shortreport

Regione Emilia-Romagna
SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA
osservatorio regionale per l'innovazione

INNOVATIVE MEDICAL DEVICES FOR DIABETES MANAGEMENT

n. 6

TECHNOLOGY

- Devices for continuous subcutaneous insulin infusion (CSII)
- Devices for the continuous glucose monitoring (CGM)
- Sensor-Augmented Pumps (SAPs)

Fully integrated/closed loop systems and implantable devices are not covered by this report.

COMMERCIAL TECHNOLOGY NAME AND PRODUCER'S/SUPPLIER'S NAME

Seven manufacturers of CSII/SAPs are registered in the Italian Ministry of Health Database of medical devices (CND code = Z1204021601) and four manufacturers of CGM devices (CND code = Z12040115). For details please visit the Italian Ministry of Health website (http://www.dati.salute.gov.it/dati/dettaglioDataset.jsp?menu=dati&idPag=1).

USE

n therapeutic

n diagnostic

¨ other: prognostic

CATEGORY

Therapeutic / diagnostic devices.

THERAPEUTIC / DIAGNOSTIC FIELD OF APPLICATION

Patients with type 1 or 2 diabetes mellitus undergoing multi-daily injective (MDI) insulin therapy.

PATIENTS / CLINICAL CONDITION

Candidates to the use of CSII, CGM or SAP devices are:

- children or adolescents with type 1 diabetes mellitus
- adults with type I diabetes mellitus
- adults with type II diabetes mellitus

treated with multi-daily insulin injections.

The World Health Organization (WHO) estimates that, worldwide, the number of patients with any form of diabetes mellitus is around 177 millions of people. The increasing prevalence of the disease is due to population increase and ageing, progressive urbanization, increasing prevalence of obesity and physical inactivity. The WHO forsees that by 2025 people with diabetes mellitus could double in number (Shaw 2009).
Type 1 diabetes mellitus consists in approximately 10-15% of all cases of diabetes with and it is increasing at a yearly rate of around 3% (Diabetes Outreach 2009).
Italy's National Institute of Statistics (Istituto Nazionale di Statistica Italiano, ISTAT) estimates that 4.9% of Italians are affected by type 1 or 2 diabetes, adding up to around three millions of people (ISTAT 2011).

THE REPORT

A brief presentation of a technology, providing sufficient information to decide whether to undertake a comprehensive assessment process.

The reported information derives from:

› the consultation of web materials supplied by the producer and of current national and/or regional registries

› the search of secondary studies on HTA databases and of primary studies, indexed on Medline.

! The report does not represent a definitive assessment of the technology.

UPDATED

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ISSUED BY

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In 2007 the prevalent diabetic population in the Emilia-Romagna region totalled 208.738 patients (4,98% of regional population; 4,70% of women and 5,28% of men living in Emilia-Romagna) (Dossier 179/ 2009).
In order to estimate the number of Emilia-Romagna patients treated with multi-daily insulin injections in 2011, we selected from the regional pharmaceutical database all patients assuming multi-daily insulin injections (drugs with the following ATC code: A10A) in 2011. To estimate the number of patients with type 1 diabetes in 2011, patients assuming insulin (ATC code: A10A) in 2011 and not assuming oral antidiabetics (ATC code: A10B) neither in 2011 nor in the four previous years were selected from the regional pharmaceutical database (Arno 2007).
The estimated number of patients with type 1 or 2 diabetes treated with multi-daily insulin injections in 2011 was 45.109 (2011-cohort of diabetic patients), whilst the estimated number of patients with type I diabetes mellitus was 17.748, of which 836 were children or adolescents (<18 years of age).
If not properly treated, diabetes can lead to serious complications, avoidable or limited by maintaining target blood glucose levels. To evaluate the effectiveness of diabetic patients' management and to single out possible critical aspects, we studied the prevalence of micro- and macrovascular complications in patients with type I diabetes (17.748 cases) living in Emilia-Romagna. The analysis aimed at estimating the prevalence of complications in 2011. Data on hospital admissions and healthcare services for diabetes complications from 2006 to 2011 were extracted only for adult patients (> 18 years of age) with type I diabetes included in the 2011-cohort of diabetic patients.
Diabetes complications included in the analysis were: retinopathy, renal complications and dialysis (microvascular complications), stroke, myocardial infarction, hischemic cardiomiopathy, peripheral vascular disease and surgical amputations (macrovascular complications).
Data showed that 10.7% of patients with type I diabetes had retinopathy, 14.5% renal complications and 2.4% required dialysis; 12.8% of patients suffered a stroke, 5.5% myocardial infarction and 16.8% cardiovascular complications. Diabetic patients that underwent peripheral re-vascularization were 12.0% whilst 2.5% underwent surgical amputation.

STANDARD TREATMENT / PRACTICE

The alteration in the production/release of insulin, typical of diabetes mellitus, leads to (hyperglycaemia) that can cause, in the short term, hyperglycemia hyperosmolar state and diabetic ketoacidosis. If prolonged, high blood glucose levels can, in the long-term, can cause micro- and macrovascular complications. Long-term diabetes complications include vision loss, renal failure, angina pectoris, myocardial infarction, stroke, diabetic foot, polineuropathy and erectile dysfunction.
The main aim of treatment consists in preventing acute and chronic complications. This aim is pursued by maintaining a good glycaemic control and avoiding fluctuations towards hyper- or hypoglycaemia. In type I diabetic patients (children, adolescents and adults) standard treatment consists in multiple daily injections (MDI) – according to basal.-bolus scheme, using rapid and long-acting insulin analogues – (AMD 2010). Self-monitoring of blood glucose (SMBG) by means of finger-pricking and a glucometer is a fundamental part of the streatment strategy (AMD 2010) and it is performed three-four times daily. It requires finger-pricking to produce a drop of blood to be tested with a testing strip and blood glucose meter (Cummins 2010).
Once a day or multiple daily insulin injections may also be indicated for patients with type II diabetes not reaching targets in blood glucose, despite treatment with oral antidiabetic drugs (AMD 2010). SMBG monitoring several times a day is indicated also in patients with type II diabetes (AMD 2010).

TECHNOLOGY DESCRIPTION

Continuous Subcutaneous Insulin Infusion (CSII) pumps

Infusion pumps are medical devices that allow continuous insulin infusion in subcutaneous tissue (Continuous Subcutaneous Insulin Infusion, CSII). Infusion pumps contain a cartridge or a syringe fullfilled with short-acting insulin. Syringe/cartridge is connected to the subcutaneous tissue through an infusion set made by a plastic catheter and either a small needle or soft plastic cannula , usually placed on the abdomen. The needle or cannula should be changed every 3 days. The insulin pumps releases insulin with two modalities: continuous (basal infusion) and on request (insulin boluses).

Continuous Glucose Monitoring (CGM) devices

Continuous glucose monitoring (CGM) devices are proposed as an alternative to SMBG performed several times a day.
They are devices that carry out frequent measures of glycaemic levels, allowing to quickly obtain the glycaemic profile of a diabetic patient. CGM devices measures glycaemic levels in the subcutaneous interstitial fluid (ISF). Particular attention should be given to the time span required by the glucose to pass from blood to tissues, as it represents the lag-time in variations between haematic and tissutal glucose levels. This lag-time is particularly important during rapid variations of glycaemia.

CGM devices are made of:

1. a small monitor (similar to a beeper) that reads and shows glucose levels in real-time or retrospectively;
2. a glucose sensor, inserted in the subcutaneous tissue of the abdomen, wrist or arm;
3. a transmitter sending to the monitor the data on glucose concentrations read by the sensor (by means of a wire or through a wireless technology)

The device should be calibrated using several finger stick blood sugar readings taken with a standard glucose meter. The sensor measures the level of glucose in the tissue every 5-10 seconds and gives a mean value of glucose every five minutes that can be visualised on the monitor. The sensor needs replacing every 3 to 7 days

Two types of CGM devices are available at the moment:

- CGM off-line: glucose levels are not visualised in real-time, but are recorded to be later downloaded. The device measures glucose concentrations in the interstitial fluid for a certain period of time, information is recorded and data can then be downloaded.
- Real-Time CGM (rt-CGM): mean glucose levels are visible on the monitor and patients can use them to adjust insulin therapy.

The main relevant limit of this type of devices is the accuracy in measurement as the sensor is subject to deterioration that leads to systematic errors in measuring.

During use, frequent calibrations are therefore required, by comparing values of SMBG through finger stick blood readings with those concurrently provided by the CGM device. Accuracy of CGM device's glucose readings strongly depends on the calibration phase, that should be performed when blood glucose levels are reasonably stable.

Sensor-Augmented insulin Pumps (SAP)

The semi-integrated (open loop) system for the management of diabetes (SAP) integrates two different technologies: a continuous subcutaneous insulin infusion pump (CSII) and a continuous glucose monitoring (CGM) device. The insulin delivery through subcutaneous tissue is managed by the patient on the basis of the glucose levels measused by the CGM device. This system differs from the fully integrated (closed loop, artificial pancreas) system that is aimed at being fully automated and not requiring patient's intervention for the adjustment of insulin delivery.

TARGET PATIENTS

No consensus has yet been reached, in literature, on characteristics of patients who could potentially benefit from these devices.

Some Health Technology Assessment (HTA) reports and clinical practice guidelines evaluate the use of these devices - in place of standard multiple daily injections or of self-monitoring blood glucose - in patients that have an uncontrolled diabetes and/or recurrent hypoglycaemic episodes. Other documents consider the use of these devices in highly motivated patients with a proven good compliance to MDI treatment during the previous 6-12 months.

MAIN EXPECTED BENEFITS

Hypothesised expected benefits include better glycaemic control, reduction in hypoglycaemic episodes and improvement in quality of life and other health status measures (such as weight reduction). Improvement in these surrogate clinical outcomes is expected to reduce both short- and long-term complications.

Use of CGM devices is expected to improve glycaemic control and/or reduce hypoglycaemic episodes (AMD 2010).

The use of semi-integrated devices (SAP) is proposed as an alternative to MDI coupled with SMBG, to CSII with SMBG, and to MDI with CGM devices.

FROM THE HTA REPORTS AND CLINICAL PRACTICE GUIDELINES PUBLISHED IN THE LAST FIVE YEARS

We performed a systematic search of Health Technology Assessment (HTA) and Horizon Scanning (HS) reports evaluating efficacy and safety of CSII and CGM devices. Moreover, a systematic review of clinical practice guidelines for diabetes management reporting recommendations on us of the devices was performed.
The methodological quality criteria used for the documents' inclusion in our systematic review were description of the search strategy, the applied limits, the criteria for inclusion/exclusion of studies, methods used for studies' quality appraisal of studies.
Due to the recent introduction in the market of these devices, only conclusions from documents published in the last five years (from 2008 till now) are reported.
All retrieved documents judged as low the quality of the presently available studies, highlighting the small number of enrolled patients, the short duration of studies and, as a consequence, the absence of efficacy data on primary clinical outcomes, such as diabetes complications.

CONTINUOUS SUBCUTANEOUS INSULIN PUMPS (CSII)

HTA reports

Two HTA reports were included: HSAC 2008, Cummins 2010. The report published in 2008 (HSAC 2008) by the New Zealand Health Services Assessment Collaboration includes 11 RCTs comparing CSII versus MDI in patients with type 1 or 2 diabetes. Included studies are affected by several biases that compromise their internal validity. The report concludes that elective treatment for type 1 diabetic patients, both adult and children, should continue to be MDI, that CSII pumps should be reserved to a small and selected group of patients with type 1 diabetes and recommends development of common selection criteria.
The report published by NICE in 2010 (Cummins 2010) includes 16 RCTs on type 1 or 2 diabetes, 48 observational studies, 6 studies on pregnant women and 4 systematic reviews. Authors highlight that the large majority of RCTs include small numbers of patients, are short in duration and that studies of good methodological quality are still lacking.
Due to the scarcity of data drawn by RCTs, authors conclude that, on the basis of observational studies, only in patients with type 1 diabetes the use of CSII pumps could offer some benefits over MDI, such as better glycaemic control. Any such gain is highly dependent on the HbA1c at baseline. Other possible benefits include fewer problems related to hypoglycaemia and a gain in quality of life, particularly in terms of a more flexible lifestyle. No advantages either for pregnant women or for patients with type 2 diabetes were found.
Favourable results for the use of CSII pumps derive only from observational studies - mainly case-series - that, as underlined by authors, are affected by serious methodological bias and include highly selected patients compared to the clinical practice.

Clinical practice guidelines

Seven guidelines were selected (AMD 2010, SIGN 2010, VA/DoD 2010, AACE 2011, ADA 2011, CDA 2008, Wisconsin 2011).
Three guidelines (AMD 2010, SIGN 2010, VA/DoD 2010) agree in limiting the use of CSII pumps in young/adult patients with type 1 diabetes when standard MDI treatment fails to reach glycaemic targets or when targets are reached but accompanied by disabling episodes of hypoglycaemia.
The guideline published in 2010 by AMD suggests similar criteria of use of CSII pumps for paediatric patients and when it can facilitate disease management. The remaining four guidelines (AACE 2011, ADA 2011, CDA 2008, Wisconsin 2011) consider CSII pumps as an alternative to MDI treatment in adults and children/adolescents (CDA 2008) with type 1 diabetes limiting their use to motivated and trained patients (AACE 2011, Wisconsin 2011).
In patients with type 2 diabetes, the use of CSII pumps is clearly not recommended by the VA/DoD guideline while it is explicitly recommended by the AACE 2011 in case of deficiency in insulin production (AACE 2011).

DEVICES FOR CONTINUOUS GLUCOSE MONITORING (CGM)

HTA reports

Three HTA reports were retrieved and included: CTAF 2009, WA HTA 2011, OHTAS 2011.
The HTA report produced by the California Technology Assessment Forum (CTAF 2009) includes 22 studies (11 RCTs and 11 observational studies) testing the efficacy of CGM devices in patients with type I diabetes and concludes that these devices do not have necessary requirements in terms of safety, efficacy and improvements of clinical outcomes in children, adolescents, young adults and pregnant women with diabetes. A single RCT with a large sample of patients shows benefits only in patients older than 25.
The HTA report by Washington State Health Authority (WA HTA 2011) included studies evaluating self-monitoring of blood glucose (SMBG) versus CGM plus SMBG. Conclusions are that available evidence is not sufficient to assign a specific role to these devices as a significant improvement of glycaemic control from a clinical point of view is not evident and effects on long-term diabetes outcomes are not known.
The report published by the Ontario Medical Advisory Secretariat (OHTAS 2011) compares SMBG to CGM plus SMBG and includes two RCTs, both enrolling more that one hundred type 1 diabetes. No studies including patients with type 2 diabetes, nor cost-effectiveness studies were retrieved. The report concludes that evidence of moderate quality shows that CGM devices associated to SMBG are not better than SMBG alone in reducing glycaeted haemoglobin (HbA1c) levels and hypoglycaemic events.
Finally, two systematic reviews both produced by the Catalunyan Health Technology Assessment Agency (Agència d'Informaciò, Avaluaciò i Qualitat en Salut, AIAQS) were retrieved. The first one (AIAQS 2010a) compares real-time continuous glucose monitoring systems (rt-CGM) to SMBG in patients with type 1 diabetes and includes 14 RCTs and 2 observational studies. The report concludes that available evidence shows that rt-CGM are effective in adult patients whilst in children specific conditions must be accomplished. Authors highlight that efficacy of these devices strictly depends on patient's motivation and on his/her capacity in type 1diabetes management.
The second systematic review (AIAQS 2010b) explicitly and exclusively evaluates devices produced by Medtronic-MiniMed for patients with type 1 diabetes. Conclusions are that in some studies of good quality a reduction in glucose levels is shown, while the methodological quality studies evaluating reduction of hypo- and hyperglycaemic events is low. Moreover, it is not possible to draw any conclusion on the efficacy of these devices in paediatric patients and evidence on pregnant women with type 1 diabetes is lacking.

Clinical practice guidelines

Six guidelines were included: AACE 2011, ADA 2011, AMD 2010, CDA 2008, SIGN 2010, Wisconsin 2011.
Three guidelines (AACE 2011, ADA 2011, AMD 2010) agree in considering CGM systems useful in young/adult patients with type 1 diabetes to reduce HbA1c levels and hypoglycaemic episodes. Two guidelines (ADA 2011, AMD 2010) consider them useful in paediatric patients, as well, even if they acknowledge that data are lacking. Two other documents (CDA 2008, SIGN 2010) emphasize that data on the continuous monitoring of glucose are scarce but recommend health care authorities to keep their usefulness monitored. The last guideline (Wisconsin 2011) explicitly does not recommend the use of these devices.
None of the above-mentioned guidelines expresses any indication on the use of CGM devices in patients with type 2 diabetes.

SENSOR-AUGMENTED INSULIN PUMPS (SAP).

An HTA report on the use of SAP in paediatric children produced by Agenas and the Italian network for HTA (Rete Italiana per l'HTA, RIHTA) is in press and due to be published by the end of 2012.
No guidelines taking in consideration the use of SAP in patients with type 1 or 2 diabetes were found.

AVAILABLE EVIDENCE AND RESULTS

Bibliographic research

The Short Report methodology consists in identifying primarily up-to-date and good quality systematic reviews. A bibliographic research of primary studies is performed only if good quality systematic reviews are lacking. Given the quantity and quality of the available secondary literature, search for primary studies was judged unnecessary.

Bibliographic research of systematic reviews has been performed in the main bibliographic databases (PubMed, Embase, Cochrane Library) using the keywords describing the disease and the devices. The systematic review produced by the American Agency for Healthcare and Quality Research (AHRQ) was identified as the most recent one (Yeh 2012). It includes all the primary studies included in the previous systematic reviews; the bibliographic search is updated to February 2012.
The systematic review considers CSII pumps, CGM devices and integrated systems (SAP). The methodological quality of the review was considered good according to the AMSTAR checklist (AMSTAR 2007).

Number and type of studies

Considering the completeness of research questions and the update of the bibliographic research, the presently reported data are based on the results provided by the systematic review of Yeh (Yeh 2012). The systematic review includes 33 RCTs: 19 compare CSII pumps with standard MDI, 10 compare CGM with SMBG, and 4 compare SAP system (CSII pump plus CGM device) with MDI plus SMBG.
Included studies enrolled a small number of patients (median number of patients: 72, range: 12-485), had a short duration ($\leq$ 52 weeks) and mostly included adult patients, with older and younger patients scarcely represented. Considered outcomes are short-term and mostly surrogate ones: glycaemic control (mean difference in HbA1C levels and time in hyperglycaemia), hypoglycaemic episodes, health status measures, quality of life; no study assessed long-term clinical outcomes such as micro- and macrovascular complications.
Most included studies were judged to carry a high or intermediate risk of bias. Especially open-label studies measuring subjective outcomes (e.g. quality of life) may be affected by performance bias. Finally, according to the Authors, results are transferable only to highly specialised diabetic centres and to highly motivated diabetic patients.

Results

When possible, data reported in the following sections are mean meta-analytic values as calculated by the authors of the systematic review (Yeh 2012).

TECHNICAL PERFORMANCE / SAFETY

Specific complications due to CSII comprise site-of-infusion infections, blockage of the plastic cannula and pump's malfunctioning. Studies do not report data on these problems but only narrative comments. For CGM devices only cutaneous irritations are reported.
Data on adverse events, like hypoglycaemia, are reported in the efficacy paragraph.

EFFICACY

Continuous Subcutaneous Insulin Infusion versus Multi-Daily Injections

In paediatric patients with type 1 diabetes (7 studies, 238 patients), CSII is not statistically superior to MDI in reducing Hb1Ac (mean difference: -0.1%, CI95% from -0.48 to 0.27%). No statistically significant differences in weight, quality of life (data reported qualitatively) and severe hypoglycaemia (incidence rate: 0.99, CI 95% from 0.57 to 1.71, data from 5 studies for a total of 168 patients). Data are not sufficient to establish a difference in incidence of hyperglycaemic events.
For adult patients with type 1 diabetes (8 studies of which only 4 suitable for meta-analysis, 170 patients), a statistically significant difference between groups in HbA1c reduction is reported (mean difference -0.30%, CI 95% from -0.58% to -0.02%). This result was judged by the reviewers not clinically significant - being below the threshold of -0.50% - and based on highly heterogeneous results. In particular, the only study that reports an improved result - in contrast with the other three studies - enrolled patients with a baseline value for HbA1c greater that 9%, suggesting the improvement to be probably determined by at start worst conditions of patients.
No differences in number of hyperglycaemic episodes, weight increase and severe hypoglycaemic events are reported (OR = 0.69, CI 95% from 0.24 to 1.94 - data from 3 studies, 143 patients). Quality of life resulted to be slightly better for the CSII group (data reported only qualitatively).
In adult patients with type 2 diabetes mellitus (4 studies, 338 patients) no statistically significant difference in reduction of HbA1c is reported between groups (mean difference: -0.18%, CI 95% from -0.43% to 0.08%).
There were no differences in weight and incidence of severe hypoglycaemic episodes (RR = 0.76, CI 95% from 0.26 to 2.19 - data from three studies, number of patients not reported).
Data are not sufficient to assess a difference in hypoglycaemic episodes and quality of life.

Continuous glucose monitoring versus self-blood glucose monitoring

In patients with type 1 diabetes mellitus (10 studies, 1068 patients, children/adolescents and adults) a statistically significant reduction of HbA1c was observed between groups (mean difference -0.26%, CI 95% from -0.33% to -0.19%) and a statistically significant reduction of time spent in hypoglycaemia (-68.5 minutes/day, CI 95% from -101.17 to -35.96). The difference in the HbA1c decrease was judged clinically significant - being below the threshold of -0.50% - and based on heterogeneous results. The heterogeneity is partly explained by the different compliance to glucose monitoring reported in the studies. There are no differences in quality of life and in severe hypoglycaemic episodes (OR = 0.88, CI95% from 0.53 to 1.46, data from 9 studies, 1232 patients).

Sensor-augmented pump versus multi-daily injections and self-monitoring blood glucose

In type 1 diabetes mellitus patients (4 studies, 600 patients, paediatrics and adults) a statistically and clinically significant difference in HbA1c between groups is shown (mean difference: -0.68%, CI95% from -0.81% to -0.54%) and a statistically significant reduction of time spent in hyperglycaemia (p< 0.001, mean difference not reported). Results for HbA1c are heterogeneous and the mean calculated value is highly dependent on a single study which represents approximately the 80% of patients in this group. There are no differences between groups in weight gain or reduction and in incidence of severe hypoglycaemic episodes (RR = 1.2, 95%CI from 0.7 to 2.3 - data reported only for a single study that enrolled 485 patients). Data are not sufficient to establish a difference in QOL. All the studies used the same device (MiniMed Paradigm REALTime Revel System, Medtronic, Northridge, California).

COSTS

Subcutaneous insulin pumps

Data on costs of insulin pumps drawn by the HTA report made by NICE-UK range from 2.375 to 2.750£ (corresponding to 3.027-3.504€) with a four-year warranty, extendable by two additional years at an extra cost of 500£. The yearly cost for disposables is 1.773-2.060£ (2.421-2625€) (Cummins 2010). Authors report that the incremental yearly cost for a patient using CSII instead of MDI is 1.700£ (2.200€).
Preliminary data from a survey carried out in 2012 in diabetololgic centers of Emilia-Romagna region (data from 4 out of 11 centers) show that mean cost for insulin pumps (considering CSII and SAP together) is 5653€ (range: 5.444-5.847€) and mean yearly cost for disposable materials is 3.233€ (range 2.784-3.737€).

Continuous glucose monitoring devices

Data from the Horizon Scanning published by the Australia and New Zealand Horizon Scanning Network (ANZHSN) in 2006 (ANZHSN 2006) report the following costs for the continuous glucose monitoring devices marketed in New Zealand and Australia. The device by Medtronic Australasia costs 5.800 Australian dollars (4.670€) whilst boxes of 4 or 10 glucose sensors cost 300 or 700 Australian dollars (240 or 563€), respectively. The device by produced by Medica Pacifica costs 8.000 New Zealand dollars (5.100€) and each sensor 78 New Zealand dollars (approximately 50€).

PRESUMED IMPACT

Clinical issues

To date, the presumed clinical impact consisting in a better glycaemic control leading to, in the long run, a reduction in micro- and macrovascular adverse effects caused by prolonged hyperglycaemia is not confirmed by the available evidence.

Economic issues

The use of these devices would produce an incremental cost in the management of the diabetic patients that strongly depends on the number of patients candidate to their use.
Presently univocal and shared criteria to identify characteristics of patients that could most benefit from the use of these devices do not exist, thus an e economic impact derived from their use cannot be assessed.

Organizational issues

Specifically trained personnel is required for the use of both insulin pumps and glucose monitoring devices. Personnel should be instructed to train patients and/or caregivers for the use of the devices, periodic maintenance (for example, calibration of the glucometer) and extra-ordinarily maintenance (such as occlusion of the cannula). The use of these devices should be restricted to highly specialised diabetic centres and be part of a structured program of diabetes management.

Ethical-social issues

The use of highly technological devices could be seen as an innovation in terms of a lesser involvement of the patient in the management of his/her disease. However, presently available devices require an active involvement of the patient and/or the caregiver, for example in the re-calibration of glucometer on the basis of the glycaemic values measured by SMBG and in adjustment of insulin doses according to food intake, exercise and/or concomitant diseases. Moreover, the need to wear a device around the clock/all the time may stress the perception of the disease both in patients and in people surrounding them causing embarrassment especially in children and adolescents.

ONGOING STUDIES

From the database www.clincaltrial.gov (last access: September 27th, 2012) the following randomised controlled trials are ongoing.

Continuous Subcutaeous Insulin Infusion (CSII) pumps

Study	Patients	Study design	Primary outcomes	Study deadline
NCT01616784	Adults with type 1 diabetes (n=280)	RCT CSII vs MDI	HbA1c level at 24 months	May 2015
NCT00357890	Type 1 diabetes, age range: 12-17 years (n=12)	RCT CSII vs MDI	HbA1c level at 24 months	December 2013
NCT01574508	Type 2 diabetes, age range: 25-65 years (n=120)	RCT CSII vs MDI	HbA1c level at 12 months Glycaeted albumin at 12 months	December 2013
NCT00574405	Type 1 diabetes, age range: 8-18 years (n=24)	RCT CSII vs MDI	Mixed-meal-stimulated peak C-peptide value	Completed
NCT00942318	Adults with type 2 diabetes (n=52)	RCT CSII vs MDI	HbA1c level at 12 months	Febbruary 2012 (still recruiting)
NCT00360984	Adults with type 1 diabetes (n=21)	RCT CSII vs MDI	Severe hypoglycaemia	Completed
NCT01182493	Type 2 diabetes, age range: 30-75 years (n=400)	RCT CSII vs MDI	HbA1c level at 6 months	June 2013
NCT01338922	Type 1 diabetes, age range: 6-16 (n=272)	RCT CSII vs MDI	Quality of life at 6 months	June 2013

Continuous Glucose Monitoring (CGM) devices

Study	Patients	Study design	Primary outcomes	Study deadline
NCT01175408	Type 2 diabetes, age range: 25-70 years (n=100)	RCT CGM vs Interned Based CGMS	HbA1c level at 6 months	February 2012
NCT01509157	Type 1 diabetes, age range: 4-24 years (n=40)	RCT rt-Remote Monitoring System vs CGMS	time spent in hypoglycaemia at 4 weeks Parents' stress for children's hypoglycaemia at 4 weeks	May 2013
NCT01614262	Type 2 diabetes, age range: 18-70 years (n=90)	RCT CGM vs SMBG	HbA1c level at 187 days	December 2013
NCT01586065	Type 1 diabetes, age range: 12-18 years(n=26)	RCT CGM vs SMBG	HbA1c level at 6 months	June 2013
NCT00875290	Type 1 diabetes, age range: 3 months – 3 years (n=40)	RCT rt-CGM + CSII vs CSII	HbA1c level at 12 months	November 2014
NCT00945659	Type 1 diabetes, age range: 11-16 years (n=150)	RCT CGM vs SMBG	HbA1c level at 6 months	November 2013
NCT00441129	Type 1 diabetes, age range: 2-65 years (n=120)	RCT CGM vs SMBG + CSII	HbA1c level at 6 months	October 2007 (unknown results)

Sensor-Augmented Pumps (SAP)

Study	Patients	Study design	Primary outcomes	Study deadline
NCT01454700	Type 1 diabetes, adults (n=80)	RCT SAP vs MDI	Albuminuria	December 2014
NCT01677546	Type 1 diabetes, age range: 7-18 years (n=156)	RCT SAP vs CSII	HbA1c level at 24 months	July 2012 (completed)

Moreover, 7 additional RCTs evaluating the efficacy of artificial pancreas systems (closed loop systems) were identified.

AUTHORISATION

Data collected from the database of "Repertorio dei dispositivi medici" from Italian Ministry of Health identified:

- 7 manufacturers and 17 types of CSII/SAP
- 4 manufacturers and 5 types of CGMS.

All the CSII/SAP and CGMS have CE mark (i.e. a certification that that the product conforms with the essential requirements of the applicable EC directives).
Of the 17 types of CSII/SAP, 13 have a premarket notification 510(k), i.e the FDA requirement for Class II devices. Only 1 has a premarket approval (PMA), which is required by the FDA for Class III or high-risk devices. The remaining three have neither of the two FDA certifications.
Of the 5 types of CGMS 4 have a premarket approval (PMA).

DIFFUSION/DIFFUSION PREDICTION

In absence of explicit criteria for selection of target patients it is impossible to estimate/predict diffusion. At the moment in Italy the devices are proposed to patients on an individual basis and it is hard to trace both users and prescribers. In future, the new regional database aimed at monitoring the use of medical devices (DiMe database) should allow to quantify and track current use.

BRIEF SUMMARY

International guidelines and HTA reports agree upon the lack of robust evidence supporting the use of CSII pumps, of CGM devices and of semi-integrated systems. They agree upon advising a limited use and restricted to most suitable patients, which should be identified through explicit and shared criteria.
Results form the most recent and good quality systematic review of randomised controlled trials highlight that studies have small numbers of patients, a short duration (maximum 52 weeks), evaluate only short-term clinical outcomes (glycaemic control, hypoglycaemic episodes, body parameters, quality of life) and no clinical outcomes related to micro- or macrovascular complications.
Concerning CSII pumps, the available evidence shows a slight difference in HbA1c levels - considered not significant from a clinical point of view - and in global quality of life for type 1 adults diabetic patients, while no difference both in glycaemic parameters and in QOL is shown in paediatric patients with type 1 diabetes and in adult patients with type 2 diabetes.
Data on CGM devices, drawn from studies on mixed population of patients with type 1 diabetes, children/adolescents and adults, with a short period of observation, show a statistically significant difference - that, however, was judged as clinically not significant - in glycaemic parameters (HbA1c, time in hyperglycaemia) in favour of CGM versus SMBG. Evidence in patients with type 2 diabetes are lacking. Finally, data from 4 studies show that, during a short observation time, there is a statistically - and clinically - significant difference of HbA1c and time spent in hyperglycaemia in favour of SAP in mixed populations of paediatric and adult patients with type 1 diabetes. Evidence on the use of SAP in type 2 diabetic patients is absent.
Ongoing studies are numerous, some of them enrolling large numbers of patients. However the majority of ongoing studies are of a short duration and consider only surrogate outcomes.
The presumed clinical impact on long-term micro- and macrovascular outcomes of innovative devices for diabetes is not confirmed by presently available data. Moreover, no shared criteria to identify patients who could benefit most from these devices are available.

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