shortreport

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

INNOVATIVE MEDICAL DEVICES FOR DIABETES MANAGEMENT

THIS IS AN UPDATE OF SHORT REPORT NUMBER 6.

n. 7

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 five 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, last access 22nd May 2014).

USE

■ therapeutic

■ 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 foresees 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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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-SID 2014) 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-SID 2014). SMBG monitoring several times a day is indicated also in patients with type II diabetes (AMD-SID 2014).

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 measured 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 SEVEN 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 seven years (from 2008 to May 2014) 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

Thirteen good-quality guidelines on diabetes management were selected. Seven (ADA 2014, AMD-SID 2014, APEG-ADS 2011, CDA 2013, NICE 2010, OSTEBA 2012, SIGN 2010) include recommendations on the use of CSII in children and adolescents with type 1 diabetes, eight (ADA 2014, APEG-ADS 2011, CDA 2013, NICE 2010, OSTEBA 2012, SIGN 2010, Va/Dod 2010) on its use in adults with type 1 diabetes, three (AMD-SID 201, APEG-ADS 2011, OSTEBA 2012) in diabetic pregnant women and two (ICSI 2012, Va/Dod 2010) in patients with type 2 diabetes.
Two out of seven guidelines considering CSII for children and adolescents with type 1 diabetes recommend CSII as an alternative to standard insulin therapy (ADA 20144, CDA 2013). However the remaining five (APEG-ADS 2011, NICE 2010, OSTEBA 2012, SIGN 2012) recommend its use only in selected patients not reaching glycaemic targets with traditional insulin therapy and/or presenting hypoglycaemic episodes and only for individuals (or their supervising adults) with desirable motivational factors. The guideline from SIGN specifies that an "insulin pump is recommended for those with very low basal insulin requirements (such as infants and very young children), for whom even small doses of basal insulin analogue may result in hypoglycaemia" (SIGN 2010).
The use of CSII by adult patients with type 1 diabetes is recommended as an alternative to standard insulin therapy by two out of eight guidelines (ADA 20144, CDA 2013). Six out of eight guidelines (AMD-SID 2014, APEG-ADS 2011, NICE 2010, OSTEBA 2012, SIGN 2010, Va/Dod 2010) instead recommend a restricted use in patients not reaching glycaemic targets with traditional insulin therapy and/or presenting hypoglycaemic episodes and only for individuals (or their supervising adults) with desirable motivational factors.

The strength of recommendations reported by the guidelines in support is inconsistent/heterogeneous, being between “Strong” and “Weak”. The quality of evidence in support of the recommendations ranges from high to very low for children and adolescents and from high to moderate for adults with type 1 diabetes.
The use of CSII by pregnant diabetic women is taken into consideration by three guidelines (AMD-SID 201, APEG-ADS 2011, OSTEBA 2012): APEG-ADS 2011 does not give any specific recommendation but suggests that pregnant women (ideally preconception) may benefit from the use of CSII. OSTEBA 2012 recommend the use of CSII when the use of traditional insulin therapy does not allow to reach glycaemic targets and is accompanied by some specific factors such as difficulty to deal with hypoglycaemic episodes or impaired quality of life. These recommendations are supported by panel consensus. AMD-SID 2014 indicates CSII as an alternative to traditional insulin therapy. **No guideline takes into account the use of CSII in gestational diabetes**.
Of the two guidelines (ICSI 2012, Va/Dod 2010) providing recommendations on the use of CSII in patients with type 2 diabetes and already treated with insulin therapy, the one by VA/Dod does not recommend its use whilst the one by ICSI 2012 highlights its potential benefits for patients who are interested in more intensified management of blood glucose and want more flexibility and are considered suitable for that kind of treatment by a diabetes specialist in terms of patient understanding, self-care knowledge, responsibility and commitment.
For a complete comparative report on recommendations of the thirteen included guidelines please refer to Vignatelli 2014 (in press).

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

Thirteen good-quality guidelines on diabetes management were selected. Five (ADA 2014, AMD-SID 2014, APEG-ADS 2011, NICE 2010, OSTEBA 2012) include recommendations on the use of CGM in children and adolescents with type 1 diabetes, four (ADA 2014, AMD-SID 2014, APEG-ADS 2011, OSTEBA 2012) include recommendations on its use in adult patients with type 1 diabetes and two (AMD-SID 2014, SIGN 2010) in pregnant diabetic women. **Included guidelines do not provide recommendations on the use of devices for CGM either in women with gestational diabetes or in patients with type 2 diabetes**.

Three guidelines (ADA 2014, APEG-ADS 2011, NICE 2010) out of five recommend to restrict the use of CGM systems in children and adolescents with type 1 diabetes with a good adherence to the device use and high risk of hypo or hyperglycaemia. The guideline by AMD-SID (AMD-SID 2014) judges the device useful - provided there is a good compliance in the long-term use - for reaching target HbA1c levels and reducing hypoglycaemic events. Finally, the guideline by OSTEBA (OSTEBA 2012) acknowledges the usefulness of continuous glucose monitoring in order to improve or maintain glycaemic control in motivated and trained patients but formulate a negative recommendation on its universal use.
The strength of recommendations reported by the guidelines with positive recommendations for the use of CGM is “Weak” (quality of evidence ranging from high to very low); on the other hand the negative recommendation by OSTEBA is “Strong”.
Four guidelines consider CGM use in adult patients with type 1 diabetes (ADA 2014, AMD-SID 2014, APEG-ADS 2011, OSTEBA 2012). Two (ADA 2014, APEG-ADS 2010) out of four recommend its use only if a good compliance with continuous monitoring is guaranteed and if a high risk of hypoglycaemia is present. The guideline by AMD-SID (AMD-SID 2014) considers CGM coupled with intensive insulin therapy useful to reduce HbA1c levels in patients older that 25 years. Finally the guideline by OSTEBA (OSTEBA 2012) acknowledges the usefulness of continuous glucose monitoring for adult patients, in order to improve or maintain glycaemic control in motivated and trained patients but formulate a negative recommendation on its universal use.
The strength of recommendations reported by the guidelines with positive recommendations for the use of CGM is inconsistent/heterogeneous (from “Strong” to “Weak”, with the quality of evidence ranging from high to very low); on the other hand the negative recommendation by OSTEBA is “Strong”.
The use of CGM during pregnancy ? is taken into consideration by only two documents (AMD-SID 2014, SIGN 2010): AMD-SID 2014 recommends its use – added to self-monitoring blood glucose – in selected women with type 1 diabetes and hypoglycaemia unawareness; SIGN 2010 declares that CGM use can be generically considered in pregnant women with type 1 or 2 diabetes.
None of the included guidelines formulate recommendations on CGM use either in women with gestational diabetes or in patients with type 2 diabetes.
For a complete comparative report on recommendations of the thirteen included guidelines please refer to Vignatelli 2014 (in press).

SENSOR-AUGMENTED INSULIN PUMPS (SAP)

HTA reports

One HTA report on sensor-augmented insulin pumps use in children and adolescents produced in 2012 was selected (Lo Scalzo 2012). HTA report has included only two open-label RCTs (STAR-3, Hermanides 2011), for a total of 568 patients, both adult and pediatric, comparing the efficacy of SAP against MDI plus SBGM in reducing HbA1c and improving the incidence of hypoglycaemic events and ketoacidosis.
HTA report Authors highlight the lack of data on both lon-term diabetes complications (such as eye, renal and cardiovascular complications) and quality of life and the need of good quality data on SAP (for study design, and for stratification according to age groups).

Clinical practice guidelines

Only two out of thirteen included guidelines (ADA 2014, AMD-SID 2014) have recommendations on the use of sensor-augmented pumps: the document by AMD-SID (AMD-SID 2014) focuses on children or adolescents with type 1 diabetes whilst ADA guideline refers to all - both pediatric and adult -patients with type 1 dibetes. The ADA guideline (ADA 2014) states that SAP use may be considered for patients with type 1 diabetes with frequent nocturnal hypoglycemia and/or hypoglycemia unawareness (recommendation without grading). The second document (AMD-SID 2014) reports that SAP use in children and adolescents with type 1 diabetes reduces the pooled incidence of severe and moderate hypoglycaemia without modifying HbA1c levels (strength of recommendation: “Weak”, quality of evidence high).
No guideline report recommendations on the use of SAP in diabetic pregnant women, in women with gestational diabetes and patients with type 2 diabetes.
For a complete comparative report on recommendations of the thirteen included guidelines please refer to Vignatelli 2014 (in press).

AVAILABLE EVIDENCE AND RESULTS

Bibliographic research

The Short Report methodology consists in identifying primarily up-to-date and good quality systematic reviews and primary studies possibly published after good-quality systematic reviews.
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).
Literature search of primary studies published after the systematic review by Yeh and updated to February 2014 led to the inclusion of four additional primary studies (Battelino 2012, Riveline 2012, Secher 2013, Tildesley 2013).

Number and type of studies

The presently reported data are based on the results provided by the systematic review of Yeh (Yeh 2012) and by four additional studies retrieved by the literature update. 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 (< 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.
Four additional RCTs (Battelino 2012, Riveline 2012, Secher 2013, Tildesley 2013) published after Yeh 2012 were retrieved by the literature update carried out in February 2014. They all evaluate devices for rt-CGM versus SBGM. Two RCT (Battelino 2012, Riveline 2012) of which one with a cross-over design (Battelino 2012) included a total of 331 adult and paediatric/adolescent patients with type 1 diabetes randomised to rt-CGM or SBGM for 12 months. The third RCT (Tildesley 2013) evaluated the use of rt-CGM against SBGM in 50 patients with type 2 diabetes (study duration: 6 months) and the last one (Secher 2013) the use of intermittent (3-6 days at weeks 8, 12, 21, 27 and 33 weeks) rt-CGM in addition to SBGM versus SBGM in pregnant women with type 1 or 2 diabetes.
HbA1c level was the primary outcome for all studies but Secher 2013 in which large-for-gestational-age infants was the primary outcome (but HbA1c level was considered and recorded as well).

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 not clinically meaningful - being below the threshold of -0.50% given by the Authors- 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).
Two out of four additional primary studies (Battelino 2012, Riveline 2012) were useful to update the meta-analytic data on the effectiveness of rt-CGM versus SBMG in reducing HbA1c level provided by the systematic review. Adding results of the two additional studies to estimates provided by studies included by Yeh resulted in a still statistically significant reduction of HbA1c between-groups (mean difference: -0.33% (95% CI -0.38%; -0.27%) that, however, does not still reach the reduction of 0.50% judged to be clinically meaningful.
The other two additional studies included in the update suggest that rt-CGM does not result in a significant improvement in HbA1c levels when compared to SBGM either in patients with type 2 diabetes (Tildesley 2013) or in pregnant women with type 1 or 2 diabetes (Secher 2013).

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: 30th May 2014) the following randomised controlled trials were retrieved. Some of the following studies are classified as completed but results are still not published.

Continuous subcutaneous Insulin Pumps (CSII)

Study	Patients	Study design	Primary outcomes	Study deadline	Status
Type 1 DM					
NCT00468754	Type 1 diabetes, age range: 18-60 years (n=50)	RCT crossover CSII vs MDI	Variability of blood glucose characterised by the standard deviation of the mean blood glucose [Time Frame 4 months]	May 2005 (updated January 2014)	Completed, no study results posted

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Study	Patients	Study design	Primary outcomes	Study deadline	Status
Type 2 DM					
NCT00942318	Type 2 diabetes mellitus, > 18 years (n=52)	RCT CSII vs MDI	HbA1c [Time Frame: 12 months]	February 2013	Completed, no results available
NCT01889914	Type 2 diabetes patient with insulin basal/bolus treatment for at least 6 months, age > 18 years old (n=60)	RCT CSII vs MDI	changes from baseline in insulino-resistance [Time Frame: baseline and six months after the begining of the study]	September 2015	Currently recruiting participants
NCT01182493	Type 2 diabetes, age range: 30-75 years (n=400)	RCT CSII vs MDI	Between group difference in HbA1c when comparing CSII to MDI [Time Frame: 6 months]	September 2014	Currently recruiting participants
NCT02048189	Type 2 diabetes, age range: >18 years (n=60)	RCT CSII vs MDI	Mixed measurement of insulin secretion and insulin resistance [Time Frame: 6 month after starting the treatment]	March 2015	Currently recruiting participants
Pregnancy					
NCT02064023	Pregnant women with type 1/2 diabetes, age range: >19 years (n=160)	RCT CSII vs MDI	Composite obstetrical/perinatal endpoint consisting of specific elements (see description) [Time Frame: Up to 42 weeks]	January 2017	Not yet open for participant recruitment

Devices for Continuous glucose monitoring (CGM)

Study	Patients	Study design	Primary outcomes	Study deadline	Status
Type 1 DM					
NCT00949221	Type 1 diabetes, age range: 2-18 years (n=150)	RCT rt-CGM (2 strategies) VS SBGM	Comparison of the effect of 2 strategies of real time continuous glucose monitoring vs conventional SMBG on glycated haemoglobin = HbA1c measured at inclusion, 3, 6, 9, 12 months [Time Frame: 1 year]	July 2012	Completed, no study results posted
NCT01586065	Type 1 diabetes, age range: 12-18 years (n=26)	RCT rt-CGM VS SBGM	HbA1c [Time Frame: 6 months]	August 2013	Status unknown
NCT01083433	Type 1 diabetes, age range: 10-18 years (n=62)	RCT rt-CGM + behavioural VS rt-CGM VS SBGM	HbA1c [Time Frame: 4 months]	October 2011	Completed, no study results posted
NCT01787903	Type 1 Diabetes Mellitus patients with Impaired Hypoglycemia Awareness, 18-70 years (n=52)	RCT, cross-over rt-CGM vs SBGM	Time spent in the euglycemic range [Time Frame: 45 weeks]	September 2015	Currently recruiting
NCT02092051	Type 1 diabetes, age range: >18 years (n=120)	RCT, cross-over rt-CGM vs SBGM	Difference in HbA1c between week 26 and week 69 [Time Frame: Week 26, week 69]	December 2015	Currently recruiting
Type 2 DM					
NCT01237301	Type 2 diabetes, mean age 59 years (n=124)	RCT rt-CGM vs SMBG	Percentage Change in Hemoglobin A1c [Time Frame: 2 week baseline to 18 week final]	August 2013	Has results on HbA1c: CGM: -1.12 ± 1.07 SBGM: -0.82 ± 0.12
NCT01072565	Type 2 diabetes, 18-75 Years (n=91)	RCT SBMG+ rt-CGM vs SBGM	Evaluate the efficacy of SMBG for clinical decisions related to the management of type 2 diabetes. [Time Frame: Three, six and nine months]	January 2012	Completed, no results
NCT01614262	Type 2 diabetes, 18-70 Years (n=90)	RCT rt-CGM vs SBGM	change in glycosylated hemoglobin using intensive periodic CGM monitoring vs traditional monitoring [Time Frame: baseline and day 187]	September 2014	Ongoing, but not recruiting participants
NCT02082184	Type 2 diabetes, age range: >18 years (n=210)	RCT rt-CGM VS SBGM	HbA1c at 6 months [Time Frame: Baseline and 194 days]	June 2015	Currently recruiting participants

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Study	Patients	Study design	Primary outcomes	Study deadline	Status
Pregnancy					
NCT01788527	Type 1 diabetic women pregnant or planning to become pregnant, age range: 18-40 (n=318)	RCT rt-CGM VS SBGM	Glycemic Control in pre-pregnant group [Time Frame: 24 weeks or at conception] Glycemic Control in pregnant group [Time Frame: 34 weeks gestation]	December 2015	Currently recruiting participants

Sensor-Augmented Pumps (SAP)

Study	Patients	Study design	Primary outcomes	Study deadline	Status
NCT01677546	Type 1 diabetes, age range: 7-18 years (n=156)	RCT SAP vs CSII	HbA1c (Glycated hemoglobin) [Time Frame: 3 months]	July 2012	Completed, no study results posted
NCT01295788	Type 1 diabetes, age range: 5-18 years (n=144)	RCT, Simultaneous RT-CGM and Pump Initiation VS CSII and delayed (after 6 months) Initiation of RT-CGM	Adherence to CGM (hours per week) [Time Frame: one year]	January 2015	Ongoing, but not recruiting participants
NCT01454700	Type 1 diabetes, age range: 18-75 (n=80)	RCT SAP vs MDI + SBGM	difference in change in urine albumine excretion from baseline to end of study (12 months) [Time Frame: 12 months]	December 2014	Currently recruiting participants

Closed-loop (CL) systems, artificial pancreas systems (AP)

Study	Patients	Study design	Primary outcome/s	Study deadline	Status
Free living conditions (or similar)					
NCT02105324	Type 1 diabetes, age range: 6-11 years (n=24)	RCT, crossover, bi-hormonal** closed-loop VS CSII summer camp	• Mean CGM glucose values during days 2-5 as determined by the DexCom G4 Platinum CGM data during the bionic pancreas and comparator arms. [Time Frame: 1 week] • Fraction of time spent < 60 mg/dl during days 2-5 as determined by the DexCom G4 Platinum CGM data during the bionic pancreas and comparator arms. [Time Frame: 1 week] • Change in body weight from beginning to end of each study arm [Time Frame: 1 week]	August 2014	Not yet open for participant recruitment
NCT01873066	Type 1 diabetes patients, age range: 10-18 years (n=12)	RCT crossover, 24H/7d closed-loop VS SAP home	Time spent in the target glucose range from 3.9 to 10.0 mmol/l based on subcutaneous glucose monitoring (CGM) adjusted for sensor error. [Time Frame: 7 day home study period]	May 2014	Not yet open for participant recruitment
NCT01221467	Type 1 diabetes, age range: 12-18 years (n=15)	RCT, crossover, overnight closed-loop VS CGM home	Primary Efficacy Outcome [Time Frame: At least 7 days of valid CGM nights (midnight-7:30)]	March 2013	Completed, no study results posted
NCT01726829	Type 1 diabetes, age range: 10-65 years (n=75)	RCT, crossover, overnight closed-loop VS SAP home	• time sensor glucose level spent below 70mg/dl [Time Frame: final visit (day 44)] • The percentage of nights mean overnight sensor glucose levels was within90-140 mg/dl [Time Frame: At final visit (day 44)]	December 2014	Ongoing, but not recruiting participants
NCT01778348	Type 1 diabetes, age range: 6-18 years (n=24)	RCT, crossover, overnight closed-loop VS SAP home	Time spent overnight in the target glucose range (3.9 to 8.0 mmol/l), as assessed by adjusted continuous subcutaneous glucose monitoring (CGM) [Time Frame: 3 month home study period]	May 2015	Currently recruiting participants

* insulin and glucagon
** insulin

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Study	Patients	Study design	Primary outcome/s	Study deadline	Status
Free living conditions (or similar)					
NCT01833988	Type 1 diabetes, age range: 12-20 years (n=32)	RCT, crossover, closed-loop VS CSII summer camp	• Difference in average blood glucose (BG) between closed-loop and open-loop periods as determined from all scheduled HemoCue measurements with mean evenly weighted across the daytime and nighttime hours. [Time Frame: 1 week] • Difference between closed-loop and open-loop in the percentage of the above subset of BG values less than 70 mg/dl. [Time Frame: 1 week]	December 2014	Ongoing, but not recruiting participants
NCT01666028	Type 1 diabetes patients, age range: >18 years (n=18)	RCT crossover, 24H/7d closed-loop VS SAP home	Time spent in the target glucose range from 3.9 to 10.0 mmol/l based on subcutaneous glucose monitoring (CGM) adjusted for sensor error. [Time Frame: 7 day home study period]	November 2013	Ongoing, but not recruiting participants
NCT01961622	Type 1 diabetes, age range: >18 years (n=30)	RCT, crossover, 24h/7d closed-loop VS SAP home	Time spent in the target glucose range from 3.9 to 10.0 mmol/l based on subcutaneous glucose monitoring [Time Frame: 90 days]	December 2015	Currently recruiting participants
NCT01440140	Type 1 diabetes, age range: 18-65 years (n=24)	RCT, crossover, overnight closed-loop VS SAP home	Percentage of CGM values in target (3.9 - 8.0 mmol/l). [Time Frame: 4 weeks]	January 2014	Completed

* insulin and glucagon
** insulin

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
- 5 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).

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. A literature search of primary studies (RCTs) published after the publication of the systematic review retrieved four additional studies, all evaluating rt-CGM in different population of patients.

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. Two studies investigated the use of rt-CGM in type 2 diabetic patients and in pregnant women with type 1 or 2 diabetes, respectively, without showing any statistically significant difference against SBGM.

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 (maximum length of one year) and consider only surrogate outcomes. Information on ongoing studies highlights that research is shifting towards the evaluation of fully integrated systems suggesting a decreased interest from manufacturers on providing robust and definitive data on CSII. Given this trend in the ongoing research, no further update on evidence related to CSII will be carried out.

A research focus on rt-CGM is still present including patients with type 2 diabetes and literature will be monitored.

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 even if very specific subgroup populations that could benefit from the use of rt-CGM, CSII or SAP are identified by some guidance.

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