Cardiovascular disease: major journals

Choice of antihypertensive in diabetes remains a dilemma

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Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers are used to treat hypertension in diabetes. In the recent Irbesartan Diabetic Nephropathy Trial (IDNT), the angiotensin-blocker irbesartan was more effective than amlodipine or placebo in reducing renal primary endpoints in a group of hypertensive patients with type 2 diabetes and diabetic nephropathy (Lewis et al, 2001). With a median follow-up of 2.6 years, significant reductions were seen in the development of end-stage renal disease and in the doubling of serum creatinine, but there was no effect on death from any cause.

In the principal publication a secondary cardiovascular composite was death from cardiovascular causes, non-fatal myocardial infarction, hospitalisation for heart failure, permanent neurological damage due to stroke, or lower limb amputation. No significant difference was detected in this composite outcome.

The paper by Berl et al (2003) is a more detailed examination of secondary cardiovascular outcomes, including additional information on revascularisation. Again, there was no statistical difference in the composite outcome between irbesartan, amlodipine and placebo. Among the components of the composite outcome, amlodipine lowered rates of myocardial infarction, and irbesartan lowered congestive cardiac failure. The editors caution that the trial had limited power to detect important differences in rates of mortality or stroke between the groups.

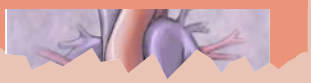
By contrast, in the Heart Outcomes Prevention Evaluation (HOPE) study (2000), significant reductions were seen in many cardiovascular outcomes and in the development of nephropathy, although data on blood pressure and proteinuria were not collected with as much rigour as in the IDNT trial.

Should we give ramipril for cardiovascular protection and probable renal protection, or irbesartan/losartan for renal protection and possible cardioprotection? Until comparative trials are performed, this will remain a dilemma.

Lewis EJ, Hunsicker LG, Clarke WR, et al for the Collaborative Study Group (2001) Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 345: 851–60

Heart Outcomes Prevention Evaluation (HOPE) Study Investigators (2000). Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 355:253–9

AMERICAN JOURNAL OF MEDICINE



Hyperlipidaemia treatment in diabetes still suboptimal

Readability	✓ ✓ ✓ ✓
Applicability to practice	✓ ✓ ✓
WOW! factor	✓ ✓

1 National guidelines recommend an LDL cholesterol of 100 mg/dL for patients with diabetes.

2 This study investigated the degree of lipid control in patients with type 2 diabetes, and temporal trends in adherence to published guidelines.

3 Post-hoc analysis of 501 patients with diabetes enrolled in the Appropriate Blood Pressure Control in Diabetes (ABCD) trial was carried out. All patients had fasting lipid profiles determined at base and during the 5-year trial period (1993–98).

4 The percentage of patients with LDL cholesterol < 130 mg/dL was 53% at baseline and 54% at the end of the 5 years. Almost 14% of patients had an LDL cholesterol > 160 mg/dL at completion of the study.

5 Of the 133 patients with known coronary heart disease, only 19% had an LDL cholesterol < 100 mg/dL at baseline, and only 16% reached this level by the end of the study.

6 Results suggest that the treatment of hyperlipidaemia is suboptimal. Efforts to bridge the gap between published guidelines and actual practice are needed urgently.

Mehler PS, Esler A, Estacio RO, Mackenzie TD, Hiatt WR, Schrier RW (2003) Lack of improvement in the treatment of hyperlipidaemia among patients with type 2 diabetes. *American Journal of Medicine* **114**: 377–82

ANNALS OF INTERNAL MEDICINE

No clear advantage for irbesartan or amlodipine in IDNT

Readability	✓ ✓ ✓ ✓ ✓
Applicability to practice	✓ ✓ ✓ ✓ ✓
WOW! factor	✓ ✓

1 Patients with diabetes are at increased risk of adverse cardiovascular events.

2 The Irbesartan Diabetic Nephropathy Trial (IDNT) compared the effect of irbesartan (angiotensin blocker), amlodipine (calcium-channel blocker) and placebo in 1715 adult patients with type 2 diabetic nephropathy.

3 Previously published results showed that irbesartan afforded better renal protection than amlodipine when given in addition to conventional antihypertensive therapy.

4 This paper anlysed the secondary cardiovascular endpoints to assess whether irbesartan or amlodipine altered the risk for cardiovascular events beyond those seen by blood pressure reduction alone (using conventional antihypertensive therapy) without such agents.

5 Patients were randomised to irbesartan 300 mg/day, amlodipine 10 mg/day, or placebo.

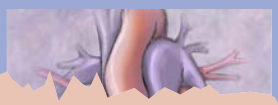
6 There was no statistically significant difference in composite cardiovascular event rate between the three groups.

7 Fewer patients given amlodipine had strokes or myocardial infarction (compared with placebo recipients).

8 In contrast, fewer patients given irbesartan had heart failure (compared with placebo or amlodipine recipients).

Berl T, Hunsicker LG, Lewis JB et al, for the Collaborative Study Group (2003) cardiovascular Outcomes in the Irbesartan Diabetic Nephropathy Trial of Patients with type 2 diabetes and Overt nephropathy. *Annals of Internal Medicine* **138**: 542–9

THE LANCET



Trial stopped early after benefits of atorvastatin emerge

Readability	✓ ✓ ✓ ✓ ✓
Applicability to practice	✓ ✓ ✓ ✓ ✓
WOW! factor	✓ ✓ ✓ ✓

1 This paper reports the lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA), a multicentre randomised trial comparing two antihypertensive strategies for prevention of coronary heart disease (CHD) in more than 18 000 hypertensive patients with no history of CHD.

2 A total of 10 305 patients with non-fasting total cholesterol levels ≤ 6.5 mmol/l from the ASCOT-LLA were randomly assigned additional atorvastatin 10 mg or placebo.

3 The primary endpoint was non-fatal MI and fatal CHD.

4 Treatment was stopped early, after a mean of 3.3 years' follow-up, when 100 primary events had occurred in the atorvastatin group *vs* 154 in the placebo group ($P = 0.0005$).This benefit emerged in the first year of follow-up.

5 Fatal and non-fatal stroke (89 atorvastatin *vs* 121 placebo, $P = 0.024$), total cardiovascular events (389 *vs* 486, $P = 0.0005$) and total coronary events (187 *vs* 247, $P = 0.0005$) were also significantly lowered.

6 Atorvastatin lowered total serum cholesterol by about 1.3 mmol/l compared with placebo at 12 months and by 1.1 mmol/l after 3 years' follow-up.

7 Cholesterol lowering with atorvastatin 10 mg therefore conferred a 36% reduction in fatal CHD and non-fatal MI in the study population compared with placebo.

Sever PS, Dahlöf B, Poulter NR et al (2003) Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOTT-LLA): a multicentre randomised controlled trial. *The Lancet* **361**: 1149–58

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

Vascular inflammatory markers in obesity

Readability	✓ ✓ ✓
Applicability to practice	✓ ✓ ✓ ✓
WOW! factor	✓ ✓ ✓

1 This trial determined the effect of sustained weight loss on vascular inflammatory markers (IL-6, IL-18 and C-reactive protein), adiponectin (an adipocytokine with anti-inflammatory and insulin-sensitising properties), and insulin resistance in 120 obese women without diabetes, hypertension or hyperlipidaemia.

2 The intervention group (60) followed a programme of lifestyle changes designed to achieve sustained weight loss, while the control group (60) received general advice on diet and exercise.

3 IL-6, IL-18 and C-reactive protein levels decreased significantly, and adiponectin levels increased significantly, in the intervention group.

4 Long-term weight loss was shown to be feasible and was associated with a reduction in markers of vascular inflammation and insulin resistance.

Esposito K, Pontillo A, Di Palo et al (2003) Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomised trial. *Journal of the American Medical Association* **289**: 1799–804

BRITISH MEDICAL JOURNAL

Raised blood glucose predicts MI

Readability	✓ ✓ ✓ ✓
Applicability to practice	✓ ✓ ✓
WOW! factor	✓ ✓ ✓

1 This study investigated the impact of raised blood glucose levels on the risk of developing MI in 1860 men who had taken part in a health study at age 50, and were re-examined at age 60, and then followed up for 17.4 years.

2 Incidence of MI after age 60 was significantly higher in men being treated for hypertension than in those not treated.

3 Men with MI after age 60 showed a significantly larger increase in blood glucose between age 50 and 60 than those without MI.

4 Increase in blood glucose was an independent risk factor for MI in men on antihypertensive treatment but not in those without such treatment.

5 An insulin-resistant state and the metabolic impact of β-blockers and diuretics increase the risk of MI.

Dunder K, Lind L, Zethelius B, Berglund L, Lithell H (2003) Increase in blood concentration during antihypertensive treatment as a predictor of myocardial infarction: population-based study. *British Medical Journal* 326: 681–84

AMERICAN JOURNAL OF MEDICINE

Heart failure linked to development of diabetes

Readability	✓ ✓ ✓ ✓ ✓
Applicability to practice	✓ ✓
WOW! factor	✓ ✓ ✓

1 This study explored the association between cardiac functional status and the development of diabetes in patients with previous MI or stable angina during 7.7 years follow-up.

2 The sample comprised 2616 patients without diabetes, who were aged 45–74 years, and with a fasting blood glucose of < 7 mmol/l.

3 Patients were categorised as New York Heart Association (NYHA) class I (1986), II (518), or III (112).

4 Development of diabetes was defined as a fasting blood glucose of ≥ 7 mmol/l during follow-up.

5 Diabetes developed in 13%, 15% and 20% of patients in NYHA classes I, II and III, respectively.

6 Advanced heart failure (NYHA class III) in patients with coronary artery disease significantly increases the risk of developing diabetes.

Tenebaum A, Motro M, Fisman EZ et al (2003) Functional class in patients with heart failure is associated with the development of diabetes. *American Journal of Medicine* **114**: 271–75

'Cholesterol lowering with atorvastatin 10 mg conferred a 36% reduction in fatal CHD and non-fatal MI in the study population compared with placebo.'

'Advanced heart failure (NYHA class III) in patients with coronary artery disease significantly increases the risk of developing diabetes.'

'Aggressive blood pressure control may be the most important factor in preventing adverse outcomes in patients with type 2 diabetes.'

ANNALS OF INTERNAL MEDICINE

Optimal treatment for hypertension in type 2 diabetes

Readability	✓ ✓ ✓
Applicability to practice	✓ ✓ ✓ ✓
WOW! factor	✓ ✓ ✓

1 This paper evaluated the goals and optimal agents for antihypertensive treatment in type 2 diabetes through review of the medical literature identified from the Cochrane Library, MEDLINE, meta-analyses, review articles and expert recommendations.

2 Antihypertensive treatment, with a blood pressure goal of 135/80 mmHg, provides dramatic benefit.

3 Thiazides, angiotensin II receptor blockers and ACE inhibitors may be the best first-line treatments, although other agents are usually necessary, and goals may not be achieved even with three or four agents.

4 Aggressive blood pressure control may be the most important factor in preventing adverse outcomes in patients with type 2 diabetes.

Vijan S, Hayward RA (2003) Treatment of hypertension in type 2 diabetes mellitus: blood pressure goals, choice of agents, and setting priorities in diabetes care. *Annals of Internal Medicine* 138(4): 593–602

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

Increasing cereal fibre intake reduces CVD risk in over-65s

Readability	✓ ✓ ✓ ✓
Applicability to practice	✓ ✓ ✓
WOW! factor	✓ ✓ ✓ ✓

1 Dietary fibre has been associated with a reduced incidence of ischaemic heart disease (IHD) and stroke in middle-aged people.

2 This population-based, multicentre study looked at whether fibre consumption from fruit, vegetable and cereal was linked with incident CVD (combined stroke, IHD, and non-fatal MI) in 3588 men and women, aged 65 years or over and free of CVD at baseline.

3 During 8.6 years mean follow-up, there were 811 incident CVD events.

4 Cereal fibre intake, but not fruit, vegetable or total fibre, were inversely associated with incident CVD. Those in the highest quintile of cereal fibre intake had a 21% lower risk than those in the lowest quintile.

Mozaffarian D, Kumanyika SK, Lemaitre RN, Olson JL, Burke GL, Siscovick DS (2003) Cereal, fruit and vegetable fiber intake and the risk of cardiovascular disease iun elderly individuals. *Journal of the American Medical Association* **289**: 1659–66

'This study is the first to directly correlate systemic levels of nitrotyrosine with presence of coronary artery disease and response to statin therapy.'

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

Nitrotyrosine levels linked with CAD and response to statins

Readability	✓ ✓
Applicability to practice	✓ ✓
WOW! factor	✓ ✓

1 Atherosclerotic lesions and atheromatous LDL contain raised levels of nitrotyrosine, a specific marker for protein modification by nitric oxide-derived oxidants.

2 This paper reports a case-control study (100 patients with CAD and 108 without CAD) and interventional study (35 patients aged ≥ 21 years, with hypercholesterolaemia, given 10 mg atorvastatin for 12 weeks).

3 The study investigated whether nitrotyrosine levels were associated with CAD and modulated by statins.

4 Levels of nitrotyrosine were significantly higher in CAD patients, and significantly reduced by statins.

5 This study is the first to directly correlate systemic levels of nitrotyrosine with presence of CAD and response to statin therapy.

Shishebor MH, Aviles RJ, Brennan et al (2003) Association of nitrotyrosine levels with cardiovascular disease and modulation by statin therapy. *Journal of the American Medical Association* **289**: 1675–80

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

Multiple lifestyle changes confer greater benefit

Readability	✓ ✓ ✓ ✓ ✓
Applicability to practice	✓ ✓ ✓ ✓ ✓
WOW! factor	✓ ✓ ✓ ✓

1 This trial determined the effect on blood pressure (BP) of simultaneously implementing two recommended lifestyle changes for reducing BP.

2 These were: weight loss, sodium reduction, increased physical activity, and limited alcohol intake; and the Dietary Approaches to Stop Hypertension (DASH) diet, which emphasises consumption of fruits, vegetables, and low-fat dairy products.

3 BP and hypertension status were measured at 6 months in 810 patients (mean age 50 years, 62% women) with above-optimal BP, including stage 1 hypertension (120–159/80–95 mmHg) randomised to: implementation of established recommendations (268); established + DASH (269); or advice only (273).

4 Mean net reduction in systolic BP was 3.7 and 4.3 mmHg in the established and established + DASH groups respectively.

5 Hypertension prevalence (vs baseline 38%) was 26%, 17% and 12% in the advice only, established, and established+DASH groups, respectively.

6 Optimal BP prevalence was 19%, 30% and 35% in the advice only, established and established+DASH groups, respectively.

7 Results indicate that multiple lifestyle changes in patients with above-optimal BP, including stage 1 hypertension were more effective than either intervention alone in lowering BP and hence reducing CVD risk.

Writing Group of the PREMIER Collaborative Research Group (2003) Effects of comprehensive lifestyle modification on blood pressure control: Main resuts of the PREMIER clinical trial. *Journal of the American Medical Association* **289**: 2083–92