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Glucose Control With Intravenous Insulin in Hospitalized Cardiac and Surgical Patients

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Editor's Note

Cardiac or other major surgery and acute myocardial infarction (MI) are all potentially life-threatening events that require intensive care. Since the publication of the Diabetes Control and Complications Trial (DCCT) (1) in 1993 and the United Kingdom Prospective Diabetes Study (UKPDS) in 1998, clinicians have become convinced of the benefits of intensively-controlled glycemia in the prevention of diabetes complications and mortality. This awareness has engendered renewed interest in and effort toward normalizing blood glucose (BG) in the outpatient setting; although laborious and expensive, it is deemed to be cost effective. With respect to the short-term, acute-care setting, new evidence suggests that the same paradigm holds true, i.e. achievement of normoglycemia reduces complications after cardiac surgery or intensive care unit (ICU) stay and reduces mortality following MI.

As reviewed by Cheng and colleagues in this issue of *Canadian Diabetes*, a seminal Belgian study showed improvement in survival for long-term-stay ICU patients who achieved excellent glycemic control with intravenous (IV) insulin infusion, targeting BG between 4.5 and 6.0 mmol/L (3). As well, the Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study showed advantages in both short- and long-term survival when acute MI patients were administered IV infusions of insulin in the short-term, followed by insulin for 3 months (4,5). Finally, further studies have suggested that outcomes of cardiac surgery in patients with diabetes are improved with the use of insulin targeting modest BG control perioperatively (7.0 to 10.0 mmol/L) (6,7). Importantly, previous observational studies suggested that outcomes were worse after MI or major surgery, depending on BG levels upon admission, regardless of the pre-existence of a diagnosis of diabetes. The results observed in these recent intervention studies in the ICU or coronary care unit (CCU) setting confirm that individuals without a diagnosis of diabetes—who may have either "stress hyperglycemia" or undiagnosed diabetes—benefit equally.

Achievement of normoglycemia reduces complications after cardiac surgery or ICU stay and reduces mortality following MI.

While these studies are helpful, some aspects remain intriguing with regard to the pathophysiology as well as the understanding of the effects achieved. The issue of whether benefit in the ICU was achieved exclusively from glycemic control, or was aided by improved attention to nutritional status, is not completely clear. As well, the question of whether the benefit in peri-acute coronary syndrome patients was due to glycemic control or an effect of insulin (and potassium) per se on the myocardium will continue to be debated. Nonetheless, these studies have prompted new guidelines for the management of hospitalized patients, with important resource implications.

To the authors' knowledge, the institution of protocols in major ICUs across Canada is widespread, but likely of relatively minor consequences in settings where hourly blood work is commonplace, and where one-on-one nurses are well-trained to administer IV insulin. On the other hand, attention to glycemic control in CCUs seems to have been more sporadic to date, with some centres embracing DIGAMI-1 (4,5), while others await the results of the DIGAMI-2 trial (8). Regardless of resources in CCUs, an additional challenge in these patients is the intensive diabetes care with multiple dose insulin that is suggested to be required for an indefinite period (at least 3 months). Further research is required to guide this practical question, but it may ultimately be moot, given the increasing recognition that good glycemic control is rarely achieved without insulin in patients with a significant duration of diabetes.

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Use of IV insulin infusion in operating suites, CCUs and ICUs will require intensification of diabetes and insulin education among physicians and nurse. Protocols will be required (which can be found in publications and websites), but are more likely to be obtained from 'favourites' of specialist teams in major teaching hospitals. In all cases, when these protocols are developed, it will be necessary to balance diabetes expertise and the pursuit of optimal BG control with safety (e.g. avoidance of hypoglycemia) and available resources (e.g. (nursing staff). The good news is that outside the ICU, where targets are tighter, a reasonable BG level of 5.0 to 11.0 mmol/L can usually be achieved through IV insulin infusion of variable rates every 2 to 4 hours, rather than hourly. These safer targets are achievable with less intense monitoring and resource demands. Regardless, the practical implications of the Canadian Diabetes Association 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada (9) are significant, since the promise of better outcomes is too important to ignore.

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Perioperative and Peri-acute Coronary Syndrome Glycemic Control: Highlights From the 2003 CPGs

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INTRODUCTION

The Canadian Diabetes Association (CDA) 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada differ from the 1998 guidelines in a variety of ways, reflecting the wealth of new evidence that has emerged since that time. New additions to the guidelines include chapters on perioperative glycemic control and peri-acute coronary syndrome (ACS) glycemic control—common and challenging aspects of inpatient diabetes management faced by physicians every day (1,2). This article summarizes the rationale and recommendations for glycemic control in these 2 situations and will provide a brief discussion of the evidence on which these guidelines were based.

PERIOPERATIVE GLYCEMIC CONTROL

Diabetes management at the time of surgery poses a number of challenges to the healthcare team. The physical stress associated with surgery typically results in acute hyperglycemia, which adversely affects immune function (3) and wound healing (4). Furthermore, hyperglycemia in the perioperative period may increase the risk of postoperative infections (5,6) and other adverse clinical outcomes (7).

Major surgery

A landmark study by van den Berghe and colleagues (8), randomized patients (with or without diabetes) admitted to a primarily surgical intensive care unit (ICU) to intensive glycemic control with continuous intravenous (IV) insulin (target plasma glucose [PG] levels of 4.4 to 6.1 mmol/L) or conventional treatment with continuous IV insulin (target PG levels of 10.0 to 11.1 mmol/L). Within the intensive group, insulin therapy was initiated for PG levels >6.1 mmol/L, while in the conventional group insulin therapy was only initiated if PG levels rose above 11.9 mmol/L. Significant reductions in morbidity and mortality were seen among intensively treated patients, compared with those treated conventionally. This benefit was observed even in those patients without a prior diagnosis of diabetes. The number needed to treat (NNT) to prevent 1 death was only 30, and among those patients requiring longer stay in the ICU (>5 days) the NNT was only 11. Based on this landmark study, the CDA's clinical practice guidelines recommend using a continuous IV insulin infusion to maintain postoperative PG levels between 4.5 and 6.0 mmol/L, in combination with continuous feeding, in patients who require intensive care and mechanical ventilation after major surgery (1).

Among patients with diabetes undergoing cardiac surgery, postoperative PG levels >6.1 mmol/L are associated with an increased risk of adverse outcomes (9). In this population, improved perioperative (both intraoperative and postoperative) glycemic control with a continuous IV insulin infusion has been shown to reduce morbidity and mortality (10-12). However, the safe implementation of intensive glycemic control with a continuous IV insulin infusion requires an appropriate protocol and staff training to ensure effectiveness and to minimize hypoglycemia.

Minor and moderate surgery

The appropriate perioperative glycemic targets for minor or moderate surgeries (those lasting >2 hours but not requiring postoperative ICU care) are less clear. To date, no intervention studies have assessed the impact of different PG levels on morbidity or mortality in this setting. However, a number of small studies that compared different methods of achieving glycemic control during minor and moderate surgeries failed to identify any adverse effects from maintaining perioperative glycemic levels between 5.0 and 11.0 mmol/L (13-15). Given the data supporting tight perioperative glycemic control during major surgeries and the compelling data showing the adverse effects of hyperglycemia, it is reasonable to target glycemic levels between 5.0 and 11.0 mmol/L for minor and moderate surgeries.

Perioperative recommendations

1. A continuous IV insulin infusion should be used to achieve glycemic levels of 4.5 to 6.0 mmol/L in postoperative patients who require intensive care and mechanical ventilation and demonstrate hyperglycemia (random PG >6.1 mmol/L) *[Grade A, Level 1A (8)]*.
2. A continuous IV insulin infusion should be used to maintain intraoperative glycemic levels between 5.0 and 11.0 mmol/L for patients with diabetes undergoing cardiac surgery *[Grade C, Level 3 (10)]*.
3. Perioperative glycemic levels should be maintained between 5.0 and 11.0 mmol/L for most other surgical situations *[Grade D, Consensus]*.

PERI-ACUTE CORONARY SYNDROME GLYCEMIC CONTROL

Patients with diabetes have greater short-term and long-term mortality after acute myocardial infarction (MI) than patients without diabetes, even in the era of thrombolytic therapy (16). Diabetes is also an independent predictor of mortality following other ACS, such as unstable angina or

non-Q-wave MI (17). Even in patients without a previous diagnosis of diabetes, hyperglycemia on admission for an acute MI is associated with higher mortality (18,19). These cases may represent previously unrecognized diabetes or glucose intolerance (20).

Rationale

Biochemical abnormalities associated with relative or absolute insulin deficiency may be harmful during the acute phase of MI. Insulin therapy in patients with diabetes presenting in this setting has been shown to be beneficial. The Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study compared the use of conventional therapy to an insulin-glucose infusion to maintain PG levels between 7.0 and 10.0 mmol/L, followed by multidose subcutaneous insulin (intensive insulin therapy) (21,22). Patients with an acute MI and admission PG levels >11.0 mmol/L were included in this study. Intensive insulin therapy resulted in a nearly 30% reduction in long-term mortality out to 3.4 years. One life was saved for every 9 patients treated with intensive insulin therapy. Particular benefit was observed in patients who had fewer cardoiavascular risk factors and those who were not using insulin prior to randomization. Given the magnitude of benefit seen in the DIGAMI study and the knowledge that diabetes is a predictor of mortality after an ACS (16), use of an insulin-glucose infusion to improve glycemic control in the acute setting may be beneficial for all patients with diabetes presenting with an ACS. Patients who are treated with a multidose insulin regimen after an MI should be followed closely by a diabetes healthcare team with experience in managing intensified insulin therapy in order to safely maintain optimal glycemic control.

Peri-ACS recommendations

1. All patients with acute MI, regardless of whether or not they have a prior diagnosis of diabetes, should have their BG level measured on admission *[Grade D, Consensus]*, and those with BG >12.0 mmol/L should receive insulin-glucose infusion therapy to maintain BG between 7.0 and 10.0 mmol/L for at least 24 hours, followed by multidose SC insulin for at least 3 months *[Grade A, Level 1A (21,22)]*. An appropriate protocol should be developed and staff trained to ensure the safe and effective implementation of this therapy and to minimize the likelihood of hypoglycemia *[Grade D, Consensus]*.

NEW EVIDENCE SINCE THE GUIDELINES

Since the publication of the CDA clinical practice guidelines in December 2003, new evidence has become available pertaining to both perioperative and peri-ACS glycemic control. In the realm of perioperative glycemic control, recent studies support the benefit of tight perioperative glycemic control, particularly for major surgeries (11,12). However, in the realm of peri-ACS glycemic control, recent evidence suggests that glycemic control itself rather than insulin therapy was responsible for the improved outcomes observed in the DIGAMI-1 study (22). A second, recently published study (DIGAMI-2) was designed to examine whether these results were due to the acute effect of insulin treatment on the myocardium, the use of multidose SC insulin after the MI or improved glycemic control after the MI (23). In this study, patients presenting with an acute MI and an admission glucose >11.0 mmol/L were randomized to one of three groups: 1) acute insulin-glucose infusion followed by intensive long term glucose control with a multidose (≥3 doses/day) SC insulin (MDI) regimen; 2) insulin-glucose infusion followed by standard glucose control and; 3) routine metabolic management according to local practice. After 2 years of follow up, there was no difference between the groups in terms of mortality, non-fatal strokes or reinfarctions. These results were strikingly different from the DIGAMI-1 study (discussed above); however, there were a number of methodological issues with DIGAMI-2 that could explain this discrepancy. The study was terminated early due to recruitment difficulties, and there was significant cross over between treatment arms. Perhaps most importantly, there was no significant difference in glycemic control between the three treatment groups throughout the length of the study. In fact, all groups achieved levels of glycemic control that were similar to or better than the intensive group of DIGAMI-1. After DIGAMI-2, one may conclude that the level of glycemic control, and not insulin therapy itself, is the more important determinant of mortality after an acute MI in patients with hyperglycemia. From a practical standpoint, a

Elements of a Successful Insulin Infusion Protocol

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1. *Monitor frequently*: Initially, blood glucose (BG) monitoring should be done every hour. After an intravenous (IV) infusion rate changes, it can generally be progressively decreased to every 4 hours if and when BG levels are stable.
2. *Set a standard starting dose* (units/hour) with a standard insulin dilution.
3. *Set target goals*: Goals can be tight (i.e. 4.0 to 7.0 mmol/L) or looser (i.e. 6.0 to 12.0 mmol/L, depending on local staff's availability, their familiarity with the protocol and patient characteristics.
4. *Establish procedures for hypoglycemia and hyperglycemia*: For mild hypoglycemia, protocol should include prompt treatment with 15 g of glucose orally. For severe hypoglycemia, protocol should include 10 to 25 g of IV glucose or glucagon 1 mg subcutaneously or intramuscularly. To avoid recurrence, a decreased or suspension of insulin perfusion should be done. (See the "Hypoglycemia" chapter in the Canadian Diabetes Association 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada) (1).
5. *Educate staff responsible for the application of the protocol*: This is a major factor in the safety and efficacy of a successful protocol. Many hospitals already have such protocols, each with their pros and cons. When developing a new protocol, individuals are encouraged to consult as many protocols as possible and adjust based on local resources and needs.

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continuous IV insulin infusion is usually required to achieve good glycemic control in the peri-ACS setting among patients with diabetes. Thus, the 2003 peri-ACS recommendations remain valid.

CONCLUSIONS

Glycemic control in the perioperative and peri-ACS settings have a significant impact on clinical outcomes. The evidence strongly supports the use of continuous IV insulin to achieve tight glycemic control for patients undergoing major surgery requiring post-operative ICU care. Although there are no outcome data for minor or moderate surgeries, it would be prudent to also target good glycemic control in those situations. In the peri-ACS setting, hyperglycemia adversely affects outcomes and the available evidence suggests that achieving good glycemic control will reduce adverse events. Most patients with diabetes experiencing the stress of ACS will require continuous IV insulin to achieve good glycemic control in the peri-ACS setting. Any time one strives for better glycemic control, the risk of hypoglycemia increases, thus standardization (establishing protocols), staff training and proper monitoring are important to ensure safe implementation and minimal hypoglycemia.

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Case Studies: Glycemic Control in the Perioperative and Peri-acute Coronary Syndrome Settings

Case 1

A 65-year-old woman with no prior history of diabetes undergoes abdominal aortic aneurysm repair and requires post-operative intensive care unit (ICU) care. Her blood glucose (BG) level is 9.0 mmol/L post-operatively.

Question:

1. *How should this woman's BG level be treated?*

Answer:

1. The Canadian Diabetes Association 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes recommend that post-operative patients who require intensive care admission and ventilation, whose BG is >6.1 mmol/L, should receive intravenous insulin for at least 24 hours, with a goal of achieving BG levels of 4.5 to 6.0 mmol/L. This recommendation is based on a large clinical trial in which intensive insulin treatment reduced mortality by 43% in post-operative ICU patients (8).

Case 2

A 59-year-old man is admitted to the coronary care unit (CCU) with an inferior ST-elevation myocardial infarction (MI). His admission BG level is 12.3 mmol/L. He has no past history of diabetes and was on no medications before admission. He has a family history of diabetes; his father had the disease, and died from MI at age 60.

Questions:

1. *What is the significance of this patient's high BG level?*
2. *Should he be treated for high BG?*
3. *What is his risk of diabetes after discharge from hospital?*

Answers:

1. This patient most likely has "stress hyperglycemia," defined as an increase in BG due to a physiologically stressful event. Stress hyperglycemia occurs in roughly 30% of people with acute MI and no previous history of diabetes, and in about three-quarters of people with known diabetes. Stress hyperglycemia has been associated with close to a 4-fold increase in post-MI mortality in people without known diabetes, compared to people without stress hyperglycemia (18).
2. Yes, this patient should be treated with IV insulin. The DIGAMI study showed that treatment with IV insulin in hospital, followed by subcutaneous insulin for at least 3 months after discharge, lowered mortality by nearly 30% over a mean follow-up of 3.4 years in patients with acute MI and hyperglycemia, whether or not they had a diagnosis of diabetes. In fact, the benefit of insulin therapy was greatest in those patients with low cardiovascular risk profile and no previous insulin treatment (21,22).
3. Research suggests that people with stress hyperglycemia post-MI are likely to have elevated BG levels after discharge as well. This patient should be tested for diabetes after hospital discharge.

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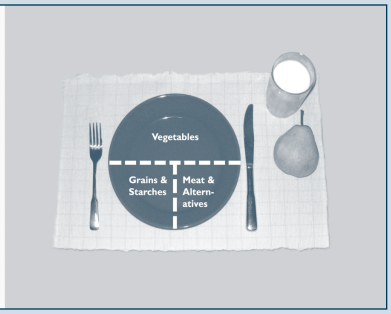
BEYOND *the* BASICS:

Meal Planning for Healthy Eating, Diabetes Prevention and Management



Revision of the Canadian Diabetes Association's Meal Planning System

Healthy eating is one of the cornerstones of effective diabetes management. A volunteer committee of experts has been working on revising the Canadian Diabetes Association's meal planning system (*The Good Health Eating Guide*). Making the system more compatible with those in Quebec and the United States and with Canada's Food Guide to Healthy Eating, as well as increasing the flexibility of meal planning were the goals. The new plan is the logical next step in nutrition management, for clients who need more information than is provided in *Just the Basics*.

The biggest change will be in food groups containing carbohydrate (Grains & Starches, Fruits, Milk & Alternatives, and Other Choices): a portion of a food in each of these groups will provide 15 g of available carbohydrate or one choice. Many traditional portion sizes have been changed due to the fibre content or the GI. There are more multicultural choices to better meet the diverse needs of Canadians.

There has been an extensive consultation process. A "close to final" version of the patient poster was presented at the CDA/CSEM professional conference for feedback from attendees in October 2004.

Copies of the poster, now called *Beyond the Basics*, became available in April 2005. A more comprehensive resource manual will be ready about one year later.

For more information, please contact Sharon Zeiler, Senior Manager, Nutrition Initiatives and Strategies, Canadian Diabetes Association via e-mail (sharon.zeiler@diabetes.ca), or check the Association website at www.diabetes.ca.

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atteints de diabète sont meilleurs lorsqu'on administre de l'insuline pour atteindre un objectif glycémique peu rigoureux avant la chirurgie (de 7,0 à 10,0 mmol/L)[6,7]. Il est important de noter que des études par observation ont laissé entendre que les résultats étaient pires après un IM ou une chirurgie lourde, selon la glycémie au moment de l'hospitalisation, qu'un diagnostic de diabète ait ou non été posé au préalable. Les résultats de ces récentes études menées dans des unités de soins intensifs ou des unités de soins coronariens confirment que les avantages sont les mêmes chez les patients chez qui un diagnostic de diabète n'a pas été posé, qui pourraient présenter une hyperglycémie liée au stress ou un diabète non diagnostiqué.

Ces études sont utiles, mais certains aspects relatifs à la pathophysiologie et à la compréhension des effets obtenus sont mal compris. La question à savoir si les bons résultats observés à l'unité de soins intensifs sont exclusivement attribuables à l'équilibre de la glycémie ou s'ils découlent de l'amélioration de la surveillance de l'alimentation n'est pas entièrement élucidée. De plus, le débat se poursuit à savoir si les bienfaits observés en présence d'un syndrome coronarien péri-aigu sont attribuables à l'équilibre de la glycémie ou un effet de l'insuline (et du potassium) sur le myocarde. Néanmoins, ces études ont abouti à l'élaboration de lignes directrices pour le traitement des malades hospitalisés, ce qui a d'importantes répercussions sur les ressources.

Selon les auteurs, l'établissement de protocoles dans les importantes unités de soins intensifs canadiennes est courant, mais a probablement peu d'effets là où on effectue couramment des prélèvements sanguins toutes les heures et là où des infirmières privées sont bien formées pour administrer l'insuline par voie intraveineuse. Par contre, la surveillance de la glycémie dans les unités de soins coronariens semble plus sporadique actuellement, certains établissements acceptant les résultats de l'étude DIGAMI[4,5] et d'autres attendant les résultats de l'étude DIGAMI 2[8]. Quelles que soient les ressources des unités de soins coronariens, les soins diabétologiques intensifs comportant l'administration de multiples doses d'insuline qui seraient nécessaires pendant une période indéfinie (au moins 3 mois) sont un défi supplémentaire chez ces patients. D'autres études devraient être effectuées pour répondre à cette question pratique, mais elle pourrait ne présenter aucun intérêt, car on reconnaît de plus en plus qu'un bon équilibre de la glycémie est rare sans l'administration d'insuline chez les patients qui souffrent de diabète depuis longtemps.

L'administration intraveineuse d'insuline dans la salle d'opération, l'unité de soins coronariens et l'unité de soins intensifs exigera une intensification de l'éducation des médecins et des infirmières en matière de diabète et d'insulinothérapie. Il faudra établir des protocoles (on en trouve dans les publications et les sites Web), mais il est plus probable qu'on obtienne les «protocoles favoris» d'équipes de spécialistes de grands hôpitaux d'enseignement. Dans tous les cas, lorsqu'on élaborera de tels protocoles, il faudra tenir compte des connaissances sur le diabète et de la recherche de l'équilibre optimal de la glycémie d'une part et de l'innocuité (c.-à-d. éviter l'hypoglycémie) et des ressources disponibles (c.-à-d. le personnel infirmier) d'autre part. La bonne nouvelle est qu'en dehors de l'unité de soins intensifs, où les objectifs sont plus rigoureux, on peut habituellement obtenir une glycémie raisonnable de 5,0 à 11,0 mmol/L en administrant une perfusion intraveineuse d'insuline à diverses vitesses toutes les 2 à 4 heures plutôt que toutes les heures. Ces objectifs sont plus sûrs et exigent moins de surveillance et de ressources. Quoi qu'il en soit, les conséquences pratiques des *Lignes directrices de pratique clinique 2003 de l'Association canadienne du diabète pour la prévention et le traitement du diabète au Canada*[9] sont significatives, car la promesse de meilleurs résultats est trop importante pour en faire abstraction.

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Équilibre de la glycémie au moyen d'insuline administrée par voie intraveineuse en milieu hospitalier

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Note de la rédaction

La chirurgie cardiaque, les autres chirurgies lourdes et l'infarctus aigu du myocarde (IM aigu) sont tous des événements qui menacent le pronostic vital et qui exigent des soins intensifs. Depuis la publication des résultats de l'étude DCCT (*Diabetes Control and Complications Trial*)[1] et de ceux de l'étude UKPDS (*United Kingdom Prospective Diabetes Study*)[2] en 1993 et 1998, respectivement, les cliniciens sont convaincus des avantages de la maîtrise rigoureuse de la glycémie pour prévenir les complications du diabète et la mortalité. Cette prise de conscience a ranimé l'intérêt pour la normalisation de la glycémie chez les malades non hospitalisés. Même si elle est difficile et coûteuse, on croît qu'elle est rentable. Pour ce qui est des établissements de soins de courte durée, de nouvelles données semblent indiquer que le même paradigme s'applique, c'est-à-dire que la normalisation de la glycémie réduit les complications après une chirurgie cardiaque ou un séjour à l'unité de soins intensifs et réduit la mortalité après un infarctus du myocarde.

D'après l'analyse de Cheng et ses collaborateurs publiée dans le présent numéro de *Le diabète au Canada*, une étude de base menée en Belgique a révélé qu'il y avait eu une amélioration de la survie chez les patients qui faisaient un séjour prolongé à l'unité de soins intensifs et chez qui la perfusion intraveineuse d'insuline avait produit un excellent équilibre de la glycémie, l'objectif étant de 4,5 à 6,0 mmol/L[3]. En outre, l'étude DIGAMI (*Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction*) a révélé qu'il y avait une amélioration de la survie à court terme et à long terme chez les patients ayant subi un IM aigu qui avaient reçu des perfusions intraveineuses d'insuline à court terme suivies d'injections d'insuline pendant 3 mois[4,5]. Enfin, d'autres études semblent indiquer que les résultats de la chirurgie cardiaque chez des patients

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