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INSULIN TREATED DIABETIC PILOT APPLICANTS: RECOMMENDATIONS

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Introduction

Whether insulin treated diabetic pilots (ITDM) should be allowed to fly has long been a controversial issue. Safe functioning may be impeded by complications of diabetes mellitus, such as autonomic neuropathy, cardiovascular disease, retinopathy, and renal disease and by complications of the therapy of which hypoglycemia represents a major threat to flight safety. In European and many other countries, pilots treated with insulin are presently disqualified and only biguanides or alphaglucosidase inhibitors are approved as medication for pilots with type 2 diabetes mellitus (JAA; EASA). Diabetic pilots who require insulin are also assessed as unfit under the regulations of the International Civil Aviation Organisation (ICAO). However, ICAO offers guidance on a fit assessment for pilots with type 2 diabetes who require insulin (ICAO). The civil aviation authorities of Australia, Canada, and USA, allow pilots -on a case by case basis and under strict conditions- to fly while treated with insulin (CASA, 2010; Transport Canada; FAA, 2004). In 2008, at least 15 Canadian commercial pilots were flying with insulin under intensive aeromedical control (Steve Steele, 2008).

The aeromedical discussions concerning ITDM pilots are concentrated on the possible conflict between the requirement of sufficiently high blood glucose levels (BG) to exclude in-flight hypoglycemia as opposed to intensive glucose lowering treatment aimed at prevention of micro- and macrovascular complications of the disease.

In the present paper we will argue that it is possible to keep insulin treated type 1 and type 2 diabetic pilots on flying status without making concessions to flight safety. The term “blood glucose” stands for plasma glucose throughout this paper.

1 Rationale for insulin treatment

Type 1 diabetes (T1DM) is a condition in which pancreatic beta cells are destroyed, resulting in a failure of the pancreas to produce insulin. Therefore, T1DM is always treated by insulin, delivered by pump or injection. In a study of the Diabetes Control and Complications Trial Research Group evidence was found that intensively treated T1DM patients with a mean glycated hemoglobin level (HbA1c) of 7.2% had a reduced risk of microvascular complications compared to a conventionally treated group with a mean HbA1c of 9.0% (DCCT, 1993). Since the publication of this study more intensive glucose lowering treatment of T1DM is generally advocated.

Because most Type 2 diabetes (T2DM) patients have residual endogenous insulin secretion, the rationale for imitating the physiological insulin secretion pattern is less convincing than in T1DM. However, a number of landmark randomised clinical trials established that insulin therapy reduces microvascular complications in T2DM (UKPDS, 1998; Ohkubo et al. 1995). In addition, recent follow-up data from the U.K. Prospective Diabetes Study (UKPDS) suggests that early insulin treatment also lowers macrovascular risk in type 2 diabetes (Holman et al. 2008). It is remarkable that in the UKPDS study blood pressure control had

greater effects on microvascular complications than intensive glucose lowering treatment. The publication of the results of these studies resulted in the use of insulin to enable a more intensive glucose-lowering treatment of T2DM. Another argument for insulin treatment of T2DM is that during the normal progression of the disease, a progressive insulin deficiency develops. By this, more and more people will require an insulin treatment, in order to obtain satisfactory glycaemic control and after some years, most of the patients with type 2 diabetes need insulin therapy to maintain optimal control.

Conclusion

There is consensus on the need for insulin in T1DM and T2DM treatment. In the consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes it is recommended to initiate insulin treatment in type 2 diabetics when glycemic goals (glycated hemoglobin level (HbA1c) of ≤7.0%) are not attained after 2–3 months of maximally dosed dual oral therapy (Nathan et al. 2009).

2 Problems associated with insulin treatment

The most common side effects of insulin treatment are hypoglycaemia and weight gain. Weight gain, which is usually 2-4 kg, is thought to be proportional to the number of insulin injections, or the total daily insulin dose (Swinnen et al., 2009).

While weight gain is usually considered manageable and/or acceptable, hypoglycaemia represents a significant hazard to transport safety. The brain primarily uses glucose as its source of energy. When blood glucose falls under 3.3 mmol/l (60 mg/dl) symptoms of neuroglycopenia and cognitive impairment develop, potentially interfering with driving and flying abilities.

The risk of severe hypoglycaemia, leading to complete incapacitation, is skewed and a subgroup of patients experience most of the severe hypoglycaemic episodes per year. The risk factors for severe hypoglycaemia are; impaired hypoglycaemic awareness; C-peptide negative status(no endogenous insulin secretion and therefore no glucagon response to hypoglycaemia); strict hypoglycaemic control; long duration of diabetes; medication (e.g. beta-blockers); and alcohol. The frequency of hypoglycaemia is generally lower in type 2 than in type 1 diabetes. The frequency of hypoglycaemia in insulin treated T2DM depends on the duration of the diabetes (Swinnen et al., 2009). Once T2DM patients lose their ability to secrete insulin after some years, the frequency for severe hypoglycaemia becomes similar to T1DM when matched for disease duration. Results of studies of the event rates for severe hypoglycaemia in insulin-treated patients show considerable differences. Relatively low rates were found in clinical trials, whereas the higher figures were reported in retrospective and population based studies. Differences are probably explained by varying durations of disease, or insulin therapy in the cited studies (Swinnen et al., 2009). Following 8655 people with diabetes for one year, Leese et al. (2003) found a risk of severe hypoglycaemia (needing emergency assistance) of 7.1% in T1DM, 7.3% in T2DM treated with insulin, and 0.8% in T2DM treated with sulfonylurea tablets.

Early warning symptoms of hypoglycaemia, such as anxiety, palpitations, hunger, sweating or tremor normally occur when the blood glucose is about 3.0mmol/l (55-60mg). Some diabetics experience a loss of the warning symptoms (largely reduced sympathetic -adrenergic and cholinergic- actions) or an impaired perception of -or reaction to- the early warning symptoms of hypoglycaemia. Patients with hypoglycaemia unawareness have a 10 times higher frequency of severe hypoglycaemia. Hypoglycaemic unawareness can be induced by frequent hypoglycaemias or by chronic hypoglycaemia alone and a vicious circle of recurrent

hypoglycaemia is created. It is observed in at least 25% of T1DM and 10 % of T2DM. After 20-30 years duration of diabetes more than 50% of the patients will display hypoglycaemic unawareness (Berne et al. 2006).

In the context of flight safety, it is noteworthy that Evans et al. (2000) found that cognitive performance became significantly impaired 20 minutes before symptomatic awareness of hypoglycemia (2.6 mmol/l = 47 mg/dl) occurred and that recovery of cognitive function lagged behind the restoration of glucose levels and the resolution of symptoms. This study was done in eight healthy volunteers and larger studies in diabetics should be done to verify these.

It is not known whether mild hypoxia, as is caused by the lowered cabin pressure, may trigger hypoglycaemia, or potentiate its effects on performance.

Conclusion

Hypoglycaemia represents a significant and unacceptable threat to flight safety. Therefore, it should be ensured that blood glucose levels in ITDM pilots are sufficiently high to function safely during the entire flight operation.

3 Can the hypoglycaemia risk be reduced?

Because the in-flight hypoglycaemia risk is the main concern in the case of ITDM pilots, everything should be done to remove this risk.

Blood Glucose Awareness Training (BGAT) is found to be useful to improve detection of hypoglycaemia and hyperglycaemia, judgement concerning when to act when blood glucose is low or high, and not drive while hypoglycaemic (Cox et al. 2001). Although, BGAT is clinically useful for many patients, the results of Cox et al. also show that after the training still 56% of the 73 type 1 diabetics was not able to correctly detect low blood glucose levels (<3.8 mmol/l). Therefore, we conclude that BGAT is useful, but does not guarantee that the risk of in-flight hypoglycaemia in pilots who have followed BGAT is absent.

Insulin analogues

The term “insulin analogue” describes insulin that has been bioengineered to modify its absorption or other properties. At present, three short-acting and two long-acting insulin analogues are available on the market. Findings of studies using short-acting insulin analogues, such as aspart, lispro, or apidra, and those using long-acting analogues, such as glargine or detemir indicate that the use of insulin analogues is associated with a tendency toward a reduced frequency of hypoglycemia in patients with type 1 diabetes (Garg et al. 2004; Shalitin and Phillip, 2008) and type 2 diabetes (Rosenstock et al. 2005). Very recently the ultra-long- acting insulin analogue degludec has been developed, which enables a dosing frequency of 3 times per week. A study by Zinman et al. (2011) in inadequately controlled type 2 diabetics taking metformin, found that hypoglycaemia risk and efficacy of degludec, given once a day or 3 times per week, did not differ with that of glargine given once daily (Zinman et al. 2011).

We conclude that, although, treatment with insulin analogues is associated with a tendency toward a reduced hypoglycaemia risk, the risk of in-flight hypoglycaemia in pilots who are treated with insulin analogues is still existent.

Continuous subcutaneous insulin infusion (CSII or "Pumps")

In their review, Pickup and Sutton (2008) found that the severe hypoglycaemia rate with Type 1 diabetes is significantly lower during CSII than multiple daily insulin injections (MDI), with the greatest reduction in those with most severe hypoglycaemia on MDI and those with the longest duration of diabetes. Results of studies of CSII in Type 2 diabetes appear to be controversial with some authors finding no advantages (Monami et al. 2009; Cummins et al. 2010). It can be concluded that that in some diabetic patients, the frequency and severity of hypoglycemia can be reduced with CSII treatment and/or blood glucose levels can be better controlled (Pickup and Sutton, 2008; Shalitin and Phillip, 2008). It is further assumed that continuous glucose monitoring will improve the ability of patients to monitor for hypoglycemia. In the context of flight safety, we consider that, although CSII is associated with a reduced hypoglycaemia risk, but such treatment cannot guarantee the absence of in-flight hypoglycaemia in ITDM pilots.

Consider alternatives for insulin: GLP-1 receptor agonists, or DPP-4 inhibitors?

The glucagon-like peptide-1 (GLP-1) receptor agonists have the potential to address fasting and postprandial glucose control with weight loss and a low risk of hypoglycaemia (Diamant et al. 2010). The first approved GLP-1 receptor agonist, exenatide, was administered twice daily, but has recently been developed into exenatide in a once weekly dosing formulation. Trials in type 2 diabetics showed that exenatide once weekly was superior for reduction of HbA1c compared with sitagliptin, pioglitazone, or insulin glargine, with a minimal number of hypoglycaemic episodes (Bergenstal et al. 2010; Diamant et al. 2010). It appears that exenatide may be a useful alternative for insulin in type 2 diabetes with the advantages of a lower risk of hypoglycaemia, better glycaemic control, and weight loss. However, the disadvantage is that exenatide and all approved GLP-1 receptor agonists cause nausea, vomiting, and sometimes diarrhoea in a substantial proportion of patients. Usually, these episodes are mild or moderate in intensity and wane over time. In the context of flight safety, we consider that, although exenatide once weekly is associated with a very low hypoglycaemia risk and may be a useful alternative for some pilots, this treatment cannot guarantee the absence of in-flight hypoglycaemia (and nausea) in ITDM pilots.

The di-peptidyl peptidase-4 inhibitors (DPP-4 inhibitors) reduce the proteolysis of GLP-1 and prolong its half-live, thereby increasing the concentration of endogenously released incretins (eg, the GLP-1 concentration is increased 2- to 3-fold). This results in a modest reduction in HbA1c, up to approximately 0.8% (Vilsboll et al. 2010). Three DPP-4 inhibitors (sitagliptin, saxagliptin and vildagliptin) are currently approved for the treatment of type 2 diabetes and can be considered as monotherapy, or in combination with metformin. This treatment generally has a low incidence of adverse events (Peters, 2010), although a hypoglycaemia risk should still be considered. In contrast with GLP-1 receptor agonists, DPP-4 inhibitors have no effect on body weight. There are some post-marketing reports of pancreatitis in association with DPP-4 inhibitors, but a causal link has not been established (Engel et al. 2010).

Conclusion

Hypoglycemia risk may be reduced by Blood Glucose Awareness Training, treatment with insulin analogues, continuous subcutaneous insulin infusion, or alternative treatment with exenatide or DPP-4 inhibitors, but none of these methods can completely exclude the occurrence of in-flight hypoglycaemia in the individual ITDM pilot. The only method to exclude in-flight hypoglycaemia will be to ensure that blood glucose levels in ITDM pilots are sufficiently high to function safely during the entire flight operation (i.e. $\geq$5 mmol/l = $\geq$91 mg/dl; Evans et al. 2000).

4 Intensive glycemic control: how low should one go?

Based on the results of the DCCT (1993), UKPDS (1998), and Holman et al. (2008) studies, it was advocated to intensify glycemic control as much as possible to prevent micro- and macrovascular complications. In that context, some aeromedical experts consider that it is ethically not justifiable to require ITDM pilots to maintain pre- and in-flight blood glucose at normal to high normal levels. The question is "how low should one go?" Controversy exists between experts advocating intensive therapy, aimed at HbA1c below 6.0%, and those advocating a standard therapy aimed at HbA1c 6.5 and 7.5%. As intensive glucose-lowering therapy inevitably results in an increased rate of hypoglycaemia (Cryer, 2002), the benefits of intensive treatment should outweigh the disadvantages. These benefits appear to differ between type 1 and type 2 diabetes.

Poor glycaemic control has been associated with cardiovascular disease in observational studies of type 1 diabetes (Eeg-Olofsson et al. 2010). Eeg-Olofsson et al. (2010) found that a baseline mean HbA1c of 7.2% showed considerably reduced risks of CHD and CVD. A Cox regression analysis showed a hazard ratio of 1.31 for fatal/nonfatal coronary heart disease per 1% unit increase in baseline or updated mean HbA1c (Eeg-Olofsson et al. 2010). A very recent study by Lind et al. (2011) provided evidence that tight control of glycaemia in T1DM is essential to prevent heart failure besides other aspects of cardiovascular disease. In a cohort of 20.985 Swedish patients, it was found that patients with HbA1c of more than 10.5% had a four times greater risk of heart failure than did those with HbA1c of 6.5% or less. Lind et al. found a 1.30 hazard ratio for heart failure per 1% increase of HbA1c. Moreover, the duration of diabetes was highly predictive of heart failure, with an increased risk of 34% for every 10 years of earlier diagnosis. It can be concluded that tight control of glycaemia appears to be useful to prevent macrovascular complications and heart failure in type 1 diabetes.
In their 2011 Standards of Care the American Diabetes Association argues that "Lowering HbA1c to below or around 7% has been shown to reduce microvascular and neuropathic complications of diabetes and, if implemented soon after the diagnosis of diabetes, is associated with long-term reduction in macrovascular disease. Therefore, a reasonable HbA1c goal for many nonpregnant adults is <7%. Analyses from several studies also suggest that further lowering of HbA1c from 7 to 6% is associated with further reduction in the risk of microvascular complications, albeit the absolute risk reductions become much smaller"(ADA, 2011).

For the treatment of type 2 diabetes, the findings of the Action to Control Cardiovascular Risk in Diabetes Study Group (ACCORD, 2008) have provided landmark data. In this study intensive therapy (aimed at HbA1c <6.0%) was compared with standard therapy (aimed at HbA1c 7.0 to 7.9%) in 10,251 patients (mean age 62.2 years). The intensive glycaemia treatment arm of this study was discontinued after 3.5 years because of significant higher mortality in this group compared with the standard therapy group. It was also found that the intensive therapy did not significantly reduce major cardiovascular events. The ACCORD authors concluded that intensive glucose lowering in high-risk patients with Type 2 diabetes may be harmful. The association between mortality and HbA1c forms a U-shaped curve, with the lowest mortality at HbA1c of about 7.1-7.8% (Opie et al. 2011). There is strong evidence that the emphasis in type 2 diabetes should remain on tight control of lipids and blood pressure, with reasonable but not exaggerated efforts to control glycaemia (Opie, 2011; Yudkin et al. 2011).

The ACCORD (2008) study also found annual rates of hypoglycemic episodes requiring medical assistance (severe hypoglycaemia) of 3.1% in the intensive therapy group and 1.0%

in the standard therapy group, by that confirming that intensive glucose-lowering therapy leads to an increased hypoglycaemia rate.

Conclusion
In the context of prevention of micro- and macrovascular complications, it is medically and ethically justifiable to treat type 1 diabetic pilots with the aim to maintain HbA1c levels of 6.5 to 7% and treat type 2 diabetic pilots with standard therapy aiming at HbA1c 7.0 to 7.8%.

5 Safe BG levels when flying have no negative consequences for prevention

We have argued that from a preventive point of view it is justifiable to aim treatment of pilots with type 1 diabetes at HbA1c levels below 7% and preferably around 6.5% and for pilots with type 2 at HbA1c levels between 7 and 7.8%. When considering a plasma glucose level of 5 mmol/l (91 mg/dl) as a lower limit for adequate cerebral functioning (Evans et al.2000), it can be seen that for type 1 diabetics HbA1c levels between 6.5 and 7% still enable to have sufficiently safe in-flight plasma glucose levels, because these HbA1c values are considered to correlate with average estimated glucose levels (eAG) between 7.8 mmol/l (140 mg/dl) and 8.6 mmol/l (154 mg/dl) using the equation applicable to adults with stable glycemic control: eAG [mg/dl] = 28.7 x HbA1c – 46.7 (ADA, 2011; Nathan et al. 2008). For type 2 diabetics, HbA1c levels between 7 and 7.8% also enable to have sufficiently safe in-flight glucose levels, as average estimated glucose levels can be kept between 8.6 mmol/l (154 mg/dl) and 9.8 mmol/l (177 mg/dl) (ADA, 2011; Nathan et al. 2008).

Because abnormally high blood glucose levels may also impair flight safety and health, it is also justifiable to require pre- and in-flight blood glucose levels to be less than 15 mmol/l (273 mg/dl).

We emphasize that ITDM treated pilots should only be allowed to fly when they are in a stable glycemic condition.

6 Existing protocols for ITDM pilot applicants for aeromedical certification

Protocols for medical certification of ITDM applicants have been developed and issued by Transport Canada (Appendix 3; Appendix 4), the US Federal Aviation Administration (FAA, 2004), and the Civil Aviation Safety Authority of Australia (CASA, 2010). These protocols have much in common concerning exclusion criteria e.g. “The applicant must have had no recurrent (two or more) episodes of hypoglycaemia (resulting in intervention by another party) in the past 5 years and none in the preceding 1 year. Presence of significant complications such as: autonomic neuropathy, significant cardiovascular disease, retinopathy, renal disease.” For detailed information the reader is referred to the respective documents listed in the reference list. The three protocols differ slightly in the pre-flight and in-flight blood glucose levels that are required: Transport Canada requires blood glucose levels to be 6 mmol/l (110 mg/dl) or higher, while FAA requires blood glucose levels to be between 5.5 and 16.5 mmol/l (100-300 mg/dl) and CASA requires levels between 5 and 15 mmol/l (91-273 mg/dl).

Recommendation
The CASA protocol, published in 2010, is based on expert knowledge reflecting the most recent developments in diabetology. Therefore, we recommend using the CASA protocol as a blueprint for a European (EASA) protocol. The complete CASA protocol can be found in the Designated Aviation Medical Examiner's Handbook (CASA, 2010) or using the link: http://www.casa.gov.au/wcmswr/_assets/main/avmed/download/casainsulinprotocol.pdf

If necessary to improve feasibility and/or enforcement in the EASA context, additions and/or adaptations of the CASA protocol can be made. When a European protocol will be implemented, it is recommended to concentrate all ITDM cases at AMS/AMC level and to implement procedures for follow-up study of treatment efficacy, hypoglycaemia risk, and flight safety issues (e.g. cohort studies of incidents, feasibility to measure pre- and in-flight blood glucose levels, epidemiology of in-flight blood glucose levels).

7 Applicability of a European protocol: ATPL, CPL, PPL, LPL?

In-flight blood glucose management appears to be easier for pilots engaged in multi-pilot operations than for pilots flying alone. Airline pilots have the opportunity to plan and share tasks and thus might have sufficient opportunities to measure and manage their in-flight blood glucose levels. On the other hand, management of diabetes in airline pilots needs to anticipate adjustments due to time zone crossing, night duties, irregular work schedules, and delays. Ultra-long-acting insulin analogues, such as degludec may provide a solution to cope with these specific problems (Zinman et al. 2011). Doses given three times a week might improve adherence, improve glycaemic control without an increase in hypoglycaemia, and cause less disruption to the patient's lifestyle (Kudva and Basu, 2011).

For pilots engaged in single-pilot operations it may be more difficult to measure in-flight blood glucose levels under difficult flight conditions. In such cases it is recommended to follow the guidelines of the CASA protocol, which states: "In respect to determining blood glucose concentrations during flight, the aviator must use judgment in deciding whether measuring concentrations or operational demands of the environment (e.g., adverse weather, etc.) should take priority. In cases where it is decided that operational demands take priority, the aviator must ingest a 15 gm glucose snack and measure his or her blood glucose level 1 hour later. If measurement is not practical at that time, the aviator must ingest a 30 gm glucose snack and land at the nearest suitable airport so that a determination of the blood glucose concentration may be made" (CASA, 2010).

We recommend that insulin treated diabetic pilots preferably use a Continuous Glucose Monitoring System to monitor pre- an in-flight BG levels and they are only allowed to fly when they have demonstrated to be compliant with pre- and in-flight requirements concerning blood glucose management.

We propose that the requirements for aeromedical licensing of insulin treated applicants should be applicable to applicants for ATPL, CPL, PPL, and LPL. Medical certification should be considered on a case by case basis.

8 References

ACCORD (2008). Action to Control Cardiovascular Risk in Diabetes Study (ACCORD) Group. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med; 358(24):2545-59.

ADA (2011). American Diabetes Association. Standards of Medical Care in Diabetes—2011. Diabetes Care 2011; 34 Suppl 1:S11-S61.

Bergenstal RM, Wysham C, Macconell L, et al. (2010). Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. Lancet; 376(9739):431-439.

Berne C, Sheppard D, Boyd B, Albrecht M, et al. (2006) Diabetes and Driving in Europe. A Report of the Second European Working Group on Diabetes and Driving, Brussels. http://ec.europa.eu/transport/road_safety/behavior/doc/diabetes_and_driving_in_europe_final_1_en.pdf. retrieved 5 January 2011.

CASA (2010). Designated Aviation Medical Examiner's Handbook, Version 3.8: November 2010. Civil Aviation Safety Authority, Government of Australia. www.casa.gov.au.

Cox DJ, Gonder-Frederick L, Polonsky W, et al. (2001). Blood glucose awareness training (BGAT-2). Diabetes Care; 24:637-642.

Cryer PE. (2002). Hypoglycaemia: the limiting factor in the glycaemic management of type I and type II diabetes. Diabetologia; 45:937–948.

Cummins E, Royle P, Snaith A, et al. (2010) Clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes: systematic review and economic evaluation. Health Technol Assess; 14(11):iii-iv, xi-xvi, 1-181.

DCCT (1993). The Diabetes Control and Complications Trial Research Group. The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. N Engl J Med; 329(14):977-986.

Diamant M, Van Gaal L, Stranks S, et al. (2010) Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. Lancet; 375(9733):2234-2243.

EASA. European Aviation Safety Agency. EASA MED.B.020 — Metabolic and Endocrine Systems. http://www.easa.eu.int/ws_prod/r/doc/crd/CRD%20a.1%20-%20Explanatory%20Note%20A. pdf. Retrieved 30 July 2011.

Eeg-Olofsson K, Cederholm J, Nilsson PM, Zethelius B, Svensson AM, Gudbjörnsdóttir S, Eliasson B. (2010) Glycemic control and cardiovascular disease in 7,454 patients with type 1 diabetes: an observational study from the Swedish National Diabetes Register (NDR). Diabetes Care; 33(7):1640-1646.

Engel SS, Williams-Herman DE, Golm GT, et al. (2010) Sitagliptin: review of preclinical and clinical data regarding incidence of pancreatitis. Int J Clin Prac.t; 64:984-990.

Evans ML, Pernet A, Lomas J, Jones J, Amiel SA. (2000) Delay in onset of awareness of acute hypoglycemia and of restoration of of cognitive performance during recovery. Diabetes Care; 23:893-897.

FAA (2004). FAA Medical Certification Guidelines for Pilots with Insulin-treated Diabetes. Federal Aviation Administration, Civil Aerospace Medical Institute - April 21, 2004. http://www.cami.jccbi.gov/aam-300/insulin.html Retrieved 5 January 2011.

Garg SK, Paul JM, Karsten JI, Menditto L, Gottlieb PA. (2004). Reduced severe hypoglycemia with insulin glargine in intensively treated adults with type 1 diabetes. Diabetes Technol Ther; 6(5):589-95.

Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. (2008) 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med; 359:1577–1589.

ICAO. International Civil Aviation Organisation. Doc 8984-AN/895 Part III. Manual of Civil Aviation Medicine -. Preliminary edition 2008. Chapter 4 and Appendix 1. http://www.icao.int/icaonet/dcs/8984/8984_Part_3_en.pdf.Retrieved 30 July 2011.

JAA. Joint Aviation Authorities. JAR-FCL 3 - Flight Crew Licensing (Medical) http://www.jaa.nl/publications/jars/606984.pdf - Retrieved 30 July 2011.

Kudva YC, Basu A. (2011). Ultra-long-acting insulins for a lifestyle-related pandemic (Editorial). Lancet; 377:880-881.

Leese GP, Wang J, Broomhall J, et al. (2003). Frequency of severe hypoglycemia requiring emergency treatment in Type 1 and Type 2 diabetes. Diabetes Care; 26:1176-1180.

Lind M, Bounias I, Olsson M, et al. (2011). Glycaemic control and incidence of heart failure in 20 985 patients with type 1 diabetes: an observational study. Lancet; 378:140-146.

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

Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ. (2008) A1c-Derived Average Glucose Study Group. Translating the A1C assay into estimated average glucose values. Diabetes Care 2008;31:1473–1478

Nathan DM, Buse JB, Davidson MB, et al.(2009). Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care; 32:193–203.

Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M. (1995) 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; 28:103–117.

Opie LH, Yellon DM, Gersh BJ. (2011). Controversies in the cardiovascular management of type 2 diabetes. Heart; 97:6-14.

Opie LH. (2011). Glycaemia and heart failure in diabetes types 1 and 2. (Editorial). Lancet; 378:103-104.

Peters A. (2010) Incretin-based therapies: review of current clinical trial data. Am J Med; 123:S28-S37.

Pickup JC, Sutton AJ. (2008) Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. Diabet Med; 25(7):765-774.

Rosenstock J, Dailey G, Massi-Benedetti M, Fritsche A, Lin Z, Salzman A. (2005) 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.

Shalitin S, Phillip M. (2008) Hypoglycemia in Type 1 Diabetes - A still unresolved problem in the era of insulin analogs and pump therapy. Diabetes Care 31 (Suppl. 2):S121–S124.

Steve Steele (2008). Flying on Insulin. http://www.diabeteshealth.com/read/2008/06/26/5807/flying-on-insulin/ Retrieved 9 July 2011.

Swinnen SG, Hoekstra JB, De Vries JH. (2009) Insulin Therapy for Type 2 Diabetes. Diabetes Care; 32 (Suppl. 2):S253-259.

Transport Canada. Appendix 3 - Selection Conditions for Insulin Treated Diabetes Applicants (ITDM). http://www.tc.gc.ca/CivilAviation/Cam/TP13312-2/diabetes/appendix3.htm Retrieved 5 January 2011.

Transport Canada. Appendix 4 - Selected ITDM Applicants who Meet Category 4 R.P.P, Student Pilot & Category 1R Airline Transport Pilot Licence (ATPL) (Airplane) Medical Certification Conditions. http://www.tc.gc.ca/CivilAviation/Cam/TP13312-2/diabetes/appendix4.htm Retrieved 5 January 2011.

UKPDS (1998). U.K. Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet; 352: 837–853

Vilsboll T, Rosenstock J, Yki-Jarvinen H, et al. (2010) Efficacy and safety of sitagliptin when added to insulin therapy in patients with type 2 diabetes. Diabetes Obes Metab; 12:167-177.

Yudkin JS, Richter B, Gale EAM. (2011). Intensified glucose control in type 2 diabetes-whose agenda? Lancet; 377:1220-1222.

Zinman B, Fulcher G, Rao PV, et al. (2011). Insulin degludec, an ultra-long-acting basal insulin, once a day or three times a week versus insulin glargine once a day in patients with type 2 diabetes: a 16-week, randomised, open-label, phase 2 trial. Lancet; 377(9769):924-931.