Eur J Vasc Endovasc Surg **33**, 583–591 (2007)
doi:10.1016/j.ejvs.2007.01.012, available online at http://www.sciencedirect.com on ScienceDirect

EDUCATIONAL ARTICLE

Diabetes Care for Patients with Peripheral Arterial Disease

M. Heikkinen,[1*] M. Salmenperä,[2] A. Lepäntalo[3] and M. Lepäntalo[1]

Departments of [1]Vascular Surgery, [2]Anesthesiology, and [3]Division of Hematology, Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland

The number of diabetics will increase almost 70% in developed countries during the next 20 years: peripheral arterial disease is a common and costly complication. The incidence of cardiovascular disease (mortality and morbidity) due to atherosclerosis, is higher among patients with diabetes than in those without diabetes. Intensive management of diabetes, including glycaemic control, treatment of hypertension and dyslipidemia, as well as nonpharmacological interventions, decreases both micro- and macrovascular complications. Aspirin and clopidogrel have less antiplatelet effect in patients with diabetes. Metformin therapy is considered a risk factor for lactic acidosis if not withdrawn 2 days before angiography, but this risk is extremely low in patients with normal renal function. Peri-operative hyperglycaemia and large fluctuations in plasma glucose increase postoperative mortality and morbidity and careful measures are required to minimise these effects.

Keywords: Diabetes; Atherosclerosis; Macrovascular complications; Peripheral arterial disease; Prevention.

Introduction

The global prevalence of diabetes mellitus has increased continuously and it has been predicted that the number of adult diabetics will double within 30 years. Almost 250 million people, nearly 6% of adults in the world, have diabetes.[1] Patients with diabetes have an average reduction in life expectancy of 5–10 years, mainly because of premature cardiovascular disease (CVD).[2] In Finland, 90% of the total health care costs of diabetes are due to the complications of the disease. The treatment of type II diabetes alone cost 370€ per person annually, but the cost of complications increases this to 8900€ per person.[2,3] The onset of complications reduces the quality of life, particularly when both microvascular and macrovascular disease are present.[4,5] Multiple modifiable risk factors, including hyperglycaemia, hypertension, and dyslipidemia, increase the risk of poor outcome.[6,7]

Diabetes as a Risk Factor for Peripheral Arterial Disease

Excess mortality from cardiovascular disease (CVD) compared to general population can be seen in all age groups, especially in young people with type 1 diabetes. Macrovascular disease, which usually is diffuse and distal affecting many vessels, is the main cause of death in type 1 and type 2 diabetes.[6] The prevalence and mortality from all forms of CVD is 2–8 fold higher in the presence of diabetes.[6,7] Diabetes increases the risk of asymptomatic peripheral arterial disease (PAD) (Odds Ratio (OR) 3.8).[8,9] The Epidemiology of Diabetes Interventions and Complications study compared carotid intima-media thickness in subjects with and without diabetes: after 6 years, intima-media thickness was greater in those with diabetes.[10] During an 11-year follow-up study, almost a quarter (31/131) patients with type 2 diabetes, aged at 58 at entry, developed PAD during follow-up and 21/29 deaths were attributed to CVD.[11] In patients with diabetes, for every 1% increase in hemoglobin A1c (HbA1c) there is a corresponding 26–28% increase risk of PAD.[12] Insulin resistance is

One of a series of educational articles edited by Janet Powell, UK.

*Corresponding author. M. Heikkinen, MD, PhD, Department of Vascular Surgery, Helsinki University Hospital, P.O. Box 340, 00029 Helsinki, HUS, Finland.
E-mail address: mheik@netti.fi

1078–5884/000583 + 09 $32.00/0

a risk factor for PAD even in subjects without diabetes, increasing the risk by about 50%.[13]

About half of all lower extremity amputations are related to diabetes.[9,14] Although the majority of diabetic ulcers are neuropathic, almost 60% also have an ischaemic component, with 10% being solely ischaemic.[15] Atherosclerosis is probably present in all patients with long-duration diabetes.[16] In critical limb ischemia (CLI), PAD impairs blood flow so that the nutritive requirements of the tissue cannot be met.[9] This is usually caused by multilevel arterial occlusive disease.[9] Patients with diabetes comprise 45–70% of those undergoing bypass surgery for CLI.[14,17,18]

Improving Outcome by Treatment of Diabetes

The metabolic and haemodynamic abnormalities of diabetes both contribute to the development of complications. Microvascular complications are strongly associated with CVD. The primary defect in PAD is atherothrombotic occlusion of large vessels and microangiopathy is not seen as a primary factor in the development of tissue ischemia in patients with diabetes. However, microvascular dysfunction can be observed in the skin, which could render this organ more susceptible to a reduction in perfusion pressure.[19] In addition, diabetic neuropathy, in both type 1 and 2 diabetic patients, results in increased shunting of blood flow and an impaired inflammatory response to various stimuli.[20] Endothelial function, which is impaired by most cardiovascular risk factors, eg hypercholesterolemia, smoking appears to be a useful marker of diabetic control.[21] Recent reports indicate that an improved metabolic control in diabetes, whatever the treatment used, is associated with near normalization or restoration of normal endothelial function.[22]

In both type 1 and type 2 diabetes, the lower the glycated haemoglobin achieved the lower the risk of microvascular complications.[23–25] In Diabetes Control and Complication Trial (DCCT), conventional therapy of type 1 diabetes consisted of 1–2 insulin injections per day. Intensive therapy aimed to achieve blood glucose values as close to the normal range as possible with 3 or more daily insulin injections or with insulin pump.[23] During the mean follow-up of 6.5 years, patients in the intensively treated group had significantly less microvascular complications, nephropathy and retinopathy. When major cardiovascular events and peripheral vascular events were combined, intensive therapy reduced the risk of macrovascular disease by 41%, although this was not statistically significant. The prevalence and amount of arterial calcification, 7–9 years after the trial, were significantly lower in the intensive treatment group compared with the conventional therapy group despite, even though there was no difference in HbA1c between the groups at late follow-up.[26] However mean HbA1c level during the study period was significantly lower in the intensive treatment group.

In the UK Prospective Diabetes Study (UKPDS), the relation between exposure to glycaemia over time and the risk of macrovascular or microvascular complications in patients with type 2 diabetes were determined in 3600 patients. Each 1% reduction in updated mean HbA1c was associated with reductions in risk of 21% for any end point related to diabetes ($P < 0.0001$), 21% for deaths related to diabetes ($P < 0.0001$), 14% for myocardial infarction ($P < 0.0001$), and 37% for microvascular complications ($P < 0.0001$). The lowest risk was in those with HbA1c values in the normal range (<6.0%).[27]

Current evidence suggests best therapy for diabetes is associated with the targets in Table 1. If the vascular surgeon identifies that these targets are not being met or approached a patient with diabetes, the diabetologists should be requested to optimise therapy for the patient.

Table 1. Hemoglobin A1c (HbA1c), cholesterol, blood pressure targets and other important factors for patients with DM to prevent or slow cardiovascular disease

HbA1c (%)	≤6.5 mmol/l
Fasting	<6.0 mmol/l
Post-prandial (peak)	Individuals with type 1 diabetes <7.5 mmol/l Individuals with type 2 diabetes 7.5–9.0 mmol/l
Cholesterol	LDL: Individuals without CVD <2.6 mmol/l Individuals with CVD <1.8 mmol/l Triglycerides<1.7 mmol/l HDL: Men >1.0 mmol/l1.0 mmol/l Women>1.2 mmol/l
Blood pressure	Systolic blood pressure <130 mmHg Diastolic blood pressure < 80 mmHg
Other important factors	Aspirin therapy Smoking cessation Regular physical exercise (>35–45 min/day) Weight control Dietary habits

These goals are for patients in general and have to be adjusted for an individual patient taking all aspects in consideration, for example age (very young children or older adults may need modifications), history of severe hypoglycemia (HbA1c recommendation higher), renal impairment, limited life expectancy and other comorbid conditions.
Modified from the European Guidelines for Cardiovascular disease prevention and American Diabetes Association, Standards of medical cari in diabetes 2007.[70,71]

The Role of Other Risk Factors

Smoking

Smoking cessation is a particular advantage to patients with diabetes and peripheral arterial disease. The highest relative risk associated with PAD is current smoking of 25 or more cigarettes daily (OR = 7.3, 95% confidence interval (CI) 4.2−12.8).[21] Both hyperglycemia and smoking can result in the formation of advanced glycation end products and in enhanced oxidative stress within the vessel wall, suggesting that these process might play a central role the development or progression of PAD.[28] Diabetes combined with smoking has high positive predictive value for asymptomatic PAD (15%), when both are lacking, rates for predicting asymptomatic PAD is low (1%).[8] The weight of evidence also suggests that smoking adversely influences the success of bypass surgery.

Blood pressure

By the age of 45 about 40% of patients with type 2 diabetes are hypertensive, the proportion increasing to 60% by the age of 75.[29] This combination provides additive increases in the risk of major cardiovascular events. Aggressive blood pressure control may be the most important factor in preventing major cardiovascular events in patients with type 2 diabetes.[30−32] In a Cochrane review, a reduction in systolic blood pressure of 10 mmHg was associated with a 13% reduction in risk of microvascular events and an 11% reduction for myocardial infarction.[30] In the Multiple Risk Factor Intervention Trial Diabetic Cohort, cardiovascular mortality was increased by 2−4 fold and the association between systolic blood pressure and complications had no threshold value.[31] In UKPDS, reductions in risk in the group assigned to tight blood pressure control (achieved 144/82) compared with the group assigned to less tight blood pressure control (achieved 154/87) were significant, reductions of 32% in deaths related to diabetes ($p = 0.019$), 44% in strokes ($p = 0.013$) and 37% in microvascular endpoints ($p = 0.0092$) after mean follow-up of 8.4 years.[32] Since diabetes is an important cardiovascular risk factor, a lower target value for those with diabetes (130/85 mmHg) than for others (140/90 mmHg) has been proposed.[33] All classes of antihypertensive agents are effective in reducing blood pressure in diabetes, with evidence of a concomitant reduction in cardiovascular risk. Hypertensive patients have a significantly increased risk for development of type 2 diabetes, which is dependent on the class of anti-hypertensive drug used. Diuretics and beta-blockers have a prodiabetic effect, but angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers may prevent diabetes more effectively than the metabolically neutral calcium channel blockers.

Dyslipidaemia

The metabolic abnormalities that cluster in patients with type 2 diabetes and the metabolic syndrome are all independent risk factors for atherogenesis and dyslipidemia is an important, modifiable risk factor for CVD. Two placebo-controlled trials have shown, that treatment with statins reduces the risk of a major cardiovascular event by 37% in patients with type 2 diabetes without clinically apparent CVD.[34,35] In a meta-analysis of randomized controlled trials, lipid lowering drug treatment was at least as effective in diabetic patients as in non-diabetic patients.[36] For primary prevention, the risk reduction for major coronary events was 21% (95% CI 11%−30%) and 23% (12%−33%) in patients with and without diabetes respectively. For secondary prevention, the corresponding risk reductions were 21% (10%−31%) and 23% (19%−26%). All those aged 40 years with diabetes and younger patients with diabetes at particularly high risk (microvascular or macrovascular complications, hypertension, metabolic syndrome or a strong family history for CVD) should be offered statins.

Foot Care

Neuropathy with subsequent loss of protective sensations, muscular weakness and structural deformity as well as autosympathectomy is the main cause for diabetic foot ulceration. Ischaemia alone is the cause only in 10%,[15] whereas inadequate tissue often perfusion prevents healing. Neuropathy causes reulceration in case of inappropriate offloading. Therefore continuous education of patients regarding skin care, foot hygiene, off-loading, and proper footwear is crucial to reducing the risk of an injury that can lead to ulceration. A careful foot examination that tests for neuropathy and arterial insufficiency can identify legs at risk and should be a routine to the diabetic patient. If foot ulcer has not shown any evidence for healing in two weeks, careful examination of the lower limb circulation with subsequent vascular reconstruction as appropriate is indicated. These measures decreased first amputations in Finland

1988–2002 from 924 to 387 per 100000 patients with diabetes.[37]

Life-style Interventions

Type 2 diabetes is increasingly common, primarily because of increases in the prevalence of a sedentary lifestyle and obesity. In about half of patients with recently diagnosed type 2 diabetes, life-style interventions such as weight reduction and increased physical activity may reverse the diabetes.[38,39] In the Finnish Diabetes Prevention Study (FDPS), 522 middle-aged, overweight subjects with impaired glucose tolerance were randomly assigned to either the intervention group or the control group. Each subject in the intervention group received individualized counselling aimed at reducing weight, total intake of fat, and intake of saturated fat and increasing intake of fibre and physical activity.[39] The cumulative incidence of diabetes after four years was 11% (95% CI 6%–15%) in the intervention group and 23% (17%–29%) in the control group, a 58% risk reduction in the intervention group ($P < 0.001$). After a median of 4 years of active intervention period, participants who were still free of diabetes were further followed up for a median of 3 years, with median total follow-up of 7 years. Beneficial lifestyle changes achieved in the intervention group were maintained after the discontinuation of the intervention, and the corresponding incidence rates of diabetes during the post-intervention follow-up were 4.6 and 7.2 ($p = 0.0401$), indicating 36% reduction in relative risk.[40]

Life-style intervention should be the initial management of newly diagnosed diabetic type 2 patients. Since almost half of all those with type 2 diabetes are not diagnosed it seems necessary to improve early diagnoses of the disease.[38,39]

Antiplatelet Therapy

Aspirin (acetylsalicylic acid, ASA), which is recommended for primary and secondary prevention in patients with PAD, has been shown to have lower antiplatelet activity in those with diabetes.[41,42] The reduced response of platelets from diabetic subjects to aspirin is associated with a higher level of HbA1c, lower concentration of HDL-cholesterol and a higher total cholesterol concentration.[41,42] Increased platelet activity and decreased sensitivity to aspirin have also been reported in patients with dyslipidemia, and one suggestion is that metabolic differences in diabetics and metabolic syndrome might be the reason to decreased aspirin efficacy in diabetics.[43] There are several other mechansisms thay may contribute to the diminished anti-platelet activity of aspirin in diabetes.[44,45] In addition the normal anti-platelet activity of insulin has been reported to be abolished in patients with diabetes or insulin-resistance patients.[46] Therefore, in the presence of diabetes higher doses of aspirin have been proposed.[44] However, there is no studies on the possible optimal aspirin dose to the diabetics.

Patients with diabetes also seem to benefit less from clopidogrel, shown by objective measures of platelet activation.[47–49] Lepäntalo *et al*. studied the efficacy of a loading dose (300 mg) of clopidogrel in patients undegoing elective percutaneous coronary intervention.[50] In patients with poor long-term glucose balance (HbA1c) and elevated insulin C-peptide, the clopidogrel-induced inhibition of platelet aggregation was significantly less than in normoglycaemic patients. Also, the patients with limited response to clopidogrel (change in aggregation <10%) had higher serum C-peptide levels than patients who responded well to clopidogrel.[50] The reasons for these differences are unknown.

Metformin Therapy

The biguanide metformin (dimethylbiguanide) is an oral anti-hyperglycemic drug used in non-insulin dependent diabetes. The UKPDS indicated that metformin treatment was associated with a reduction in total mortality compared to other oral anti-hyperglycaemic treatments.[51] Metformin has been considered to increase the risk of lactic acidosis and is contraindicated in many chronic hypoxaemic conditions, such as cardiovascular, renal, hepatic and pulmonary disease as well as advancing age. Traditionally, metformin has been stopped 48 hours before angiography or general anaesthesia (approximately 90% of metformin is eliminated via the kidneys in 24 h). Renal insufficiency (GFR < 70 ml/min or serum creatinine >140 μmol/L) results in tissue retention of biguanides with the potential for development of fatal lactic acidosis. Therefore, metformin is contraindicated in patients with chronic renal failure.

However in patients with normal renal function a Cochrane review, evaluating the incidence of fatal and nonfatal lactic acidosis for metformin treatment and for placebo or other treatments, showed no cases of fatal or nonfatal lactic acidosis in 47,846 patient-years of metformin use or in 38,221 patients-years in the non-metformin group.[52] The true incidence of metformin-associated lactic acidosis was 6.3 cases

per 100,000 patient-years, and the upper limit for the true incidence of lactic acidosis in the non-metformin group was 7.8 cases per 100,000 patient-years.[52] There was no difference in lactate levels, either as mean treatment levels or as a net change from baseline, for metformin compared to placebo or other non-biguanide therapies. Therefore metformin use does not appear to be associated with an increased risk of lactic acidosis, or with increased levels of lactate, compared to other anti-hyperglycemic treatments if prescribed under the study conditions.

Angiography and revascularization angioplasty or bypass operation is often needed in patients with PAD and diabetes. The use of contrast media in patients receiving metformin should be carried out with care. Contrast media can induce a reduction in renal function, which occurs after the contrast medium has reached the kidney, leading to retention of metformin that may induce lactic acidosis. There is no conclusive evidence that the intravascular use of contrast media precipitates the metformin induced lactic acidosis in patients with normal serum creatinine (<130 μmol/L). The complication has almost always been observed in patients with non-insulin dependent diabetes with abnormal renal function. Serum creatinine level should be measured in all patients treated with metformin before intravascular administration of contrast media. If serum creatinine is normal, the radiological examination can be performed and intake of metformin stopped from the time of the study. Metformin should not be resumed for 48 hours and should only be restarted if renal function/serum creatinine remains within the normal range.[53] If renal function is abnormal, metformin should be stopped and the contrast study should be delayed for 48 hours. Patients with abnormal renal function should be hydrated before and after angiography. Recommendations for patients on metformin therapy undergoing angiography and/or vascular surgery are summarised in Table 2.

Table 2. Perioperative care of a patient with diabetes undergoing peripheral vascular surgery

Preoperatively	+Schedule a preoperative visit for an anesthesia consultation at least two weeks before planned surgery. During this visit consider preoperative interventions if: HbA1c > 7% → Need of improvement of diabetic control (diabetology consultation) Ischemic heart or brain disese, renal insufficiency → Institute beeta-blockade Ischemic heart disease → Revascularization (PMI or CABG) only if indicated independently of the planned vascular surgey (cardiology consultation) +Discontinue (last dose) of sulfonylureas 24 hours and biguanides 48 hours before the scheduled surgery
Perioperatively	+Nil by mouth 6 hours before anesthesia induction +Glargine-insulins continued with the prescribtion dose +Diabetics need to be scheduled as a first case in the morning +Arterial catheter for direct blood pressure measurement and frequent blood samples +Blood glucose between 5.0−8.0 mmol/l (sampling interval 0.5−2 hours) +Infuse glucose 5 g/hour as long as patient can take *per os* +Short acting insulins *sc* or *iv* +Regional anesthetic techcniques preferable +PONV*- prophylaxis with 5 HT_3 receptor antagonists
Postoperatively	+Blood glucose between 5.0−10 mmol/l (sampling interval 6 hours) in the ward and/or intensive care in the euglycemic range (sampling interval 1−2 hours) +Normal prescribed insulin regimen in the patients taking orally. If not, glucose-insulin-potassium (GIK) infusion iv on the ward and separate glucose and insulin-infusions in intensive care.

HbA1c = hemoglobin A1c, PMI = percutaneous myocardial intervention, CABG = coronary artery bypass, NPO = nothing per os, PONV = perioperative nausea and vomiting, ICU = internal care unit.
* PONV postoperative nausea and vomiting.

Peri-operative Diabetic Care

Strategies to improve operative results and long-term prognosis of vascular surgery pose formidable practical challenges to scheduling of surgery. Pre-operative assessment 2 weeks before scheduled surgery permits evaluation of diabetic control and comorbidities and the need to institute therapies to decrease operative risk. Poor pre-operative glycaemic control is associated with hyperglycaemia and increased insulin requirements peri-operatively. An ideal marker of poor glycaemic control is yet to be defined but it is good practice is to consult a diabetologist about intensifying therapy if the value of plasma HbA1c exceeds 7%. Higher levels are associated with increased 30-day mortality (OR 4.8, 95% CI 1.4−16.8) after vascular surgery.[54] Accumulating evidence shows the value of peri-operative beta-blockade in reducing cardiac morbidity and mortality associated with surgery in high risk patients.[55,56] There is a body of evidence to support Institutional protocols advocating the use of peri-operative beta blockade in patients with diabetes undergoing high risk vascular surgery. However, level 1 evidence is lacking and a recent randomized trial of patients with diabetes undergoing major non-cardiac surgery failed to demonstrate a benefit with

metoprolol.[57] Interventional coronary procedures before vascular surgery should be considered only if they are indicated independently, despite the planned surgery.[58] Oral hypoglycemic agents may be associated with hypogycemia during anaesthesia and surgery, and should be stopped before surgery. Although discontinuation 24 hours before surgery seems advisable, many institutional protocols usually suggest withholding of metformin for 48 hours before major surgery. This practice is based only on circumstantial evidence from case reports and observational studies associating metformin with lactic acidosis. Some authors suggest also that prior to surgical procedures under general anaesthesia, withdrawal of metformin the evening before is safe in patients with normal renal function.[59]

Insulin-dependent patients should be scheduled as first cases in the morning. Peri-operative fast will aggravate metabolic imbalances due to anaesthesia and surgery. Oral fluid restriction before anaesthesia induction has in been reduced to 2 hours for many, but in those with diabetes restriction of all oral intake for 6 hours before surgery is still recommended because of the anticipated gastroparesis as a result of autonomic neuropathy.[60] Longer periods without any intake force the use of intravenous glucose and insulin, which can be challenging in a ward setting. As a general rule regional anaesthesia should be preferred over general anaesthesia because early institution of oral intake and restitution of the prevailing diabetes care is easier. Due to the autonomic neuropathy in patients with long-standing diabetes, patients are liable to haemodynamic instability during anaesthesia.[61] Therefore invasive arterial blood pressure measurement and extended haemodynamic monitoring often should be instituted promptly to minimize haemodynamic deterioration. Monitoring also is the most efficacious renal protective strategy in patients with borderline renal compromise and recent angiography. Although n-acetylcysteine may counteract against the contrast media-induced nephropathy it fails to have any protective effect in patients during abdominal aortic surgery.[62]

Table 3. Intravascular administration of contrast media and patients taking metformin or other biagunides

General	+Low- or iso-osmolar contrast media should always be used. +Serum creatinine level should be measured before the examination in every patients before the administration of contrast media +If renal function is abnormal, alternative imaging techniques (MRI, CO2 angiography) should be considered. If contrast media administration is seen necessary, patient should be hydrated, renal function monitored and symptoms/signs for lactic acidosis (vomiting, somnolence, nausea, epigastric pain, anorexia, hyperpnoea, lethargy, diarrhoea, thirst, lactic acidosis in blood test (pH < 7.25, lactic acid >5 mmol/l)	
Elective examinations		
	Current recommendation	Suggested new recommendation
Normal renal function	+Metformin intake is stopped 48 hours prior to examination in all patients taking metformin and restarted 24 hours after the procedure if renal function is normal. If creatinine level is elevated after the examination, metformin is restarted 48 hours after the examination	+Intake of metformin should be stopped from the time of study +The use of metformin can be restarted 48 hours after intravascular administration of contrast media if the postexamination creatinine is within normal range
Abnormal renal function (Alternative imaging techniques should be considered)	+Metformin intake is stopped 48 hours prior to examination in all patients taking metformin and restarted 48 hours after the procedure if renal function is unchanged	As the current recommendation
Emergency examinations		
	Current recommendation	Suggested new recommendation
Normal renal function	+If urgent examination is seemed necessary, metformin is stopped at the time of study. +Otherwise, netformin intake is stopped 48 hours prior to examination in all patients taking metformin +Metformin is restarted 24 hours after the procedure if renal function is normal	+Intake of metformin should be stopped from the time of study +The use of metformin can be restarted 48 hours after intravascular administration of contrast media if the postexamination creatinine is within normal range
Abnormal renal function (Alternative imaging techniques should be considered)	+Metformin should be stopped 48 hours prior to examination if possible. +If urgent examination is seemed necessary, metformin is stopped at the time of study +Metformin is restarted 48 hours after the procedure if renal function unchanged	As the current recommendation

The fasting patient does not tolerate the standard morning insulin dose. An exception is newer long-acting insulin analogue glargine, which can be administered for basal insulin coverage through-out the surgical period. Usually it is advisable to resort to short-acting insulins and dose them according to point-of-care blood glucose analysis. If resumption of oral intake is anticipated later on the day of surgery, subcutaneous insulin administration and intravenous glucose can be used. More extensive surgery requires continuous insulin and glucose infusion. The goal should be avoidance of hyperglycaemia, although the studies that show benefits of this are from cardiac surgery. During coronary bypass surgery patients with tight glycaemic control had a lower incidence of atrial fibrillation, fewer episodes of myocardial ischemia, fewer wound infections and a survival advantage 2 years after surgery.[63]

In the intensive care unit, maintenance of euglycaemia is associated with improved survival both on the unit and in-hospital.[64] These results can be extrapolated to patients undergoing vascular surgery. Poor glycaemic control has been associated with the development of renal insufficiency, infectious complications and poor outcome i.e. death, amputation and graft occlusion.[65] Despite this evidence, the optimal blood glucose target window remains to be determined. Euglycemia may not be a safe or rational goal during anaesthesia due to the likelihood of hypoglycaemic episodes. In the ''classic'' study the incidence of hypoglycaemia (glucose < 2.2 mmol/l) was 39% in the euglycemic group versus 6% in the group with moderate hyperglycemia.[64] Hypoglycaemic episodes can be masked by anaesthesia and sedation and point of care measurements may provide erroneous glucose estimates, up to $+/-$ 2 mol/l from the true value.[66]

Deep infections after coronary artery bypass increased only after blood glucose values exceeded 12 mmol/l.[67] Finney *et al*. were able to show that the predicted threshold glucose range for mortality benefit in intensive care was in the range 8.0–11.1 mmol/L.[68] Therefore we believe that our target window of 5.0–8.0 mmol/l for vascular surgery is appropriate. Conventional sliding scale insulin infusion has been challenged by the hyperinsulinaemic normoglycaemic clamp technique, where insulin is administered at a constant rate and blood glucose controlled by varying the rate of glucose administration. This method has been shown to prevent the hyperglycaemia and increased insulin requirements after surgery.[69] Recommendations for perioperative management of patients with diabetes undergoing major vascular surgery are summarised in Table 3.

Finally the transition of intensive insulin therapy to a more conventional therapy applicable to ward conditions is challenging. Separate intravenous insulin and glucose administration routes are not safe on the ward. Therefore prolongation of stay in intensive care or recovery may be indicated to provide the benefits of tight glucose control to vascular surgery patients.

References

1 Mayor S. Diabetes affects nearly 6% of the world's adults. *BMJ* 2006;**9**:1191.
2 Marshall SM, Flyvbjerg A. Prevention and early detection of vascular complications of diabetes. *BMJ* 2006;**2**:475–480.
3 Finnish Diabetes Association. *Developement program for prevention of type 2 diabetes. Population Strategy 2003–2010*. Tampere: Hermes Oy, 2003.
4 Jonsson B. CODE-2 Advisory Board. Revealing the cost of Type II diabetes in Europe. *Diabetologia* 2002;**45**:S5–S12.
5 Kulzer B. Diabetes mellitus: how important is it to measure the quality of life? *Dtsch Med Wochenschr* 2006;**131**(Suppl. 8):S259–S263.
6 Adlerberth AM, Rosengren A, Wilhelmsen L. Diabetes and long-term risk of mortality from coronary and other causes in middle-aged Swedish men. A general population study. *Diabetes Care* 1998;**21**:539–545.
7 Muntner P, He J, Astor BC, Folsom AR, Coresh J. Traditional and nontraditional risk factors predict coronary heart disease in chronic kidney disease: results from the atherosclerosis risk in communities study. *J Am Soc Nephrol* 2005;**16**:529–538.
8 Eason SL, Petersen NJ, Suarez-Almazor M, Davis B, Collins TC. Diabetes mellitus, smoking, and the risk for asymptomatic peripheral arterial disease: whom should we screen? *J Am Board Fam Pract* 2005;**18**:355–361.
9 Norgren L, Hiatt WR, Dormandy JA, Nehler M, Harris KA, Fowkes FGR on behalf of the TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease. *Eur J Vasc Endovasc Surg* 2007;**33**(Suppl. I):S1–S75.
10 Nathan DM, Lachin J, Cleary P, Orchard T, Brillon DJ, Backlund JY, *et al*. Diabetes Control and Complications Trial, Epidemiology of Diabetes Interventions and Complications Research Group. Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. *N Engl J Med* 2003;**5**: 2294–2303.
11 Kallio M, Forsblom C, Groop PH, Groop L, Lepäntalo M. Development of new peripheral arterial occlusive disease in patients with type 2 diabetes during a mean follow-up of 11 years. *Diabetes Care* 2003;**26**:1241–1245.
12 Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR *et al*. Meta-analysis: glycosylated hemoglobin and CVD disease in diabetes mellitus. *Ann Intern Med* 2004;**21**: 421–431.
13 Muntner P, Wildman RP, Reynolds K, Desalvo KB, Chen J, Fonseca V. Relationship between HbA1c level and peripheral arterial disease. *Diabetes Care* 2005;**28**:1981–1987.
14 Eskelinen E, Lepäntalo M, Hietala EM, Sell H, Kauppila L, Mäenpää I *et al*. Lower limb amputations in Southern Finland in 2000 and trends up to 2001. *Eur J Vasc Endovasc Surg* 2004; **27**:193–200.
15 Oyibo SO, Jude EB, Voyatzoglou D, Boulton AJM. Clinical characteristics of patients with diabetic foot problems: changing patterns of foot ulcer presentation. *Pract Diabetes Int* 2002;**19**:10–12.
16 Jude EB, Boulton AJM. Diabetic foot. In: Beard J, Gawes P, eds. *Vascular and Endovascular Surgery*. 3rd edn. Elsevier Saunders, 2006:118–137.
17 Virkkunen J, Heikkinen M, Lepäntalo M, Metsänoja R, Salenius JP, Finnvasc Study Group. Diabetes as an independent

risk factor for early postoperative complications in critical limb ischemia. *J Vasc Surg* 2004;**40**:761–767.
18 Chung J, Bartelson BB, Hiatt WR, Peyton BD, McLafferty RB, Hopley CW *et al*. Wound healing and functional outcomes after infrainguinal bypass with reversed saphenous vein for critical limb ischemia. *J Vasc Surg* 2006;**43**:1183–1190.
19 Houben AJ, Nieuwenhuijzen Kruseman AC, Bouhouch E, Slaaf DW, Schaper NC. Peripheral macro- and microcirculation in short-term insulin-dependent diabetes mellitus: the role of prostaglandins in early haemodynamic changes. *Eur J Clin Invest* 1993;**23**:662–667.
20 Flynn MD, O'Brien IA, Corrall RJ. The prevalence of autonomic and peripheral neuropathy in insulin-treated diabetic subjects. *Diabet Med* 1995;**12**:310–313.
21 Fowler B, Jamrozik K, Norman P, Allen Y. Prevalence of peripheral arterial disease: persistence of excess risk in former smokers. *Aust N Z J Public Health* 2002;**26**:219–224.
22 Guerci B, Bohme P, Kearney-Schwartz A, Zannad F, Drouin P. Endothelial dysfunction and type 2 diabetes. Part 2: altered endothelial function and the effects of treatments in type 2 diabetes mellitus. *Diabetes Metab* 2001;**27**(4 Pt 1):436–447.
23 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* 1993;**30**:977–986.
24 UK 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* 1998;**12**: 837–853.
25 Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003;**30**:383–393.
26 Cleary PA, Orchard TJ, Genuth S, Wong ND, Detrano R, Backlund JY, *et al*. DCCT/EDIC Research Group. The effect of intensive glycemic treatment on coronary artery calcification in type 1 diabetic participants of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC). *Study. Diabetes* 2006;**55**:3556–3565.
27 Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA *et al*. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;**12**:405–412.
28 Baynes JW, Thorpe SR. Role of oxidative stress in diabetic complications: a new perspective on an old paradigm. *Diabetes* 1999;**48**: 1–9.
29 Hypertension in Diabetes Study (HDS): I. Prevalence of hypertension in newly presenting type 2 dia-betic patients and the association with risk factors for cardiovascular and diabetic complications. *J Hypertens* 1993;**11**:309–317.
30 Strippoli GF, Craig M, Craig JC. Antihypertensive agents for preventing diabetic kidney disease. *Cochrane Database Syst Rev* 2005; **19:** CD004136.
31 Domanski M, Mitchell G, Pfeffer M, Neaton JD, Norman J, Svendsen K, *et al*. MRFIT Research Group. Pulse pressure and cardiovascular disease-related mortality: follow-up study of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 2002;**22-29**:2677–2683.
32 UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998;**12**:703–713.
33 Morgensen CE. New treatment guidelines for a patient with diabetes and hypertension. *J Hypertens Suppl* 2003;**21**:S25–S30.
34 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**6**:7–22.
35 Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ *et al*. CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;**21-27**:685–696.
36 Costa J, Borges M, David C, Vaz Carneiro A. Efficacy of lipid lowering drug treatment for diabetic and non-diabetic patients: meta-analysis of randomised controlled trials. *BMJ* 2006;**13**: 1115–1124.
37 Winell K, Niemi M, Lepäntalo M. The National Hospital Discharge Register data on lower limb Amputations. *Eur J Vasc Endovasc Surg* 2006;**32**:66–70.
38 Gilis-Januszewska A, Szurkowska M, Szybinski K, Glab G, Szybinski Z, Spodaryk K *et al*. The efficacy of non-pharmacological intervention in obese patients with newly diagnosed diabetes mellitus type II. *Pol Arch Med Wewn* 2001;**106**:853–860.
39 Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P *et al*. Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001;**3**:1343–1350.
40 Lindstrom J, Ilanne-Parikka P, Peltonen M, Aunola S, Eriksson JG, Hemio K *et al*. Finnish Diabetes Prevention Study Group. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet* 2006;**11**:1673–1679.
41 Watala C, Golanski J, Pluta J, Boncler M, Rozalski M, Luzak B *et al*. Reduced sensitivity of platelets from type 2 diabetic patients to acetylsalicylic acid (aspirin)-its relation to meta-bolic control. *Thromb Res* 2004;**113**:101–113.
42 Sacco M, Pellegrini F, Roncaglioni MC, Avanzini F, Tognoni G, Nicolucci A, PPP Collaborative Group. Primary prevention of cardiovascular events with low-dose aspirin and vitamin E in type 2 diabetic pa-tients: results of the Primary Prevention Project (PPP) trial. *Diabetes Care* 2003;**26**:3264–3272.
43 Meade TW, Brennan PJ. Determination of who may derive most benefit from aspirin in primary prevention: subgroup results from a randomised controlled trial. *BMJ* 2000;**321**:13–17.
44 Watala C, Pluta J, Golanski J, Rozalski M, Czyz M, Trojanowski Z *et al*. Increased protein glycation in diabetes mellitus is associated with decreased aspirin-mediated protein acetylation and reduced sensitivity of blood platelets to aspirin. *J Mol Med* 2005;**83**:148–158.
45 Roffi M, Topol EJ. Percutaneous coronary intervention in diabetic patients with non-ST-segment eleva-tion acute coronary syndromes. *Eur Heart J* 2004;**25**:190–198.
46 Ferreira IA, Mocking AI, Feijge MA, Ferreira IA, Mocking AI, Feijge MA *et al*. Platelet inhibition by insulin is absent in type 2 diabetes mellitus. *Arterioscler Thromb Vasc Biol* 2006;**26**:417–422.
47 CAPRIE steering committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). *Lancet* 1996;**348**:1329–1339.
48 CURE trial investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;**345**:494–502.
49 Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Ramirez C, Sabate M, Jimenez-Quevedo P *et al*. Platelet function profiles in patients with type 2 diabetes and coronary artery disease on combined aspirin and clopido-grel treatment. *Diabetes* 2005;**54**: 2430–2435.
50 Lepäntalo A, Virtanen KS, Heikkila J, Wartiovaara U, Lassila R. Limited early antiplatelet effect of 300 mg clopidogrel in patients with aspirin therapy undergoing percutaneous coronary interventions. *Eur Heart J* 2004;**25**:476–483.
51 UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;**12**:854–865.
52 Salpeter S, Greyber E, Pasternak G, Salpeter E. Risk of fatal and nonfatal lactic acidosis with met-formin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2003;(2). CD002967.
53 Thomsen HS, Morcos SK. Contrast media and the kidney: European Society of Urogenital Radiology (ESUR) guidelines. *Br J Radiol* 2003;**76**:513–518.

54 O'Sullivan CJ, Hynes N, Mahendran B, Andrews EJ, Avalos G, Tawfik S *et al*. Haemoglobin A1c (HbA1C) in non-diabetic and diabetic vascular patients. Is HbA1C an independent risk factor and predictor of adverse outcome? *Eur J Vasc Endovasc Surg* 2006; **32**:188–197.
55 Maggio PM, Taheri PA. Perioperative issues: myocardial ischemia and protection–beta-blockade. *Surg Clin North Am* 2005; **85**:1091–1102.
56 Poldermans D, Boersma E, Bax JJ, Thomson IR, van de Ven LL, Blankensteijn JD *et al*. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Car-diac Risk Evaluation Applying Stress Echocardiography Study Group. *N Engl J Med* 1999;**9**:1789–1794.
57 Juul AB, Wetterslev J, Gluud C, Kofoed-Enevoldsen A, Jensen G, Callesen T, *et al*. DIPOM Trial Group. Effect of perioperative beta blockade in patients with diabetes undergoing major non-cardiac surgery: randomised placebo controlled, blinded multicentre trial. *BMJ* 2006;**24**:1482.
58 Kertai MD, Bax JJ, Klein J, Poldermans D. Is there any reason to withhold beta blockers from high-risk patients with coronary artery disease during surgery? *Anesthesiology* 2004;**100**:4–7.
59 Holstein A, Egberts EH. Traditional contraindications to the use of metformin – more harmful than beneficial? *Dtsch Med Wochenschr* 2006;**20**:105–110.
60 Soreide E, Eriksson LI, Hirlekar G, Eriksson H, Henneberg SW, Sandin R, *et al*. (Guidelines, Clinical Practice Committee Scandinavian Society of Anaesthesiology and Intensive Care Medicine). Pre-operative fasting guidelines: an update. *Acta Anaesthesiol Scand* 2005;**49**:1041–1047.
61 Jermendy G. Clinical consequences of cardiovascular autonomic neuropathy in diabetic patients. *Acta Diabetol* 2003;**40**(Suppl. 2): S370–S374.
62 Hynninen MS, Niemi TT, Poyhia R, Raininko EI, Salmenpera MT, Lepantalo MJ *et al*. N-acetylcysteine for the prevention of kidney injury in abdominal aortic surgery: a randomized, double-blind, placebo-controlled trial. *Anesth Analg* 2006;**102**:1638–1645.
63 Lazar HL, Chipkin SR, Fitzgerald CA, Bao Y, Cabral H, Apstein CS. Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcomes and decreases recurrent ischemic events. *Circulation* 2004;**30**:1497–1502.
64 van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M *et al*. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001;**8**:1359–1367.
65 Malmstedt J, Wahlberg E, Jorneskog G, Swedenborg J. Influence of perioperative blood glucose levels on outcome after infrainguinal bypass surgery in patients with diabetes. *Br J Surg* 2006; **93**:1360–1367.
66 Kanji S, Buffie J, Hutton B, Bunting PS, Singh A, McDonald K *et al*. Reliability of point-of-care testing for glucose measurement in critically ill adults. *Crit Care Med* 2005;**33**:2778–2785.
67 Furnary AP, Wu Y, Bookin SO. Effect of hyperglycemia and continuous intravenous insulin infusions on outcomes of cardiac surgical procedures: the Portland Diabetic Project. *Endocr Pract* 2004;**10**(Suppl. 2):21–33.
68 Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. *JAMA* 2003;**15**:2041–2047.
69 Carvalho G, Moore A, Qizilbash B, Lachapelle K, Schricker T. Maintenance of normoglycemia during cardiac surgery. *Anesth Analg* 2004;**99**:319–324.
70 De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongville J *et al*. Third Joint Task Force of the European and other Societes. European Guidelines on Cardiovascular Disease Prevention. *Eur J Cardiovasc Preven Rehab* 2003;**10**(S1):S1–S78.
71 American Diabetes Association. Standards of Medical Care in Diabetes 2007. *Diabetes Care* 2007;**30**(S1):S4–S41.

Accepted 30 January 2007
Available online 26 March 2007