

Cardiovascular disease and type 2 diabetes

The risk of developing cardiovascular disease (CVD) is more than doubled in patients with type 2 diabetes (T2D). Projections of current epidemiological data suggest a continuing rise in the prevalence of T2D over the coming decades, and the majority of these people will die from cardiovascular events. However, in spite of advances in CVD prevention strategies, T2D continues to be associated with poor outcomes, so novel therapeutic strategies remain an important research focus. This brief review summarises the pathogenesis of CVD associated with T2D, and discusses risk reduction strategies in these patients.

**Richard M Cubbon,
Mark T Kearney**

Division of Cardiovascular and Diabetes Research, Leeds Institute of Genetics, Health & Therapeutics, The University of Leeds, Clarendon Way, Leeds, LS2 9JT, UK.

Prim Care Cardiovasc J 2008; **1**: 158–63
doi: 10.3132/pccj.2008.040

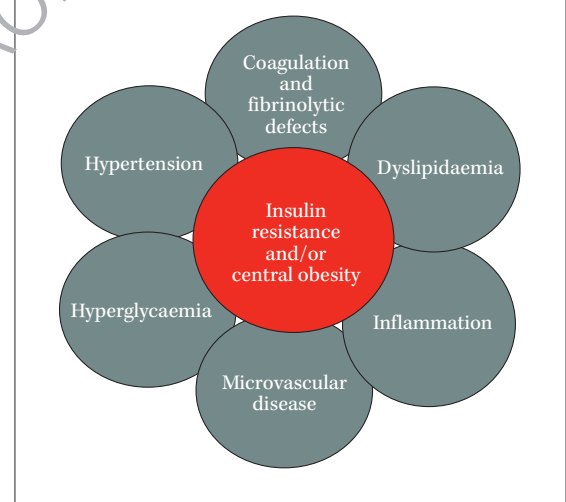
The majority of patients with type 2 diabetes (T2D) die as a result of cardiovascular disease (CVD).¹ Diabetes effectively ages the vasculature by around 15 years,² increasing the risk of cardiovascular events by at least two-fold.³ This enhanced risk develops insidiously, and even in the pre-diabetic phase (impaired glucose tolerance or impaired fasting glycaemia) risk is enhanced by at least 50%.⁴ The increasingly obese and ageing global population is anticipated to contribute to a continued rise in T2D prevalence, with some reports projecting a 4.4% global prevalence by 2030.⁵ This represents a major public health challenge, and is a contributor to concerns that for the first time in living memory average life expectancy in some 'Western' populations will fall, despite advances in healthcare.

Pathogenesis

The burgeoning prevalence of T2D over recent decades supports a strong environmental influence in its pathogenesis, although genetic factors are also important. Sedentary lifestyles in 'Westernised' populations have contributed to net caloric excess, and thus to obesity. When deposited around the abdominal viscera (central obesity), this is linked with insulin resistance and unfavourable changes in cardiovascular risk profile, in part via the production of detrimental cytokines from visceral adipocytes.⁶ Hence, T2D and the CVD associated with it develop from common pathophysiological origins.

Many 'traditional' and 'novel' CVD risk factors are associated with central obesity and insulin resistance (Figure 1) and their clustering plays a major role in the significant cardiovascular morbidity of patients with T2D and pre-diabetes. As demonstrated in Figure 2,

Figure 1. Clustering of cardiovascular risk factors in T2D and pre-diabetes



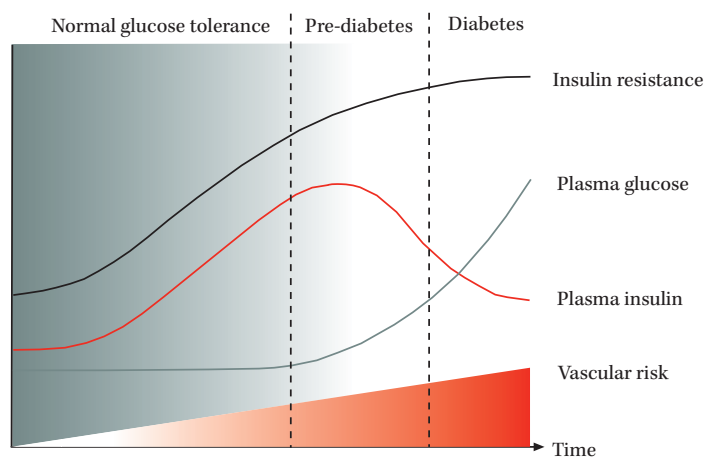
CVD risk continuously rises before the development of T2D; this is probably a result of deteriorating insulin resistance, which drives progressive clustering of CVD risk factors. Hyperglycaemia occurs much later as compensatory hyperinsulinaemia initially counteracts the impact of insulin resistance on glucose metabolism. Eventually, however, the pancreas can no longer mount a sufficient compensatory response and so hyperglycaemia progresses, resulting in pre-diabetes followed by T2D.

The combined impact of these clustering risk factors, and the later development of hyperglycaemia, damages the structural and functional integrity of the vascular endothelium. This monolayer of cells plays a pivotal role in vascular homeostasis,⁷ preventing the development of atherosclerosis through release of important vasoactive

Key points

- The prevention of CVD events in T2D remains an important public health challenge
- Effective control of hypertension, dyslipidaemia and lifestyle factors has demonstrated significant benefits in terms of CVD prevention
- Greater adherence to guidelines will yield further benefits for individual and public health
- Novel therapies are likely to be required to improve cardiovascular outcomes of patients with T2D

Figure 2. The increasing CVD risk associated with worsening insulin resistance



molecules, such as nitric oxide which has vasodilator, antiplatelet and anti-inflammatory properties.⁸ Endothelial dysfunction is generally accepted to represent the earliest phase of atherosclerosis;⁹ systemic inflammation and toxicity from lipids and glucose rapidly promote the development of the typical diffuse and severe atherosclerosis seen in T2D.

Prevention of CVD

It has long been recognised that diabetes confers increased risk of cardiovascular events, though our current CVD risk reduction strategies owe much to the concept of diabetes as a CVD risk equivalent as first proposed by Haffner *et al.*¹⁰ Their data suggested that patients with T2D and no prior myocardial infarction (MI) had the same risk of future MI as non-diabetic patients with a prior history of MI. In other words, patients with T2D alone appear to warrant the same intensity of risk reduction as offered to patients with manifest CVD who would receive aggressive secondary prevent therapy. Whilst the validity of these data has been questioned,¹¹ consensus guidelines recommend intensive risk reduction strategies for the majority of patients with T2D.¹²⁻¹⁴ Given that intensive risk reduction is offered to the majority of T2D patients we will not place particular focus on primary *vs.* secondary prevention in our discussion. Instead, we will briefly summarise current recommendations and the evidence they are based upon.

Lifestyle factors

Though often difficult to achieve,¹⁵ lifestyle modification plays an important role in holistic risk reduction. Even

modest weight loss, achieved through dietary and exercise intervention,¹⁶ or bariatric surgery,¹⁷ is known to improve risk factor profile and surrogate markers of vascular health. Pharmacological adjuncts can also be helpful as part of a weight loss programme and some have been shown to improve surrogate markers of CVD or risk factors for CVD,¹⁸⁻²⁰ although none have been proven to reduce hard clinical endpoints. Smoking cessation is also paramount and routine cessation strategies should be offered. Small studies assessing the role of intensive lifestyle modification, in addition to standard pharmacological therapy, have demonstrated sustained long-term mortality benefit.^{21,22} Further evidence regarding lifestyle intervention is anticipated from ongoing trials.^{23,2}

Dyslipidaemia

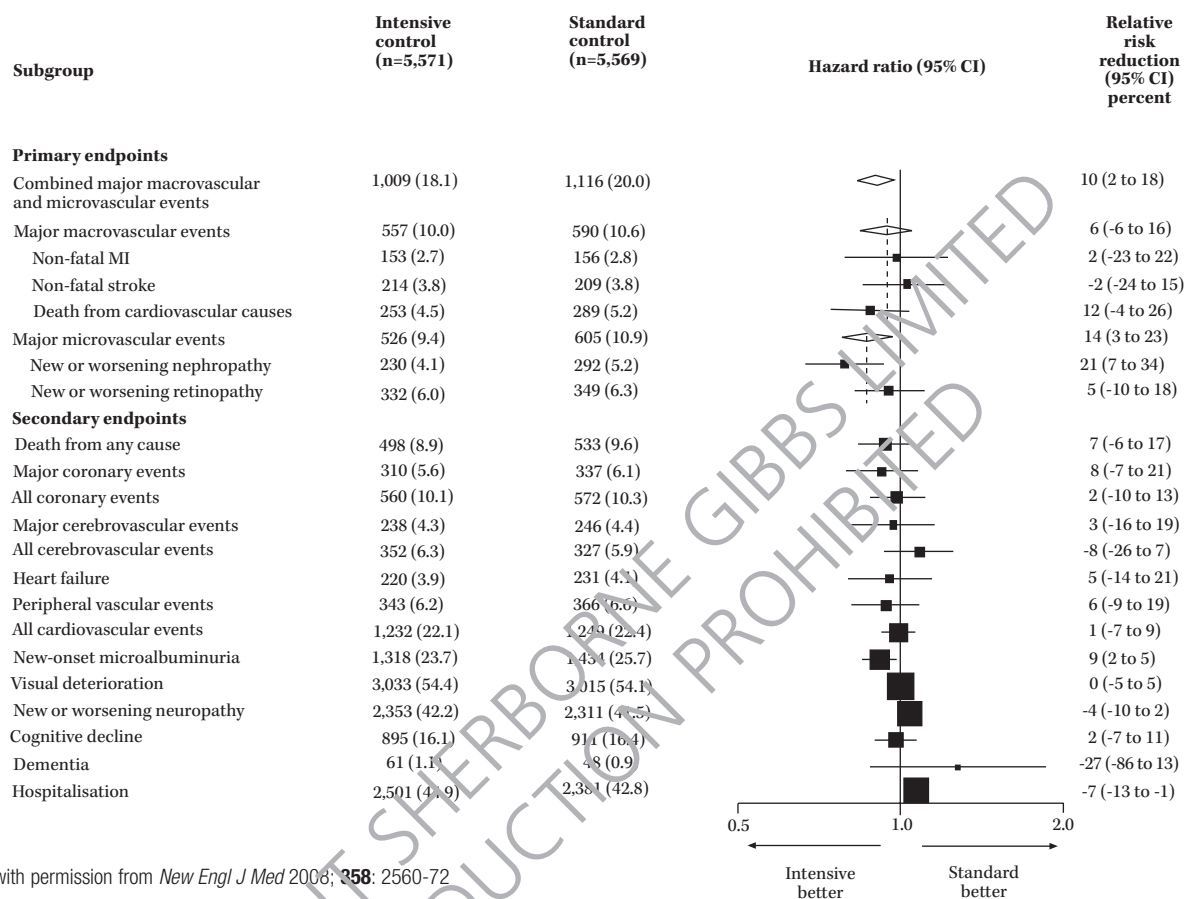
A large body of evidence supports lipid modification for the reduction of CVD risk in T2D. Subgroup analyses from early statin trials suggested similar magnitudes of relative risk reduction in patients with and without diabetes, and so a potentially greater absolute benefit in the higher-risk group with T2D.²⁵ More recently diabetes-specific trials have confirmed these findings; for example, atorvastatin 10 mg daily over 3.9 years reduced cardiovascular events by 37% in T2D sufferers free of known CVD, compared with placebo, in the CARDS study.²⁶ The target LDL-cholesterol concentration remains unclear, although atorvastatin 80 mg reduced endpoints further than atorvastatin 10 mg in the diabetes subgroup of the TNT trial.²⁷ Consensus guidelines suggest aiming for LDL-cholesterol below 1.8–2.0 mmol/L.^{12,14} Other lipid-modifying agents, such as fibrates, have so far proven less promising in randomised trials and so are not routinely recommended.

Hypertension

Again, a wealth of data supports blood pressure (BP) reduction in the optimal management of patients with diabetes.²⁸⁻³⁰ Many trials are not diabetes-specific, though a large proportion of patients in these suffered from T2D, and subgroup analyses have agreed the benefit of BP reduction. Current consensus suggests aiming for blood pressure below 130/80 mmHg,^{12,14} and for many patients this means a multi-drug regimen.³¹ However, where two or fewer agents are used, ACE inhibitors and angiotensin receptor blockers (ARBs) should be first-line, given their reno-protective benefit,³² and dihydropyridine calcium channel blockers are suggested as second-line agents. Beta-blockers and thiazide diuretics are associated with poorer

“
A large body of evidence supports lipid modification for the reduction of CVD risk in T2D
”

Figure 3. Relative effects of glucose control strategy on all pre-specified primary and secondary outcomes in the ADVANCE study⁵¹



Reproduced with permission from *New Engl J Med* 2008; **358**: 2560-72

outcomes,³³ due perhaps to increased association with new-onset diabetes,³⁴ and so are used as third-line agents. The role of newer antihypertensives, such as direct renin inhibitors, in improving CVD outcomes remains uncertain.

Antiplatelet therapy

Whilst consensus guidelines recommend the use of aspirin to prevent CVD events in patients with T2D,¹²⁻¹⁴ the evidence for its benefit in patients with diabetes is limited. The largest meta-analysis to date of antiplatelet therapy (the vast majority of data relating to aspirin) showed only a non-significant 7% relative risk reduction, compared with 22% in the overall population.³⁵ Our own work has suggested similar findings in real-world practice.³⁶ Post-hoc analysis of the Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events trial suggested that clopidogrel conferred a 13% risk reduction compared to aspirin in patients with diabetes.³⁷ Until further trial data are available, consensus guidelines are likely to advise aspirin and

clopidogrel use in the same manner as in patients without diabetes.

Hyperglycaemia

The question of whether optimal glycaemic control can reduce cardiovascular risk, in addition to its well-established microvascular benefits, has been surrounded by uncertainty. The United Kingdom Prospective Diabetes Study (UKPDS) was the first large-scale study to address this question in patients with T2D. The study suggested only a trend towards reduced CVD events with intensive glycaemic control,³⁸ though some commentators suggested that the relatively small difference in glycaemic control between groups (glycosylated haemoglobin [HbA_{1c}] 7.9% vs. 7.0%) could explain this. Furthermore, multiple agents were used and it has been proposed that insulin-sensitising strategies may actually address the underlying insulin resistance which is thought to cause CVD events, whereas insulin-providing strategies fail to address this. Indeed, a sub-study of the UKPDS suggested

“
It is evident that significant advances have been made in the development of strategies to modify the high cardiovascular risk of patients with T2D, though many challenges remain
 ”

cardiovascular benefit in overweight T2D sufferers treated with metformin, compared with sulphonylureas or insulin, though the analysis was not pre-specified.³⁹ More recently, a meta-analysis of randomised trials suggested intensive glycaemic management reduced CVD events by a significant 19%;⁴⁰ however, such analyses should always be treated with caution.

Pioglitazone and rosiglitazone were developed to improve insulin sensitivity, thus addressing the underlying insulin resistance which is thought to be so important in the pathophysiology of diabetic CVD. The PROactive study followed patients with macrovascular disease and T2D and demonstrated a trend towards reduction of a composite of cardiovascular events associated with pioglitazone *vs.* placebo.⁴¹ A secondary endpoint of all-cause mortality, stroke and MI was reduced by a significant 16%, though debate as to whether this endpoint was adequately pre-specified contributed to reluctance to recommend pioglitazone for reduction of CVD risk.⁴² Pioglitazone has also been shown to retard progression of atherosclerosis using the surrogate measure intravascular ultrasound,⁴³ and also beneficially modifies dyslipidaemia and inflammation, beyond its glucose-lowering properties.⁴²

However, in 2007 a high-profile meta-analysis suggested that rosiglitazone was associated with a significant 43% increase in MI and a near-significant 64% increase in cardiovascular death.⁴⁴ Since then, unplanned interim analysis of a randomised trial assessing potential cardiovascular benefits of rosiglitazone could not confirm non-inferiority of this agent compared with placebo.⁴⁵ A further analysis including GlaxoSmithKline data has again shown a trend towards increased MI risk associated with rosiglitazone.⁴⁶ However, methodological issues with all of these studies mean no firm conclusions can be drawn and ongoing studies are eagerly awaited.^{47,48} Furthermore, the promising findings of PROactive suggest that adverse cardiovascular profile may not be a class effect of glitazones, and that further investigation is warranted. Concerns have also been raised regarding increased risk of heart failure and fracture associated with glitazones.^{49,50} However, the former may relate to an unmasking of pre-existing occult myocardial disease due to fluid retention, and in the case of pioglitazone, this does not appear to have translated into an increase in cardiovascular mortality.

Two recently published trials (ADVANCE and ACCORD) of very intensive glycaemic control (HbA_{1c} approx 6.5% *vs.* 7.5%) have suggested that compared

with standard controls, cardiovascular outcomes were unchanged (Figure 3) or significantly worse, respectively.^{51,52} The reasons for this are unclear, though the almost universal use of rosiglitazone in the intensive arm of ACCORD has been highlighted along with significant weight gain in the intensive therapy group. It is notable though that post-hoc analysis of ACCORD showed rosiglitazone was not associated with increased CVD events. These findings have further clouded the confusing evidence base surrounding glycaemic control and CVD outcomes, and before further evidence is available, aiming for HbA_{1c} of 7% appears reasonable, given its proven microvascular benefit.

Coronary revascularisation

A comprehensive discussion of coronary revascularisation, or its use in acute coronary syndromes, is beyond the scope of this discussion. However, in stable coronary artery disease surgical revascularisation is generally thought to confer mortality benefit compared with percutaneous coronary intervention.^{53,54} The ever-changing nature of both modalities makes it difficult to be absolutely confident of such a statement, and the established benefit of adjunctive medical therapy must not be forgotten. Indeed, ongoing studies will hopefully address the question of whether modern revascularisation is any more effective at reducing cardiovascular events than contemporary intensive risk factor reduction alone.⁵⁵

Conclusions

It is evident that significant advances have been made in the development of strategies to modify the high cardiovascular risk of patients with T2D, though many challenges remain. Even in clinical trial settings, comprehensive use of evidence-based strategies is made in fewer than 10% of these patients,⁵⁶ and so significant improvements in individual and public health would be anticipated with more stringent adherence to guidelines. However, our own work points to a failure of significantly improved CVD outcomes post-MI over the last decade, despite dramatic improvements in the use of such evidence-based therapies.⁵⁷ Clearly, these findings require further investigation and novel therapies are likely to be required to improve the persistently poor cardiovascular outcomes of patients with diabetes. However, the convincing findings of many randomised controlled trials of statin therapy and blood pressure reduction, along with lifestyle modification, cannot be ignored and these 'basics' must not be forgotten in the search for new management strategies.

Acknowledgements

Dr Cubbon is supported by a British Heart Foundation Clinical PhD Fellowship.

References

- Morrish NJ, Wang SL, Stevens LK *et al*. Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia* 2001; **44**: S14-S21.
- Booth GL, Kapral MK, Fung K *et al*. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. *Lancet* 2006; **368**: 29-36.
- Fox CS, Coady S, Sorlie PD *et al*. Trends in cardiovascular complications of diabetes. *JAMA* 2004; **292**: 2495-9.
- Saydah SH, Loria CM, Eberhardt MS *et al*. Subclinical states of glucose intolerance and risk of death in the U.S. *Diabetes Care* 2001; **24**: 447-53.
- Wild S, Roglic G, Green A *et al*. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; **27**: 1047-53.
- Fantuzzi G, Mazzone T. Adipose tissue and atherosclerosis: exploring the connection. *Arterioscler Thromb Vasc Biol* 2007; **27**: 996-1003.
- Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation* 2000; **101**: 1899-906.
- Davignon J, Ganz P. Role of endothelial dysfunction in atherosclerosis. *Circulation* 2004; **109**: 1127-32.
- Ross R. Atherosclerosis – an inflammatory disease. *N Engl J Med* 1999; **340**: 115-26.
- Haffner SM, Lehto S, Ronnemaa T *et al*. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998; **339**: 229-34.
- Lee CD, Folsom AR, Pankow JS *et al*. for the Atherosclerosis Risk in Communities (ARIC) Study Investigators. Cardiovascular events in diabetic and nondiabetic adults with or without history of myocardial infarction. *Circulation* 2004; **109**: 855-60.
- Ryden L, Standl E, Bartnik M *et al*. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary: The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2007; **28**: 88-136.
- Eckel RH, Kahn R, Robertson RM *et al*. Preventing cardiovascular disease and diabetes: A call to action from the American Diabetes Association and the American Heart Association. *Circulation* 2006; **113**: 2943-6.
- British Cardiac Society, British Hypertension Society, Diabetes UK, HEART UK, Primary Care Cardiovascular Society, The Stroke Association. JBS 2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005; **91**(s5): v1-52.
- Anderson JW, Vichitbandra S, Qian W *et al*. Long-term weight maintenance after an intensive weight-loss program. *J Am Coll Nutr* 1999; **18**: 620-7.
- Maiorana A, O'Driscoll G, Cheetham C *et al*. The effect of combined aerobic and resistance exercise training on vascular function in type 2 diabetes. *J Am Coll Cardiol* 2001; **38**: 860-6.
- Williams IL, Chowienczyk PJ, Wheatcroft SB *et al*. Endothelial function and weight loss in obese humans. *Obes Surg* 2005; **15**: 1055-60.
- Miles JM, Leiter L, Hollander P *et al*. Effect of orlistat in overweight and obese patients with type 2 diabetes treated with metformin. *Diabetes Care* 2002; **25**: 1123-8.
- Nissen SE, Nicholls SJ, Wolski K *et al*. Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease: The STRADIVARIUS randomized controlled trial. *JAMA* 2008; **299**: 1547-60.
- Scheen AJ, Finer N, Hollander P *et al*. Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. *Lancet* 2006; **368**: 1660-72.
- Gaede P, Vedel P, Larsen N *et al*. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003; **348**: 383-93.
- Gaede P, Lund-Andersen H, Parving HH *et al*. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* 2008; **358**: 580-91.
- The ADDITION study. Intensive treatment and complication prevention in screen detected type 2 diabetes. <http://www.clinicaltrials.gov/ct/show/NCT00237549>. 07-07-2008
- The Look AHEAD research group. Baseline characteristics of the randomised cohort from the Look AHEAD (Action for Health in Diabetes) study. *Diab Vasc Dis Res* 2006; **3**: 202-15.
- Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003; **361**: 2005-16.
- Colhoun HM, Betteridge DJ, Durrington PN *et al*. 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; **364**: 685-96.
- Shepherd J, Barter P, Carmena R *et al*. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. *Diabetes Care* 2006; **29**: 1220-6.
- Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000; **355**: 253-9.
- UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998; **317**: 703-13.
- Hansson L, Zanchetti A, Carruthers SG *et al*. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998; **351**: 1755-62.
- Johnson ML, Singh H. Patterns of antihypertensive therapy among patients with diabetes. *J Gen Int Med* 2005; **20**: 842-6.
- Barnett AH, Bain SC, Bouter P *et al*. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med* 2004; **351**: 1952-61.
- Dahlof B, Sever PS, Poulter NR *et al*. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005; **366**: 895-906.
- Sarafidis PA, Bakris GL. Antihypertensive therapy and the risk of new-onset diabetes. *Diabetes Care* 2006; **29**: 1167-9.
- Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death,

- myocardial infarction, and stroke in high risk patients. *BMJ* 2002; **324**: 71-86.
36. Cubbon RM, Gale CP, Rajwani A *et al*. Aspirin and mortality in patients with diabetes sustaining acute coronary syndrome. *Diabetes Care* 2008; **31**: 363-5.
 37. Bhatt DL, Marso SP, Hirsch AT *et al*. Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. *Am J Cardiol* 2002; **90**: 625-8.
 38. 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; **352**: 837-53.
 39. 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; **352**: 854-65.
 40. Stettler C, Allemann S, Juni P *et al*. Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: Meta-analysis of randomized trials. *Am Heart J* 2006; **152**: 27-38.
 41. Dormandy JA, Charbonnel B, Eckland DJ *et al*. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005; **366**: 1279-89.
 42. Betteridge DJ, DeFronzo RA, Chilton RJ. PROactive: time for a critical appraisal. *Eur Heart J* 2008; **29**: 969-83.
 43. Nissen SE, Nicholls SJ, Wolski K *et al*. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: The PERISCOPE randomized controlled trial. *JAMA* 2008; **299**: 1561-73.
 44. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007; **356**: 2457-71.
 45. Home PD, Pocock SJ, Beck-Nielsen H *et al*. Rosiglitazone evaluated for cardiovascular outcomes – an interim analysis. *N Eng J Med* 2007; **357**: 23-38.
 46. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA* 2007; **298**: 1189-95.
 47. Nathan DM. Rosiglitazone and cardiotoxicity – weighing the evidence. *N Eng J Med* 2007; **357**: 64-6.
 48. Drazen JM, Morrissey S, Curfman GD. Rosiglitazone – continued uncertainty about safety. *N Eng J Med* 2007; **357**: 63-4.
 49. Hampton T. Diabetes drugs tied to fractures in women. *JAMA* 2007; **297**: 1645.
 50. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. *Lancet* 2007; **370**: 1129-36.
 51. The ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; **358**: 2560-72.
 52. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358**: 2545-59.
 53. Anzaid A, Costa MA, Centemero M *et al*. Clinical and economic impact of diabetes mellitus on percutaneous and surgical treatment of multivessel coronary disease patients: insights from the Arterial Revascularization Therapy Study (ARTS) trial. *Circulation* 2001; **104**: 533-8.
 54. The BARI Investigators. Seven-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI) by treatment and diabetic status. *J Am Coll Cardiol* 2000; **35**: 1122-9.
 55. Sobel BE, Frye R, Detre KM. Burgeoning dilemmas in the management of diabetes and cardiovascular disease: rationale for the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial. *Circulation* 2003; **107**: 636-42.
 56. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA* 2004; **291**: 335-42.
 57. Cubbon RM, Wheatcroft SB, Grant PJ *et al*. Temporal trends in mortality of patients with diabetes mellitus suffering acute myocardial infarction: a comparison of over 3000 patients between 1995 and 2003. *Eur Heart J* 2007; **28**: 540-5.