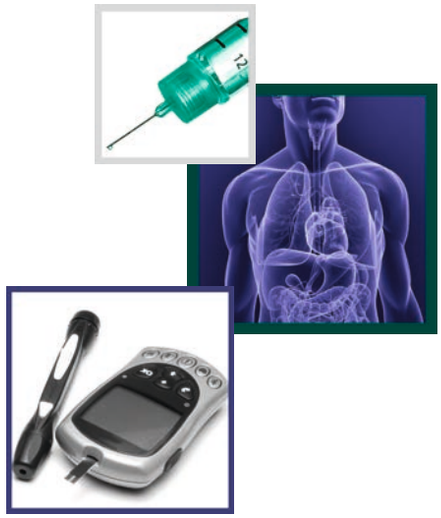
REVIEW

In search of improved glucose control: helping the patient decide between insulin injections and infusion pump therapy



Erin D Roe[1], Jason S Woo[2] & Philip Raskin*[3]

Practice Points

- Insulin remains the mainstay treatment for all patients with Type 1 diabetes and those with Type 2 diabetes inadequately controlled on oral agents, and may be delivered through multiple daily injections or continuous subcutaneous insulin infusion.
- The selection of insulin delivery method may change based on patient needs, lifestyle and treatment goals.
- Insulin replacement therapy is designed to deliver long-acting basal insulin to cover hepatic glucose output in the fasting state and bolus doses of short- or rapid-acting insulin to minimize postprandial glucose excursions.
- Basal multiple daily injection therapy uses 1–2 injections of long-acting basal insulin to target nocturnal hyperglycemia, or may be more complicated, requiring 2–4 injections of human or analog long- or short-acting insulin either delivered alone or in premixed combinations.
- Analog short-acting insulins have more rapid onset and offset compared with human regular insulin; analog basal insulins contain amino acid substitutions that enable heximerization in subcutaneous tissue and create prolonged flattened activity curves compared with human neutral protamine Hagedorn insulin.
- Continuous subcutaneous insulin infusion primarily employs analog insulin in variable rates to approximate basal and bolus insulin doses; the technique can be safely used in children, hospitalized patients and pregnant women and may be combined with continuous glucose-monitoring systems.
- Intraperitoneal insulin delivery reduces peripheral hyperinsulinemia, provides better glycated hemoglobin control and reduces hypoglycemia, but is considerably more invasive and not available in all countries.
- Continuous subcutaneous insulin infusion improves neuronal function independent of glucose control and may slow nephropathy and retinopathy progression, but further research is needed to better characterize long-term microvascular, as well as any macrovascular, benefits.

[1]Division of Endocrinology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, G4.100, Dallas, TX 75390-8858, USA
[2]University of Texas Southwestern Medical School, 5323 Harry Hines Blvd, Dallas, TX 75390-9006, USA
[3]Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9006, USA
*Author for correspondence: Tel.: +1 214 648 2017; Fax: +1 214 648 4854; philip.raskin@utsouthwestern.edu

Future Medicine part of fsg

SUMMARY Current diabetes treatments offer an array of options to suit patient needs and preferences. Beyond oral and incretin-based agents used in Type 2 diabetes, insulin remains a mainstay of outpatient diabetes therapy. Delivery methods include intermittent injections, continuous subcutaneous infusion and intraperitoneal infusion pumps that aim to mimic physiologic insulin secretion. The attributes of each approach for the treatment of Type 1 and Type 2 diabetes are discussed. Use in special diabetic populations, namely children, pregnant women and hospitalized patients, are reviewed. Lastly, the impact on diabetic complications, including end-organ dysfunction and cardiovascular disease, are covered.

The incidence and prevalence of diabetes continues to rise at an alarming rate. According to 2011 estimates from the United States Centers for Disease Control, 25.8 million people (8.3% of the US population) are afflicted with diabetes [101], and nearly three-quarters of them use insulin as either monotherapy or in combination with oral agents.

Treatment goals for patients with Type 1 and Type 2 diabetes have been established by the American Diabetes Association (ADA) based upon a glycated hemoglobin (HbA_{1c}) level of less than 7%. Additionally, new consensus guidelines published in collaboration with the European Association for the Study of Diabetes (EASD) recommend individualized glycemic targets [1]. These targets incorporate patient attitudes, resources available and social support with disease-specific parameters, including duration, comorbidities, complications and overall life expectancy. Accordingly, HbA_{1c} targets can run as low as 6–6.5% in young patients with short diabetes duration and no complications, while they can be 8% or above in those with long-standing diabetes, advanced complications, high hypoglycemia risk and short life expectancy.

Insulin delivery is initiated in all patients with Type 1 diabetes at the time of first diagnosis. In patients with Type 2 diabetes, exogenous insulin therapy is required when pancreatic β-cell function is insufficient to produce increased insulin necessary to overcome insulin resistance. Those with Type 2 diabetes presenting with a HbA_{1c} in excess of 10% typically require insulin therapy, since each additional oral agent contributes only approximately 1% decline in HbA_{1c}, insufficient to reach 7%. Lastly, elderly patients are more likely to be treated with insulin. Reduced drug metabolism and clearance capacity contraindicates use of many oral agents in this population. Approximately one-quarter of elderly patients with Type 2 diabetes receive insulin [2]. Therefore, there is great need for flexible insulin products and delivery devices that conform physiologically to the patient's nutritional intake and activity level, reduce hypoglycemia risk and cause minimal pain and lifestyle disruption.

Supplemental insulin regimens are designed to reproduce the activity curve of endogenous insulin, with basal coverage suppressing hepatic glucose production in the fasting state and bolus insulin doses minimizing postprandial glucose excursions. Overzealous insulin treatment may increase the risk for hypoglycemia, while the resulting compensatory food intake to defend against hypoglycemia can lead to unintended weight gain. Current modalities commonly used to deliver basal–bolus insulin treatment include multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII).

Several landmark studies have established goals for insulin treatment in diabetic populations. In Type 1 diabetes, the Diabetes Control and Complications Trial (DCCT) showed that patients with minimal background diabetic retinopathy treated with intensive insulin therapy compared with conventional therapy showed a reduction in microvascular complications over a 6.5-year period [3]. In a subsequent 4-year follow-up study, the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) research group reported persistent improvements in retinopathy and nephropathy once HbA_{1c} goals were liberalized in patients previously maintained on intensive insulin therapy. In Type 2 diabetes, a small study compared multiple daily insulin injections to conventional therapy on primary and secondary prevention of retinopathy and neuropathy and found a reduction in microvascular complications [4]. The United Kingdom Prospective Diabetes Study Group (UKPDS 33) subsequently found that intensive insulin therapy targeting a HbA_{1c} of 7% reduced microvascular complications in patients newly diagnosed with Type 2 diabetes [5]. Prolonged intensive insulin treatment for Type 2 diabetes lowered cardiovascular disease burden and all-cause mortality. However, it should be noted that clinical trial experience with intensive insulin treatment carried

an increased risk for hypoglycemia events and weight gain.

Evidence to support HbA_{1c} targets under 7% in Type 2 diabetes have been mixed. The Action to Control Cardiovascular risk in Diabetes Study Group (ACCORD), a secondary prevention trial in patients with existing cardiovascular disease and Type 2 diabetes [6], was stopped early due to increased mortality in the intensive therapy group. Conversely, the ADVANCE trial in patients with Type 2 diabetes showed reduced composite end points in the intensive-treated group (HbA_{1c}: 6.5%) versus the standard control group (HbA_{1c}: 7.3%), but these gains were seen primarily in the reduction of microvascular complications – retinopathy and nephropathy [7]. The Veterans Affairs Diabetes Trial (VADT) compared intensive insulin versus standard therapy in men with long-standing Type 2 diabetes and found no difference in major cardiovascular events, death or microvascular complications, but did observe improved albuminuria [8].

Insulin delivery through MDI or CSII requires both patient commitment and education. Nonadherence with insulin therapy can lead to serious complications in both Type 1 and Type 2 diabetes. The review will outline both MDI and CSII, as well as less commonly used delivery methods, such as continuous intraperitoneal insulin infusion (CIPII). Application of MDI and CSII in special populations, including children, pregnant woman and hospitalized patients, is discussed. Lastly, available data on long-term vascular complications associated with the use of each modality are reviewed.

Insulin: options for intermittent or continuous subcutaneous delivery

When selecting insulin therapy, multiple considerations factor into treatment decisions. Patient-specific characteristics including lifestyle, dietary habits, activity level, financial resources, social support, ability for diabetes self-care, and presence of diabetic complications (e.g., peripheral neuropathy limiting manual dexterity) may be considered, and certain features may increase or decrease in importance over time. For example, certain insulins (i.e., insulin glargine) are not approved for use during pregnancy in the USA [9]. Therefore, the clinician should inform the patient of the potential risks, available data, and, if needed, modify the type of insulin used during gestation. After delivery, maternal insulin is secreted in breast milk, but is denatured in the infant's digestive tract. Therefore, women may resume their prior MDI regimen during lactation, albeit at reduced doses in Type 1 diabetes [10].

To design a MDI regimen, long-acting basal insulin injected once or twice daily (insulin glargine [rDNA origin; Lantus®, Sanofi, Paris, France], insulin detemir [rDNA origin; Levemir®, Novo Nordisk, Bagsvaerd, Denmark] or human neutral protamine Hagedorn [NPH] insulin) is combined with prandial bolus coverage with rapid-acting or short-acting insulins (insulin aspart [rDNA origin; Novolog®, Novo Nordisk], insulin lispro [rDNA origin; Humalog®, Eli Lilly and Co., IN, USA], insulin glulisine [rDNA origin; Apidra®, Sanofi] or human regular insulin. Alternatively, long-acting and short-acting insulin may be combined in fixed proportions (e.g., 70/30, 75/25, 50/50 and so on) to provide basal and prandial coverage with fewer injections. Human regular insulin has slower onset, lower peak activity and longer duration of action compared with analog rapid-acting formulations. Compared with human long-acting NPH insulin, analog basal insulins contain amino acid substitutions that facilitate heximerization. As dissociation occurs in subcutaneous tissue, insulin is slowly absorbed, prolonging its activity.

Analog and human insulin efficacy, side effects and cost have been reviewed elsewhere [11]. While analog insulins have been promoted to reduce hypoglycemia and weight gain compared with NPH human insulin, this has not been borne out in meta-analysis. HbA_{1c} levels did not vary between insulin formulations, indicating equivalent long-term metabolic control. Patient-oriented outcomes of mortality, morbidity, quality of life and costs did not differ. However, nocturnal, symptomatic and overall rates of hypoglycemia were slightly lower with insulin glargine and insulin detemir compared with NPH insulin.

Multiple daily injections

MDI may be administered through both conventional needles and, more recently, self-contained insulin delivering devices. In the conventional insulin delivery, insulin vials and syringes with needles ranging from 28 to 32 gauge are used. The higher gauge is associated with reduced injection pain and presumably greater treatment adherence. MDI therapy with syringes is generally held to be more cost effective compared

with insulin pens and pumps. A summary of MDI clinical- and patient-specific features are shown in **Table 1**.

MDI may be used as monotherapy or in conjunction with oral antidiabetic agents in patients with Type 2 diabetes and those with Type 1 diabetes complicated by extreme insulin resistance (i.e., 'Type 1.5' or 'Type 3' diabetes). Patients with Type 2 diabetes inadequately controlled on metformin or a combination of oral agents may be initiated on a once-daily injection of human NPH insulin at bedtime to protect against nocturnal hyperglycemia. Alternatively, a single bedtime injection of insulin glargine or insulin detemir offers 24-h basal coverage; a feature particularly convenient in elderly patients in whom altered metabolism and renal clearance may cause insulin bioaccumulation and erratic hypoglycemia. Oral agents and incretin-based therapies primarily used in Type 2 diabetes are discussed in greater detail elsewhere [12,13].

Self-contained insulin pens include replaceable needles and refillable or disposable insulin cartridges. In these devices, an audible click dial allows for more precise dosing and enhances safety for patients with impaired vision or limited manual dexterity [14]. Self-contained memory features, such as in the HumaPen® Memoir™ (Eli Lilly) containing insulin lispro, record the time, date and dose for the 16 preceding injections and reportedly reduce overdosing. However, the product was recently discontinued. Another example of a memory device is Timesulin™ (Patients Pending Ltd, London, UK), a removable pen cap with timer that records the most recent insulin administration time and fits pens made by Eli Lilly, Sanofi and Novo Nordisk [102]. Regional disparities also exist in patient adoption of insulin pens. A recent review found that two-thirds of insulin prescriptions in Europe and three-quarters in Japan were for pen devices [15], while only 15% of patients in the USA were estimated to use insulin pens. This disparity may be due to limitations in insurance coverage or lack of awareness among healthcare providers.

Continuous subcutaneous insulin infusion

CSII utilizes an external battery-powered, pager-size infusion pump that is worn on the belt or underneath clothing, that contains dispensing controls, a processing module and a durable insulin reservoir. Insulin is infused through disposable tubing that leads to a small subcutaneous cannula. Modern insulin pumps are programmable to deliver both continuous, low-volume basal doses and larger bolus doses to accommodate food intake. A list of advantages and disadvantages are included in **Table 2**.

Rapid-acting insulin analogs are generally selected for CSII because of their low propensity to precipitate and occlude the infusion tubing and their rapid subcutaneous absorption. Insulin lispro has been associated with reduced weight gain and better glycemic control [16], although a second study [17] found that insulin aspart performed similarly. Additionally, pumps can be programmed to prolong meal boluses (i.e., 'extended bolus' or square-wave) or combined with a standard bolus followed by an extended square-wave pattern. These functions accommodate high-fat, high-carbohydrate meals that slow gastric transit time and increase absorption ordinarily

Table 1. Advantages and disadvantages of multiple daily injections.

Multiple daily injections	Advantages	Disadvantages
Clinical perspective	Improved and more physiologic blood glucose control vs other insulin injection regimens (e.g., two-dose regimen) Improvement of HbA_{1c} levels vs two-dose regimen in all patient populations with T2DM Decreased long-term diabetic complications including retinopathy, nephropathy, neuropathy and macrovascular complications, secondary to better controlled HbA_{1c} [7–9]	Blood glucose levels exhibit a peak and trough effect
Patient perspective	Increased injection time flexibility to accommodate lifestyle (meal and exercise times) Cheaper financial cost of care vs CSII [71]	Patient discomfort from administering at least four injections per day [46] Finger-prick blood glucose monitoring required several times a day Strong level of knowledge required about rapid-acting insulin and meal planning

CSII: Continuous subcutaneous insulin infusion; HbA_{1c}: Glycated hemoglobin; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

Table 2. Advantages and disadvantages of continuous subcutaneous insulin infusion.

Continuous subcutaneous insulin infusion	Advantages	Disadvantages
Clinical perspective	Decreased frequency of severe hypoglycemic events vs MDI [37] Greater than or equal improvement of HbA_{1c} levels vs MDI in adult and pediatric populations with T1DM and adults with T2DM [27–29,31,32,57,75,77,79] Decreased long-term diabetic complications including retinopathy, nephropathy, neuropathy and macrovascular complications, secondary to better controlled HbA_{1c} [7–9] Improved control of dawn phenomenon and overnight blood glucose levels vs MDI Device can provide history of insulin usage, blood glucose levels and overall compliance to healthcare provider Some device models have ability to partner pump with CGMS	Infection susceptibility at catheter insertion site Change in patient insurance status may force discontinuation of CSII Patient must have off-pump regimen and instructions for transition to sc. injections in the event of pump malfunction
Patient perspective	Improved quality of life and increased patient satisfaction vs MDI [45] Ability to modify basal insulin rate in response to activities	Higher financial cost of care vs MDI [71] Advanced training and education required Reliance on device functionality (pump failure, dead battery, kink in infusion catheter) Requires frequent blood glucose self-monitoring Cosmetic inconvenience from wearing device

CGMS: Continuous glucose-monitoring system; CSII: Continuous subcutaneous insulin infusion; HbA_{1c}: Glycated hemoglobin; MDI: Multiple daily injections; sc.: Subcutaneous; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

inducing prolonged postprandial hyperglycemia [18]. Patients must understand basic insulin pharmacodynamics and carbohydrate counting and commit to additional blood glucose testing to manage the increased flexibility that the insulin pumps afford. Many smart pumps offer 'bolus wizards' that calculate additional corrective doses based on expected carbohydrate intake, existing blood sugar levels and active insulin already administered ('insulin-on-board'). Programmed memory features enable downloading of insulin administration history, including settings, administration of corrective boluses and infusion site changes, to a computer desktop application for review by the patient and healthcare provider. The insulin pump enables delivery of variable hourly basal rates reduced during exercise to prevent hypoglycemia or increased overnight to accommodate higher blood sugars seen in puberty or in the predawn hours (i.e., 'dawn phenomenon'). Alternate basal settings can be programmed by day to accommodate variable food intake seen over weekends, activity level for shift workers, intense exercise training schedules for endurance athletes or dialysis sessions for patients with end-stage renal disease.

Newer pump models integrate continuous blood glucose-monitoring systems (CGMS), which provides onboard alarms and automated insulin dose-correction algorithms. The use of an integrated sensor in an insulin pump transmits blood glucose data to the pump without the need for patient intervention. The interaction between the sensor and insulin pump is a step towards a closed-loop insulin delivery system. Control algorithms for feedback of glucose readings to adjust subsequent insulin doses have posed subsequent technical barriers. No control algorithm has proven more adept at managing blood sugar than a savvy patient who is educated and involved in self-care and able to anticipate future food intake or physical activity. New features in insulin pumps such as the low glucose suspend (LGS) mode of operation, enable the pump to self-suspend for up to 2 h in the event of hypoglycemia. Further clinical testing is needed to allay safety concerns. This feature is not currently approved for use in the USA.

CGMS detect more hypoglycemia and postprandial hyperglycemia compared with fingerstick capillary blood glucose testing (self-monitoring of blood glucose [SMBG]) [19]. Furthermore, when patients transition from MDI to CSII, HbA_{1c} improves when incorporated with CGMS in place of SMBG (-0.96 vs -0.55% difference; $p = 0.004$), indicating that

sensor-augmented insulin pump therapy is preferable to CSII with SMBG [20]. When sensor-augmented insulin pump therapy is compared with MDI with SMBG [21], a HbA_{1c}-lowering effect was seen over 1 year in adult and pediatric patients with Type 1 diabetes without an increase in hypoglycemic events.

For additional safety, wireless data transmission features enable parents to monitor and manage their child's insulin pump remotely. Real-time blood glucose data can be transmitted to other devices, including automobiles, to reduce hypoglycemia-related traffic accidents. Partnering with Medtronic Corporation, Ford Automotive has prototyped SYNC® technology to display real-time CGMS video feed and audible alerts and permit voice commands and steering wheel controls for pump adjustments. The on-board system also interfaces with Diabeters Manager® (WellDoc Inc., MD, USA), a cloud-based service that tracts blood sugar readings and offers real-time patient coaching, behavioral education, and medication and adherence support [103].

Use of CSII is contraindicated in patients with limited vision and severe psychiatric problems. Its use is also prohibited in settings where the pump cannot function properly, such as highly pressurized environments (i.e., SCUBA diving) or strong electromagnetic fields (i.e., MRI). Additionally, the insulin cartridge cannot withstand repeated exposure to extreme heat or cold. Patient-specific factors may make pump implementation challenging and/or dangerous, including low treatment compliance, poor hygiene (e.g., repeated *Staphylococcus* skin infections), and limited education, financial and low social support [22].

Efficacy data in patients with Type 1 diabetes show that CSII improves glycemic control with a lower total daily insulin requirement compared with patients using MDI. One crossover study compared 100 patients with Type 1 diabetes randomized 1:1 to either CSII using insulin aspart or MDI with insulin aspart and insulin glargine at bedtime [23]. Frustosamine levels improved with CSII compared with MDI (343 ± 47 vs 355 ± 50 µmol/l; $p = 0.0001$), and CGMS data showed lower glucose exposure as measured by area under the curve for glucose (AUC_G) ≥80 mg/dl (1270 ± 742 vs 1664 ± 1039 mg*h/dl, -24% reduction with CSII; $p < 0.001$) and AUC_G ≥140 mg/dl (464 ± 452 vs 777 ± 746 mg*h/dl, -40% reduction with CSII; $p < 0.001$) without an increase in nocturnal or overall hypoglycemia. Meta-analyses of randomized clinical trials confirm these observations; CSII therapy in Type 1 diabetes yielded improved glycemic control with a reduced insulin requirement and reduced severe hypoglycemic event rate compared with MDI [24–27].

In Type 2 diabetes, efficacy studies are somewhat mixed. A 6-month trial showed that CSII (using insulin aspart) produced similar reductions in HbA_{1c} (8.2 ± 1.37% for CSII, 8.0 ± 1.08% for MDI declining to 7.6 ± 1.22% and 7.5 ± 1.22%, respectively) without an increase in hypoglycemia compared with MDI [28]. Patient surveys indicated that 93% on CSII preferred the insulin pump over their previous MDI regimen due to convenience, flexibility and ease of use.

Fewer trials have been performed to support use of CSII over MDI to improve glycemic control, compared with MDI in Type 2 diabetes [27,29], although CSII use is associated with reduced insulin requirement.

Continuous intraperitoneal insulin infusion

In addition to CSII and MDI, insulin can be infused in the intraperitoneal space where it is absorbed in portal circulation to undergo first-pass metabolism. Direct insulin delivery to the liver may improve glucagon secretion and hepatic glucose output to minimize hypoglycemia [30]. Initial studies with intermittent intraperitoneal insulin infused weekly in conjunction with MDI showed improvements in glycemic control, hypoglycemic events, blood pressure, diabetic nephropathy and some diabetic neurologic manifestations [31,32].

CIPII may be delivered through a pump that is either externally worn or surgically implanted in the abdominal wall [33]. The MiniMed Implantable Pump (MIP) model 2007 (Medtronic MiniMed, CA, USA) is inserted in a subcutaneous pocket in the lower quadrant of the abdomen and maintains negative pressure within the insulin reservior. A computer externally programmed by the patient controls 'pump-stroke' frequency to infuse basal or bolus insulin doses. An internal battery powering the motor and computer may last up to 7–10 years.

The Roche DiaPort® System (Roche Diagnostics-Disetronic AG, Burgdorf, Switzerland) is an externally worn device connected to an intraperitoneal catheter that is available only in several European countries and Australia.

Company studies report that patients using the system required 30–50% less total daily insulin. CIPII may be especially attractive to patients with insulin resistance requiring hundreds of units of insulin daily and those with site reactions, impaired absorption or lipodystrophy precluding the use of conventional CSII. Compared with patients using CSII with insulin lispro, use of the DiaPort system reduced severe hypoglycemia, weight gain and improved quality of life measures, while HbA_{1c}, mean blood glucose and glucose fluctuations did not differ between groups [34]. Intraperitoneal insulin may also elicit anti-insulin antibody production, which complex with injected insulin in circulation to impair short-term postprandial glucose control. Dissociation of the insulin–antibody complexes occurs unpredictably and may produce erratic hypoglycemia, particularly overnight when circulating insulin levels fall. Intravenous insulin administration does not require the formation of hexamers to facilitate absorption as in subcutaneous insulin, thereby enabling regular insulin to be used in place of analogs.

The largest efficacy trials on CIPII were performed by the French Evaluation dans le Diabète du Traitement par Implants Actifs (EVADIAC) study group, which observed durable improvements in HbA_{1c} (7.4 ± 1.8% declining to 6.8 ± 1.0%) over 30 months and reduced hypoglycemic events, trends that reversed once patients resumed their prior MDI or CSII therapy [35,36].

In patients with Type 1 diabetes refractory to other treatments, CIPII produced improvements in HbA_{1c} and glucose profile without an increase in body weight, daily insulin use or severe hypoglycemic events, compared with MDI [37] and CSII [38], but at a cost more than double CSII [39]. The increased cost is due to the device itself, as well as intermittent hospital visits every 6–8 weeks for insulin reservoir refills. A cost–benefit study of CIPII and MDI carried out prior to the introduction of analog insulin indicates that CIPII produced better glycemic control, less glucose variability and fewer mild hypoglycemic events with no adverse impact on quality of life, but at a monthly cost 2.6-fold higher than subcutaneous insulin.

European statistics in 2009 estimate that CIPII has been used in fewer than 1000 patients and should only be considered for those failing MDI and CSII for intensive insulin therapy. It is contraindicated in patients with repeated abdominal surgeries and altered anatomy, occupational exposure to repeated abdominal trauma, presence of high anti-insulin antibody titers, advanced diabetic complications, short life expectancy or exposure to strong magnetic fields around the pump pocket site.

Other risks associated with CIPII include infection, catheter occlusion, electronic pump failure and premature battery depletion [32,34]. Infections in the pump pocket occurred more often than peritonitis [32]; the EVADIAC study group found an overall incidence of 24% (84 out of 352 patients affected), of which 64% required pump explantation [40]. This rate has since improved with better surgical and antibiotic precautions. Compared with other forms of directed insulin delivery to portal circulation (i.e., islet cell transplantation) these complications were less severe and less frequent [32,41].

Application of CSII versus MDI in special populations

■ Pediatrics

Treatment guidelines state that all children with Type 1 diabetes, regardless of age, should be considered potential candidates for CSII therapy [42]. Timing and dosing of subcutaneous injections in young children with their variable eating habits place considerable stress on families and caregivers to monitor for hypoglycemia [43]. CSII enables small insulin doses to be administered, and with the advent of wireless monitoring and integration with CGMS, CSII can improve parental comfort in managing their child's diabetes [44]. Challenges for CSII therapy in small children include their limited skin surface area for potential insertion sites, tubing that can become dislodged with daily activity and increased sensitivity to adhesive tape used around the insertion site [45].

Pediatric trials comparing CSII to MDI have been reviewed elsewhere, but in general are neutral or slightly favor the use of CSII over MDI for HbA_{1c} reduction [45–47]. Compared with some adult trials that show equivalent control with either modality, a meta-analysis of pediatric trials found improved glycemic control, decreased insulin requirement and no weight gain in patients using CSII [48]. Another recent analysis of 26 studies on CSII and MDI in children with Type 1 diabetes showed similar or improved HbA_{1c} levels and reduced hypoglycemia compared with MDI [49]. Improved HbA_{1c} with CSII use in adolescents, however, may be influenced by

other factors [50]. Adolescents using CSII tended to have private insurance status, greater engagement in diabetes self-care (i.e., frequency of SMBG) and better caregiver support [51]. Those who discontinued CSII and returned to MDI tended to perform SMBG less frequently and maintained higher HbA_{1c} levels than adolescents continuing on CSII [52].

■ Pregnancy

Direct comparisons of CSII and MDI on pregnancy outcomes in women with Type 1 diabetes are difficult. Women using CSII during pregnancy tend to have higher rates of background retinopathy and clinical neuropathy, perhaps because they were unable to achieve satisfactory glycemic control on MDI [53]. Intrapartum use of CSII, however, does not appear to improve metabolic control or maternal outcomes. Development of fetal deformities correlates more closely with suboptimal maternal glucose control prior to conception. Likewise, fetal outcomes (i.e., birth weight, hypoglycemia, hypocalcemia, hyperbilirubinemia, fetal distress, asphyxia, hyaline membrane disease, polycythemia, shoulder dystocia and malformations) do not differ for women using CSII compared with MDI with equivalent glycemic control. Overall, maternal and perinatal outcomes were similar in patients treated either with CSII or MDI, and correlated most closely with preconception glycemic control.

Two meta-analyses confirm that CSII does not improve glycemic control in pregnant diabetic women compared with MDI [54,55]. In fact, a nonsignficant trend toward increased ketoacidotic episodes and worsening retinopathy was seen with CSII [54]. Similarly, another study observed no difference in metabolic parameters or progression of diabetic complications among pregnant women on CSII versus MDI, although daily insulin requirement declined with CSII [56]. Pregnancy in itself is not an indication for CSII initiation as a means to improve maternal and fetal outcomes. However, in women inadequately controlled on MDI, CSII may lower HbA_{1c}, which may reduce the risk of adverse outcomes during gestation and partuition.

■ Hospitalization

Patients on CSII in the outpatient setting can safely continue self-management while hospitalized provided they remain "mentally alert, psychologically sound and physically able" [57,104]. Hospital staff should provide the patient with bedside blood glucose results and dietary carbohydrate counts and correction boluses to facilitate the patient's pump management. Typically, pre-existing hospital policy must be in place to accommodate patients admitted on CSII [58]. This policy should outline who will perform bedside finger sticks and how often. Target ranges should also be defined with protocols for hypoglycemia and hyperglycemia management, including the circumstances when and by whom the insulin pump can be removed in case of emergency and contact information for the prescribing physician.

Hospital protocols should address CSII management in the peripartum and perioperative periods and the role of staff and providers to assist the patient and intervene when necessary. Bolus doses should be held during fasting, and intravenous insulin should be substituted in patients undergoing sedation and/or long procedures. Alternately, the pre-existing basal rate settings can serve as a temporary basal rate during minor surgical procedures with hourly SMBG and a 5% dextrose solution continually infused intravenously to protect against hypoglycemia [59]. CSII should be temporarily removed for imaging. If the patient's mental status deteriorates or clinical circumstances dictate, conversion from CSII to MDI can be made [59].

Clinical outcomes for hospitalized patients continued on CSII have not yet been studied. One group performed a retrospective chart review of surgical patients on CSII and found inconsistent documentation of pump use and glucose monitoring [60], and proposed sample protocols for CSII management during the perioperative period [61]. More work is needed to define the role and promote protocols for the safe implementation of CSII in inpatient glycemic management.

Effects on complications

■ Neuropathy

CSII has been shown to improve motor nerve conduction velocity and sensory action potential latency and amplitude [62]. In patients with Type 1 diabetes initiated on CSII versus continued therapy with MDI, mean conduction velocity increased 6.4% (2.75 ± 0.56 m/s; mean ± SEM) in CSII-treated patients versus 1.3% (0.57 ± 0.54 m/s) in the MDI group ($p < 0.005$), despite similar between-group improvements in glycemic control [63]. Another study similarly found improved conduction

velocities after 2 years of CSII treatment, while no improvement with MDI was found compared with conventional insulin therapy [64].

■ Nephropathy

In trials comparing MDI and CSII using intensive insulin therapy (i.e., in the post-DCCT era), improvements in diabetic nephropathy measurements have not been documented when glycemic control was held constant. The STENO-2 trial found that lower HbA_{1c} (7.2%, range: 5.9–8.8) in the CSII-treated group reduced progression to frank proteinuria in patients with existing microalbuminuria, compared with patients maintained on MDI with an unchanged HbA_{1c} (8.6%, range: 7.2–13.4, $p < 0.001$) [65]. In another study [66], kidney biopsies were followed among patients initiated on CSII (n = 9) compared with those maintained on their previous MDI regimen (n = 9). Glomeruli structural parameters and albumin excretion improved with CSII compared with MDI. However, these results were likely confounded by improvements in glycemic control; HbA_{1c} fell from 10.1% (95% CI: 8.9–11.3) to 8.6% (95% CI: 7.9–9.2) in the CSII group, but remained unchanged in MDI-treated patients, 10.1% (95% CI: 8.3–11.9) versus 9.7% (95% CI: 8.7–10.8). Cost–effectiveness studies in Type 1 diabetes confirm that CSII reduces diabetic nephropathy incidence and progression [67]. To prevent one case of end-stage renal disease, the number needed to treat with CSII is 19.

■ Retinopathy

Long-term progression of retinopathy is reduced with intensive glycemic control; however, intermittent worsening of retinopathy may occur following insulin intensification. This has been observed in several studies [68,69] and clinically, in pregnant women achieving tight control during the first timester following less strigent preconceptional glycemic control. In patients newly transitioned from MDI to CSII, one study in Type 1 diabetes documented improved visual function as measured by accelerated neuronal signaling and dark adaptation in rod photoreceptors [70]. Notably, this improvement lagged 16 weeks following CSII initation, which conincides with the early transient worsening of retinopathy seen after insulin intensification. Long-term, optimized glycemic control lessens retinopathy progression, making it difficult to discern the treatment effect of CSII [71].

One Australian study followed microvascular complications in adolescents with Type 1 diabetes over 20 years and observed that CSII-treated patients exhibited reduced retinopathy progression compared with those treated with MDI [50]. As HbA_{1c} did not differ between groups, this improvement was attributed to reduced glycemic variability in the CSII-treated cohort. These findings may be confounded by socioeconomic status – patients treated with CSII had private insurance and perhaps better overall access to healthcare, diabetes education and social support. Cost–benefit analysis, as with end-stage renal disease and peripheral vascular disease, highly favors the use of CSII; the number needed to treat with CSII to prevent one case of diabetic retinopathy is nine [67].

■ Macrovascular outcomes

Cardiovascular outcomes with CSII compared with MDI have not been well defined. To date, several short-term studies of CSII in patients with insulin resistance and Type 2 diabetes demonstrate improvements in atherosclerosis risk factors (i.e., lipid profile, coagulation factors and markers of endothelial dysfunction) [72–74]. Unfortunately, these studies were insufficient in duration (2–30 weeks) to establish any cardiovascular benefit.

Conclusion

Insulin therapy is required at initial diagnosis for all patients with Type 1 diabetes. Meanwhile, in patients with Type 2 diabetes, insulin treatment may or may not be necessary depending on the remaining degree of endogenous insulin production and insulin resistance. Insulin offers the most potent HbA_{1c}-lowering effect because, unlike oral antidiabetic agents and incretin-based therapies, insulin has no dose ceiling. For patients in developed contries, techniques for insulin delivery consist primarily of MDI or CSII, with the potential for CIPII available in only a handful of countries for select patients who fail both former methods. In general, CSII confers a larger reduction in HbA_{1c} and glucose variability compared with MDI, but requires greater patient education, training, resources, social support and commitment to regular SMBG. It is particularly well-suited for patients with severe hypoglycemic episodes, pronounced dawn phenonmenon, or marked glucose variability. CSII can be used safely in children and hospitalized patients. CSII use in pregnancy

is likewise feasible, but not shown to improve maternal or fetal outcomes.

This is not to say that MDI is not sufficient for a subgroup of patients who can achieve satisfactory glycemic control without the expense and complexity of CSII. MDI may deliver equivalent glycemic control compared with CSII [75], but at reduced cost and requiring fewer daily finger sticks. Improved glycemic control has been shown repeatedly to reduce microvascular complications. How one acheives that control makes only a small difference and has not been clearly studied. Patient education and involvement are critical for glycemic control, regardless of treatment. Ultimately, the patient's lifestyle, disease and complication status, understanding of diabetes, adherance, social support and financial resources should be considered in the context of treatment selection in order to achieve target blood glucose goals and minimize long-term complications.

Future perspective

Diabetes therapeutic research and development have long focused on more physiologic methods of insulin replacement that minimize glycemic variability, pain and lifestyle disruption for the patient. Beyond the the clinical merits of MDI and CSII treatment, increasing sophistication in sensor technology and control algorithms move closer to the realization of a closed-loop insulin delivery system. While technical challenges, particularly in the design of control algorithms, slow development, integrated sensor-augmented insulin pumps show progress toward this goal. Better wireless remote monitoring systems provide additional safeguards. The potential of infusing glucagon alongside insulin may stablize blood glucose further and protect against hypoglycemia. Lastly, hardware and software developments must dovetail with advances in insulin analogs that have more rapid onset of action and accommodate minute-by-minute changes in food intake and activity. Indeed, many engineering and pharmacologic advances must come together to achieve a fully automated 'artificial pancreas'.

Acknowledgements

The authors wish to thank H Mayo for her research assistance in the preparation of this manuscript.

Financial & competing interests disclosure

P Raskin has received research support, payable to the University of Texas Southwestern Medical Center, from Andromeda Biotech Ltd, AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals, Calibra Medical Inc., Halozyme Inc., Hoffman-La Roche Inc., Eli Lilly & Company, Osiris Pharmaceuticals Inc., Pfizer Inc., MannKind Corporation, Amylin, Sanofi-aventis, Johnson & Johnson, Takeda and Reata Pharmaceuticals Inc., is an advisor for Amgen, AstraZeneca and Novo Nordisk Inc., and is on the speakers bureau for Novo Nordisk Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:

- ■ of interest
- ■■ of considerable interest

1 Inzucchi SE, Bergenstal RM, Buse JB *et al.* Management of hyperglycemia in Type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 35(6), 1364–1379 (2012).

■■ **Recently released guidelines for diabetes management from the American Diabetes Association and European Association for the Study of Diabetes proposed metformin as a first-line agent, but were less prescriptive in the secondary and tertiary agents to be added. The guidelines also recommend greater individualization of glycated hemoglobin (HbA_{1c}) goals.**

2 Niskanen L. Insulin treatment in elderly patients with non-insulin-dependent diabetes mellitus. A double-edged sword? *Drugs Aging* 8(3), 183–192 (1996).

3 Nathan DM, Zinman B, Cleary PA *et al.* Modern-day clinical course of Type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983–2005). *Arch. Intern. Med.* 169(14), 1307–1316 (2009).

4 Ohkubo Y, Kishikawa H, Araki E *et al.* Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res. Clin. Pract.* 28(2), 103–117 (1995).

5 Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with Type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352(9131), 837–853 (1998).

6 Gerstein HC, Miller ME, Byington RP *et al.* Effects of intensive glucose lowering in Type 2 diabetes. *N. Engl. J. Med.* 358(24), 2545–2559 (2008).

7 Patel A, MacMahon S, Chalmers J *et al.* Intensive blood glucose control and vascular

outcomes in patients with Type 2 diabetes. *N. Engl. J. Med.* 358(24), 2560–2572 (2008).

8 Duckworth W, Abraira C, Moritz T *et al.* Glucose control and vascular complications in veterans with Type 2 diabetes. *N. Engl. J. Med.* 360(2), 129–139 (2009).

9 Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A, Lin Z, Salzman A. Reduced hypoglycemia risk with insulin glargine: a meta-analysis comparing insulin glargine with human NPH insulin in Type 2 diabetes. *Diabetes Care* 28(4), 950–955 (2005).

10 Riviello C, Mello G, Jovanovic LG. Breastfeeding and the basal insulin requirement in Type 1 diabetic women. *Endocr. Pract.* 15(3), 187–193 (2009).

11 Horvath K, Jeitler K, Berghold A *et al.* Long-acting insulin analogues versus NPH insulin (human isophane insulin) for Type 2 diabetes mellitus. *Cochrane Database Syst. Rev.* (2), CD005613 (2007).

12 Goldman-Levine JD. Beyond metformin: initiating combination therapy in patients with Type 2 diabetes mellitus. *Pharmacotherapy* 31(Suppl. 12), S44–S53 (2011).

13 Phillips LK, Prins JB. Update on incretin hormones. *Ann. N. Y. Acad. Sci.* 1243, E55–E74 (2011).

14 McCoy EK, Wright BM. A review of insulin pen devices. *Postgrad. Med.* 122(3), 81–88 (2010).

15 Pearson TL. Practical aspects of insulin pen devices. *J. Diabetes Sci. Technol.* 4(3), 522–531 (2010).

16 Zinman B, Tildesley H, Chiasson JL, Tsui E, Strack T. Insulin lispro in CSII: results of a double-blind crossover study. *Diabetes* 46(3), 440–443 (1997).

17 Bode B, Weinstein R, Bell D *et al.* Comparison of insulin aspart with buffered regular insulin and insulin lispro in continuous subcutaneous insulin infusion: a randomized study in Type 1 diabetes. *Diabetes Care* 25(3), 439–444 (2002).

18 Pickup JC. Insulin-pump therapy for type 1 diabetes mellitus. *N. Engl. J. Med.* 366(17), 1616–1624 (2012).

■ **This recent review provides practical tips on pump physiology, patient selection, conversion formulas, general care instructions and troubleshooting tips. Similar work sheets for multiple daily injections (MDI) to continuous subcutaneous insulin infusion (CSII) dose conversion can be found in** [52].

19 Keenan DB, Cartaya R, Mastrototaro JJ. Accuracy of a new real-time continuous glucose monitoring algorithm. *J. Diabetes Sci. Technol.* 4(1), 111–118 (2010).

20 Raccah D, Sulmont V, Reznik Y *et al.* Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled Type 1 diabetes: the RealTrend study. *Diabetes Care* 32(12), 2245–2250 (2009).

21 Bergenstal RM, Tamborlane WV, Ahmann A *et al.* Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. *N. Engl. J. Med.* 363(4), 311–320 (2010); Erratum appears in *N. Engl. J. Med.* 363(11), 1092 (2010).

22 Valla V. Therapeutics of diabetes mellitus: focus on insulin analogues and insulin pumps. *Exp. Diabetes Res.* 2010, 178372 (2010).

23 Hirsch IB, Bode BW, Garg S *et al.* Continuous subcutaneous insulin infusion (CSII) of insulin aspart versus multiple daily injection of insulin aspart/insulin glargine in Type 1 diabetic patients previously treated with CSII. *Diabetes Care* 28(3), 533–538 (2005).

24 Pickup J, Mattock M, Kerry S. Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with Type 1 diabetes: meta-analysis of randomised controlled trials. *BMJ* 324(7339), 705 (2002).

25 Jeitler K, Horvath K, Berghold A *et al.* Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. *Diabetologia* 51(6), 941–951 (2008).

26 Misso ML, Egberts KJ, Page M, O'Connor D, Shaw J. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for Type 1 diabetes mellitus. *Cochrane Database Syst. Rev.* (1), CD005103 (2010).

27 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.* 94(3), 729–740 (2009).

28 Raskin P, Bode BW, Marks JB *et al.* Continuous subcutaneous insulin infusion and multiple daily injection therapy are equally effective in Type 2 diabetes: a randomized, parallel-group, 24-week study. *Diabetes Care* 26(9), 2598–2603 (2003).

29 Monami M, Lamanna C, Marchionni N, Mannucci E. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in Type 2 diabetes: a meta-analysis. *Exp. Clin. Endocrinol. Diabetes* 117(5), 220–222 (2009).

■ **While trials in Type 1 diabetes generally favor use of CSII over MDI for glycemic control, in this meta-analysis on Type 2 diabetes, no clear advantage in HbA_{1c} lowering was seen with CSII compared with MDI.**

30 Wan CK, Giacca A, Matsuhisa M *et al.* Increased responses of glucagon and glucose production to hypoglycemia with intraperitoneal versus subcutaneous insulin treatment. *Metabolism* 49(8), 984–989 (2000).

31 Aoki TT, Grecu EO, Arcangeli MA, Benbarka MM, Prescott P, Ahn JH. Chronic intermittent intravenous insulin therapy: a new frontier in diabetes therapy. *Diabetes Technol. Ther.* 3(1), 111–123 (2001).

32 Schaepelynck P, Renard E, Jeandidier N *et al.* A recent survey confirms the efficacy and the safety of implanted insulin pumps during long-term use in poorly controlled Type 1 diabetes patients. *Diabetes Technol. Ther.* 13(6), 657–660 (2011).

■ **Long-term efficacy, safety and microvascular complication rates for patients with Type 1 diabetes transitioned from CSII or MDI to implanted insulin pump therapy are presented.**

33 Einhorn D. Advances in diabetes for the millennium: insulin treatment and glucose monitoring. *Med. Gen. Med.* 6(Suppl. 3), 8 (2004).

34 Liebl A, Hoogma R, Renard E *et al.* A reduction in severe hypoglycaemia in Type 1 diabetes in a randomized crossover study of continuous intraperitoneal compared with subcutaneous insulin infusion. *Diabetes Obes. Metab.* 11(11), 1001–1008 (2009).

35 Broussolle C, Jeandidier N, Hanaire-Broutin H. French multicentre experience of implantable insulin pumps. The EVADIAC Study Group. Evaluation of Active Implants in Diabetes Society. *Lancet* 343(8896), 514–515 (1994).

36 Jeandidier N, Selam JL, Renard E *et al.* Decreased severe hypoglycemia frequency during intraperitoneal insulin infusion using programmable implantable pumps. Evadiac Study Group. *Diabetes Care* 19(7), 780 (1996).

37 Logtenberg SJ, Kleefstra N, Houweling ST *et al.* Improved glycemic control with intraperitoneal versus subcutaneous insulin in Type 1 diabetes: a randomized controlled trial. *Diabetes Care* 32(8), 1372–1377 (2009).

38 Catargi B, Meyer L, Melki V, Renard E, Jeandidier N. Comparison of blood glucose stability and HbA_{1C} between implantable insulin pumps using U400 HOE 21PH insulin and external pumps using lispro in Type 1 diabetic patients: a pilot study. *Diabetes Metab.* 28(2), 133–137 (2002).

39 Logtenberg SJ, Kleefstra N, Houweling ST, Groenier KH, Gans RO, Bilo HJ. Health-related quality of life, treatment satisfaction, and costs associated with intraperitoneal versus subcutaneous insulin administration in Type 1 diabetes: a randomized controlled trial. *Diabetes Care* 33(6), 1169–1172 (2010).

■ **Randomized and nonrandomized clinical trials comparing CSII versus MDI on glycemic control in children with Type 1 diabetes are summarized. The article details technological advances, patient selection criteria and the advantages and disadvantages for CSII use in the pediatric population.**

40 Belicar P, Lassmann-Vague V. Local adverse events associated with long-term treatment by implantable insulin pumps. The French EVADIAC Study Group experience. Evaluation dans le Diabete du Traitement par Implants Actifs. *Diabetes Care* 21(2), 325–326 (1998).

41 Vantyghem MC, Marcelli-Tourvieille S, Fermon C *et al.* Intraperitoneal insulin infusion versus islet transplantation: comparative study in patients with type 1 diabetes. *Transplantation* 87(1), 66–71 (2009).

42 Eugster EA, Francis G. Position statement: continuous subcutaneous insulin infusion in very young children with type 1 diabetes. *Pediatrics* 118(4), E1244–E1249 (2006).

43 Opipari-Arrigan L, Fredericks EM, Burkhart N, Dale L, Hodge M, Foster C. Continuous subcutaneous insulin infusion benefits quality of life in preschool-age children with type 1 diabetes mellitus. *Pediatr. Diabetes* 8(6), 377–383 (2007).

44 Sullivan-Bolyai S, Knafl K, Tamborlane W, Grey M. Parents' reflections on managing their children's diabetes with insulin pumps. *J. Nurs. Scholarsh.* 36(4), 316–323 (2004).

45 Fuld K, Conrad B, Buckingham B, Wilson DM. Insulin pumps in young children. *Diabetes Technol. Ther.* 12(Suppl. 1), S67–S71 (2010).

46 Nahata L. Insulin therapy in pediatric patients with type I diabetes: continuous subcutaneous insulin infusion versus multiple daily injections. *Clin. Pediatr. (Phila.)* 45(6), 503–508 (2006).

47 Tamborlane WV, Sikes KA, Steffen AT, Weinzimer SA. Continuous subcutaneous insulin infusion (CSII) in children with Type 1 diabetes. *Diabetes Res. Clin. Pract.* 74(Suppl. 2), S112–S115 (2006).

48 Weissberg-Benchell J, Antisdel-Lomaglio J, Seshadri R. Insulin pump therapy: a meta-analysis. *Diabetes Care* 26(4), 1079–1087 (2003).

49 Kaiserman K, Rodriguez H, Stephenson A, Wolka L, Fahrbach JL. Continuous subcutaneous insulin infusion of insulin lispro in children and adolescents with type 1 diabetes. *Endocr. Pract.* 1–24 (2012).

50 Downie E, Craig ME, Hing S, Cusumano J, Chan AKF, Donaghue KC. Continued reduction in the prevalence of retinopathy in adolescents with Type 1 diabetes: role of insulin therapy and glycemic control. *Diabetes Care* 34(11), 2368–2373 (2011).

51 Cortina S, Repaske DR, Hood KK. Sociodemographic and psychosocial factors associated with continuous subcutaneous insulin infusion in adolescents with Type 1 diabetes. *Pediatr. Diabetes* 11(5), 337–344 (2010).

52 Wood JR, Moreland EC, Volkening LK, Svoren BM, Butler DA, Laffel LMB. Durability of insulin pump use in pediatric patients with Type 1 diabetes. *Diabetes Care* 29(11), 2355–2360 (2006).

53 Lapolla A, Dalfra MG, Masin M *et al.* Analysis of outcome of pregnancy in Type 1 diabetics treated with insulin pump or conventional insulin therapy. *Acta Diabetol.* 40(3), 143–149 (2003).

54 Mukhopadhyay A, Farrell T, Fraser RB, Ola B. Continuous subcutaneous insulin infusion vs intensive conventional insulin therapy in pregnant diabetic women: a systematic review and metaanalysis of randomized, controlled trials. *Am. J. Obstet. Gynecol.* 197(5), 447–456 (2007).

55 Farrar D, Tuffnell DJ, West J. Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes. *Cochrane Database Syst. Rev.* (3), CD005542 (2007).

56 Volpe L, Pancani F, Aragona M *et al.* Continuous subcutaneous insulin infusion and multiple dose insulin injections in Type 1 diabetic pregnant women: a case-control study. *Gynecol. Endocrinol.* 26(3), 193–196 (2010).

57 Bailon RM, Partlow BJ, Miller-Cage V *et al.* Continuous subcutaneous insulin infusion (insulin pump) therapy can be safely used in the hospital in select patients. *Endocr. Pract.* 15(1), 24–29 (2009).

58 Noschese ML, Dinardo MM, Donihi AC *et al.* Patient outcomes after implementation of a protocol for inpatient insulin pump therapy. *Endocr. Pract.* 15(5), 415–424 (2009).

59 Morviducci L, Di Flaviani A, Lauria A *et al.* Continuous subcutaneous insulin infusion (CSII) in inpatient setting: unmet needs and the proposal of a CSII unit. *Diabetes Technol. Ther.* 13(10), 1071–1074 (2011).

60 Nassar AA, Boyle ME, Seifert KM *et al.* Insulin pump therapy in patients with diabetes undergoing surgery. *Endocr. Pract.* 18(1), 49–55 (2012).

61 Boyle ME, Seifert KM, Beer KA *et al.* Guidelines for application of continuous subcutaneous insulin infusion (insulin pump) therapy in the perioperative period. *J. Diabetes Sci. Technol.* 6(1), 184–190 (2012).

■ **Perioperative use of CSII is relatively underutilized due to the coordination of multiple hospital services and nursing staff necessary to ensure patient safety. Standardized guidelines and a checklist, as well as the elements necessary for the creation of an institution-specific policy to facilitate continuation of pump therapy during planned operative procedures, are discussed.**

62 Ehle AL, Raskin P. Increased nerve conduction in diabetics after a year of improved glucoregulation. *J. Neurol. Sci.* 74(2–3), 191–197 (1986).

63 Warmolts JR, Mendell JR, O'Dorisio TM, Cataland S. Comparison of the effects of continuous subcutaneous infusion and split-mixed injection of insulin on nerve function in Type I diabetes mellitus. *J. Neurol. Sci.* 82(1–3), 161–169 (1987).

64 Dahl-Jorgensen K, Brinchmann-Hansen O, Hanssen KF *et al.* Effect of near normoglycaemia for two years on progression of early diabetic retinopathy, nephropathy, and neuropathy: the Oslo study. *Br. Med. J. (Clin. Res. Ed.)* 293(6556), 1195–1199 (1986).

65 Feldt-Rasmussen B, Mathiesen ER, Deckert T. Effect of two years of strict metabolic control on progression of incipient nephropathy in insulin-dependent diabetes. *Lancet* 2(8519), 1300–1304 (1986).

66 Bangstad HJ, Osterby R, Dahl-Jorgensen K, Berg KJ, Hartmann A, Hanssen KF. Improvement of blood glucose control in IDDM patients retards the progression of morphological changes in early diabetic nephropathy. *Diabetologia* 37(5), 483–490 (1994).

67 St Charles M, Lynch P, Graham C, Minshall ME. A cost–effectiveness analysis of continuous subcutaneous insulin injection versus multiple daily injections in type 1 diabetes patients: a third-party US payer perspective. *Value Health* 12(5), 674–686 (2009).

68 Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. *Arch. Ophthalmol.* 116(7), 874–886 (1998).

69 Dahl-Jorgensen K, Brinchmann-Hansen O, Hanssen KF, Sandvik L, Aagenaes O. Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes mellitus: the Oslo study. *Br. Med. J. (Clin. Res. Ed.)* 290(6471), 811–815 (1985).

70 Holfort SK, Norgaard K, Jackson GR *et al.* Retinal function in relation to improved glycaemic control in type 1 diabetes. *Diabetologia* 54(7), 1853–1861 (2011).

71 Diabetic retinopathy after two years of intensified insulin treatment. Follow-up of the Kroc Collaborative Study. The Kroc Collaborative Study Group. *JAMA* 260(1), 37–41 (1988).

72 Li Y, Xu W, Liao Z *et al.* Induction of long-term glycemic control in newly diagnosed Type 2 diabetic patients is associated with improvement of β-cell function. *Diabetes Care* 27(11), 2597–2602 (2004).

73 Noh YH, Lee SM, Kim EJ *et al.* Improvement of cardiovascular risk factors in patients with Type 2 diabetes after long-term continuous subcutaneous insulin infusion. *Diabetes Metab. Res. Rev.* 24(5), 384–391 (2008).

74 Jankovec Z, Cechurova D, Krcma M, Lacigova S, Zourek M, Rusavy Z. The influence of insulin pump treatment on metabolic syndrome parameters in Type 2 diabetes mellitus. *Wien Klin. Wochenschr.* 121(13–14), 459–463 (2009).

75 Bolli GB, Kerr D, Thomas R *et al.* Comparison of a multiple daily insulin injection regimen (basal once-daily glargine plus mealtime lispro) and continuous subcutaneous insulin infusion (lispro) in Type 1 diabetes: a randomized open parallel multicenter study. *Diabetes Care* 32(7), 1170–1176 (2009).

■ Websites

101 National Diabetes Fact Sheet: national estimates and general information on diabetes and prediabetes in the United States (2011). www.cdc.gov/diabetes/pubs/factsheet11.htm

102 Timesulin: 2012. http://timesulin.com

103 Ford. Ford in-car health and wellness solutions: medical device connectivity via bluetooth. http://media.ford.com/images/10031/health_wellness.pdf

104 Medtronic Inc. Bode BW, Kyllo J, Kauffmann FR. Pumping protocol. http://professional.medtronicdiabetes.com/sfc/servlet.shepherd/version/download/068C0000000IptI