR "Cost Control"/:ab,ti OR "Cost Saving"/:ab,ti OR Cost*/:ab,ti OR “Cost-effectiveness”/:ab,ti OR “Cost-utility”/:ab,ti OR

DARE, , EED, HTA database 1

Diabetes Mellitus, Type 1"[Mesh Descriptor explode all trees] OR “Diabetes Mellitus” (ti,ab,kw)	AND	CSII (ti,ab,kw) OR “Insulin Infusion” (ti,ab,kw)	AND	“multiple daily injections”/ (ti,ab,kw) OR MDI/ (ti,ab,kw) OR Injection*/ (ti,ab,kw)	"Costs and Cost Analysis"[Mesh] OR "Economics"[Mesh] OR "Cost Allocation"[Mesh] OR "Cost-Benefit Analysis"[Mesh] OR "Cost of Illness"[Mesh] OR "Cost Control"[Mesh] OR "Cost Savings"[Mesh] OR "Health Care Costs"[Mesh] OR "Direct Service Costs"[Mesh] OR "Hospital Costs"[Mesh]) OR “Cost-effectiveness” (ti,ab,kw) OR “Cost-utility” (ti,ab,kw) OR “Cost – effectiveness” OR Costs (ti,ab,kw) OR Cost (ti,ab,kw) OR Economic (ti,ab,kw)

DARE, EET HTA DATABASE 2

Diabetes Mellitus, Type 1"[Mesh Descriptor explode all trees] OR “Diabetes Mellitus” (ti,ab,kw)	AND	CSII (ti,ab,kw) OR “Insulin Infusion” (ti,ab,kw) AND “continuous blood glucose monitoring” (ti,ab,kw) OR “continuous glucose monitoring” (ti,ab,kw) OR “Continuous subcutaneous” (ti,ab,kw) OR CGM (ti,ab,kw) OR “Sensor augmented pump” (ti,ab,kw) OR SAP (ti,ab,kw) OR “Insulin Pump” (ti,ab,kw)	AND	“multiple daily injections”/ (ti,ab,kw) OR MDI/ (ti,ab,kw) OR Injection*/ (ti,ab,kw)	"Costs and Cost Analysis"[Mesh] OR "Economics"[Mesh] OR "Cost Allocation"[Mesh] OR "Cost-Benefit Analysis"[Mesh] OR "Cost of Illness"[Mesh] OR "Cost Control"[Mesh] OR "Cost Savings"[Mesh] OR "Health Care Costs"[Mesh] OR "Direct Service Costs"[Mesh] OR "Hospital Costs"[Mesh]) OR “Cost-effectiveness” (ti,ab,kw) OR “Cost-utility” (ti,ab,kw) OR “Cost – effectiveness” OR Costs (ti,ab,kw) OR Cost (ti,ab,kw) OR Economic (ti,ab,kw)

Limiti: Meta-Analysis, Randomized Controlled Trial, Systematic Review, quasi-randomized controlled trials. All Infant: birth-23 months, All Child: 0-18 years, Newborn: birth-1 month, Infant: 1-23 months, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years, Publication Date from 2005/01/01 to 2012

APPENDIX 16

Consulted websites (Ch.7)

We used a free text strategy to search the other databases listed in the text

- Agency for Healthcare Research and Quality (AHRQ)
- Australian Safety and Efficacy Register of New Interventional Procedures
- Technologies in Health (CADTH: Catalan Agency for Health Technology Assessment (CAHTA) /
- Health Canada
- International Network of Agencies for Health Technology Assessment (INAHTA)
- Medical Services Advisory Committee (MSAC):
- National Coordinating Centre for Health Technology Assessment (NCCHTA) National Horizon Scanning Centre
- National Institute for Health and Clinical Excellence (NICE):
- NHS Quality Improvement Scotland (NHS QIS)
- Trip Database.
- Cochrane Collaboration

.

APPENDIX 17

List of Excluded studies (Ch. 7)

1. Conget Donlo I, Serrano Contreras D, Rodriguez Barrios JM, Levy Mizrahi I, Castell Abat C, Roze S. [Cost-utility analysis of insulin pumps compared to multiple daily doses of insulin in patients with type 1 diabetes mellitus in Spain]. Rev Esp Salud Publica 2006; 80(6):679-95.
2. Muller-Godeffroy E, Treichel S, Wagner VM. Investigation of quality of life and family burden issues during insulin pump therapy in children with Type 1 diabetes mellitus--a large-scale multicentre pilot study. Diabet Med 2009; 26(5):493-501.
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APPENDIX 18

Questionnaire (Ch.7)

Questionario

Sistemi integrati microinfusore-monitoraggio

continuo del glucosio e terapia multiniettiva

Nome centro	Fare clic qui per immettere testo.		
Indirizzo	Fare clic qui per immettere testo.		
Regione	Fare clic qui per immettere testo.		
Responsabile centro (persona da contattare per invio questionario)	Fare clic qui per immettere testo.	**Telefono**	Fare clic qui per immettere testo.
		E-mail	Fare clic qui per immettere testo.

Tipo di ente/centro		
Pubblico	**Privato**	**Privato Convenzionato**
□Ospedaliero	□Ospedaliero	□Ospedaliero
□Ambulatoriale	□Ambulatoriale	□Ambulatoriale
□Altro-Specificare: ____	□Altro-Specificare: ____	□Altro-Specificare: ____

Indicare il numero totale annuo di pazienti pediatrici con diabete di tipo 1, per ogni fascia d'età (dati 2011)	**N°** Fare clic qui per immettere testo.
<5	Fare clic qui per immettere testo.
5-13	Fare clic qui per immettere testo.
13-18	Fare clic qui per immettere testo.

Sistemi integrati microinfusore-monitoraggio continuo del glucosio

(Sensor Augmented Pump - SAP)

PERIODO DI PROVA

1. Specificare il regime utilizzato per l'avvio del percorso	**N° pazienti**
Ricovero Ordinario	Fare clic qui per immettere testo.
Ambulatoriale	Fare clic qui per immettere testo.
Day Hospital	Fare clic qui per immettere testo.

2. Indicare il numero di pazienti per ogni fascia di età che nell'anno 2011 hanno effettuato un periodo di prova

0-5 anni	**5-13 anni**	**13-18 anni**
Fare clic qui per immettere testo.	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.

3. Qual è la durata del periodo di prova? Fare clic qui per immettere testo.

4. Indicare l'impiego del personale (numero unità) e ore lavorative al mese per il periodo di prova per singolo paziente

	Formazione inziale (paziente/genitore)	**Set up**	**Follow up**
Medico diabetologo			
– Numero	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.
– Ore (indicare la somma delle ore per unità di personale, nel caso di più medici)	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.
Infermiere			
– Numero	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.
– Ore (indicare la somma delle ore per unità di personale, nel caso di più infermieri)	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.
Dietista			
– Numero	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.
– Ore (indicare la somma delle ore per unità di personale, nel caso di più dietisti)	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.
Tecnico dell'azienda			
– Numero	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.
– Ore (indicare la somma delle ore per unità di personale, nel caso di più tecnici)	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.

5. Indicare, per ogni fascia di età, quanti dei pazienti sopra indicati sono passati alla nuova terapia <u>DOPO il periodo di prova</u>

0-5 anni	**5-13 anni**	**13-18 anni**
Fare clic qui per immettere testo.	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.

AVVIO TERAPIA INIZALE

6. Indicare l'impiego del personale (numero unità) e ore lavorative per singolo paziente) per <u>tre mesi di terapia</u>	
	Follow up
Medico diabetologo	
– Numero	Fare clic qui per immettere testo.
– Ore (indicare la somma delle ore per unità di personale, nel caso di più medici)	Fare clic qui per immettere testo.
Infermiere	
– Numero	Fare clic qui per immettere testo.
– Ore (indicare la somma delle ore per unità di personale, nel caso di più infermieri)	Fare clic qui per immettere testo.
Dietista	
– Numero	Fare clic qui per immettere testo.
– Ore (indicare la somma delle ore per unità di personale, nel caso di più dietisti)	Fare clic qui per immettere testo.

Terapia multiniettiva

(Multiple Daily Injections - MDI)

1. Specificare il regime utilizzato per l'avvio del percorso	**N° pazienti**
Ricovero Ordinario	Fare clic qui per immettere testo.
Ambulatoriale	Fare clic qui per immettere testo.
Day Hospital	Fare clic qui per immettere testo.

2. Indicare il numero di pazienti in terapia multi iniettiva nell'anno 2011		
0-5 anni	**5-13 anni**	**13-18 anni**
Fare clic qui per immettere testo.	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.

3. Indicare l'impiego del personale (numero unità e ore lavorative per singolo paziente) per <u>tre mesi di terapia</u>		
	Formazione paziente/genitore	**Follow up**
Medico diabetologo		
– Numero	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.
– Ore (indicare la somma delle ore per unità di personale, nel caso di più medici)	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.
Infermiere		
– Numero	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.
– Ore (indicare la somma delle ore per unità di personale, nel caso di più infermieri)	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.
Dietista		
– Numero	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.
– Ore (indicare la somma delle ore per unità di personale, nel caso di più dietisti)	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.

INFORMAZIONI SUI DEVICE

Sistemi integrati microinfusore-monitoraggio continuo del glucosio

1. Indicare la marca del device in uso (2011) e il nome del distributore:	Fare clic qui per immettere testo.
2. Il dispositivo è fornito gratuitamente nel periodo di prova?	Fare clic qui per immettere testo.
3. Se il dispositivo NON è fornito gratuitamente in prova, indicare costo unitario di acquisto per la prova:	Fare clic qui per immettere testo.
4. Indicare il costo unitario di acquisto del dispositivo definitivo:	Fare clic qui per immettere testo.
5. Indicare gli anni di garanzia del dispositivo:	Fare clic qui per immettere testo.
6. Il materiale consumabile monouso è fornito gratuitamente nel periodo di prova?	Fare clic qui per immettere testo.
7. Se il materiale consumabile monouso NON è fornito gratuitamente in prova, indicare tipologia e costo unitario di acquisto per la prova:	Fare clic qui per immettere testo.
8. Indicare il numero di unità di materiale che generalmente viene utilizzato per un singolo paziente/MESE?	Fare clic qui per immettere testo.

	E' monouso?	Se si, indicare il numero di unità di materiale per paziente/mese	Indicare il costo unitario
MICROINFUSORE			
Monitor	□SI □NO		
Serbatoio	□SI □NO		
Set	□SI □NO		
Insertore meccanico	□SI □NO		
Cannula sottocutanea	□SI □NO		
MONITORAGGIO GLICEMICO			
Sensore	□SI □NO		
Trasmettitore	□SI □NO		

Terapia multiniettiva

	Numero di unità di materiale per paziente/mese	Costo unitario
Lancette pungidito	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.
Strisce reattive	Fare clic qui per immettere testo.	Fare clic qui per immettere testo.