Major journals

A randomised trial of therapies for type 2 diabetes and coronary artery disease: The BARI-2D study

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There is, to date, little evidence addressing the question of optimal treatment for people with diabetes and angiographically defined coronary artery disease. The Bypass Angioplasty Investigation Type 2 Diabetes (BARI-2D) study (BARI-2D Study Group; summarised alongside) assessed two cardiac treatment strategies and two glycaemic strategies in individuals who were receiving uniform therapy for cardiovascular risk factors.

The hypotheses tested were that prompt revascularisation (surgical or catheter-based) would reduce long-term event rates compared with medical therapy alone. The second hypothesis was that insulin sensitisation (target HbA_{1c} <7.0% [<53 mmol/mol]) would be associated with reduced event rates compared with a strategy of insulin provision.

People with both type 2 diabetes and heart disease (*n*=2368) were randomised to undergo either prompt revascularisation with intensive medical therapy or intensive medical therapy alone, and to undergo either insulin-sensitisation or insulin-provision therapy.

Primary endpoints were the rate of death and a composite of death, myocardial infarction, or stroke (major cardiovascular events).

Randomisation was stratified according to the choice of percutaneous coronary intervention (PCI) or coronary-artery bypass grafting (CABG) as the more appropriate intervention.

In essence, a strategy of prompt coronary revascularisation in people with type 2 diabetes and stable ischaemic heart disease with intensive diabetes medical therapy did not significantly reduce cardiovascular mortality. Insulin sensitisation and insulin provision resulted in similar cardiovascular outcomes over a 5-year period.

"Prompt revascularisation appears to be the most effective approach in people requiring coronary bypass surgery, while PCI did not appear to confer significant outcome benefits."

Among those individuals where CABG was deemed the most appropriate treatment, prompt revascularisation reduced the rates of cardiovascular events compared with medical therapy, particularly among people receiving insulin sensitisation therapy. PCI, in people where this intervention was deemed most appropriate, did not appear to reduce cardiovascular events when added to medical therapy.

The key clinical messages arising from the BARI-2D study therefore relate to the safety of insulin sensitising therapy in people with type 2 diabetes and stable ischaemic heart disease requiring revascularisation. Furthermore, prompt revascularisation appears to be the most effective approach in people requiring coronary bypass surgery, while PCI did not appear to confer significant outcome benefits.

NEW ENGLAND JOURNAL OF MEDICINE

Revascularisation versus intensive medical therapy

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

1 This study was undertaken to determine the optimal treatment strategy for people who have type 2 diabetes and ischaemic heart disease, as this has not yet been established in the literature.

2 The authors enrolled 2368 individuals with type 2 diabetes and stable ischaemic heart disease from 49 sites between January 2001 and March 2005.

3 Participants were randomly assigned to either revascularisation with intensive medical therapy or intensive medical therapy alone, with either insulin sensitisation or insulin provision.

4 The primary endpoint was mortality rate and a composite of major cardiovascular events (death myocardial infarction or stroke).

5 At 5 years follow-up, survival rates did not differ significantly between the revascularisation group (88.3%) and the medical therapy group (87.8%), or between the insulin-sensitisation group (88.2%) and the insulin-provision group (87.9%).

6 Adverse events were similar among the groups, although severe hypoglycaemia was more frequent in the insulin provision group than in the insulin sensitisation group (*P*=0.003).

7 Prompt revascularisation in those undergoing coronary artery bypass grafting reduced major CV events.

BARI 2D Study Group (2009) A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* **360**: 2503–15

BMJ

Statins beneficial to people with CV risk but without established CVD

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

1 Statin use is proven to be effective in people with established cardiovascular disease (CVD). Their usefulness in primary prevention has been documented, and this meta-analysis was carried out to determine whether statin therapy reduces all-cause mortality and incidence of major cardio- and cerebrovascular events.

2 Studies were included provided they were of randomised controlled design comparing statins with controls, had a minimum mean follow-up of 1 year, reported on mortality or CVD as primary outcomes, with at least 80% of the participants without established CVD.

3 Ten trials were analysed, comprising 70 388 participants, of whom 34% were women and 24% had diabetes. Mean follow-up was 4.1 years, and mean age was 63 years.

4 Statin therapy significantly reduced the incidence of all-cause mortality by 12%, and the incidence of major coronary and major cerebrovascular events by 30%.

5 The highest risk group comprised men >65 years of age and CV risk factors, and women >65 years of age with diabetes with CV risk factors.

6 The authors concluded that, as statin use was associated with significantly improved survival and large reductions in the risk of major cardiovascular events, it should not be denied to people at increased risk of CVD.

Brugts JJ, Yetgin T, Hoeks SE et al (2009) The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. *BMJ* **338**: b2376

LANCET

Rosiglitazone increases heart failure risk

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

1 This study investigated cardiovascular (CV) outcomes when adding rosiglitazone to either metformin or sulphonylurea versus dual therapy alone, and assessed comparative safety.

2 Participants with type 2 diabetes using metformin or sulphonylureas were randomised to addition of rosiglitazone (n=2220) or to a combination of metformin and sulphonylurea (n=2227). Mean HbA_{1c} level was 7.9% (63 mmol/mol).

3 The primary endpoint was hospitalisation due to CV causes, or CV death.

4 The primary endpoint was reached by 321 people in the rosiglitazone group and 323 in the control group during a mean 5.5-year follow-up. Mean HbA_{1c} was lower in the rosiglitazone group by study end.

5 Heart failure occurred in 61 people in the rosiglitazone group and 29 in the control group. Fracture rates were increased, mainly in women randomly assigned to rosiglitazone.

6 Although rosiglitazone was associated with an increased risk of heart failure and fracture, the authors concluded that it does not increase the risk of overall CV morbidity and mortality.

Home PD et al (2009) Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* **373**: 2125–3

AMERICAN JOURNAL OF MEDICINE

Hypertension intervention may improve HbA_{1c} levels

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

1 The authors of this study examined the effects of a telephone-based intervention designed to reduce hypertension, on HbA_{1c} and LDL-c levels.

2 Participants with and without diabetes received usual care, or a tailored self-management programme over a 2-year period.

3 For people with diabetes (n=216), there was a significant reduction in HbA_{1c} level over the study period (P=0.03). A reduction was seen in LDL-c level, but this was not significant.

4 The study indicates that interventions may have benefits for conditions other than those they are developed for.

Powers BJ et al (2009) The effect of a hypertension self-management intervention on diabetes and cholesterol control. *Am J Med* **122**: 639–46

BMJ

Pioglitazone safer than rosiglitazone?

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

1 This study was undertaken to compare the risks of pioglitazone and rosiglitazone on risk of acute myocardial infarction (AMI), heart failure and death in people with type 2 diabetes.

2 Participants (n=39 736) were aged over 66 years at study start, and were started on pioglitazone or rosiglitazone between April 2002 and March 2008.

3 The primary outcome measure was a composite of death or hospitalisation due to AMI or heart failure, and was reached by 895 people in the pioglitazone group and 1563 in the rosiglitazone group. Secondary analysis showed significantly reduced risk of heart failure and death.

4 The authors concluded that, as rosiglitazone has no distinct clinical benefit over pioglitazone, its continued use may be unjustifiable.

Juurlink DN et al (2009) Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone: population based cohort study. *BMJ* **339**: b2942

> *"As statin use was associated with significantly improved survival and large reductions in the risk of major CV events, it should not be denied to people at increased risk of CVD."*

"This study detected changes in fasting blood glucose levels and glucose tolerance 3 years before diagnosis. This evidence could contribute to more accurate risk prediction models."

LANCET

Aleglitazar improves HbA_{1c} levels in phase II study

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

1 The authors of this double-blind study aimed to establish the safety profile, glucose-lowering and lipid-modifying effects of the dual peroxisome proliferator-activated receptor (PPAR)-alpha and PPAR-beta agonist aleglitazar.

2 A total of 332 people with type 2 diabetes (either drug-naïve or ≤two oral agents) were randomised to 16 weeks' treatment with aleglitazar once-daily at doses of 50, 150, 300 or 600 µg, or matching placebo (n=55 in each group), and 57 people were randomised to a reference group taking open-label pioglitazone 45 mg.

3 The change in HbA_{1c} from baseline was the primary efficacy endpoint.

4 Treatment with aleglitazar resulted in a significant reduction in HbA_{1c} level from baseline versus placebo in a dose-dependent manner (from –0.36% [3.9 mmol/mol] with 50 mg [P=0.048] to –1.35% [14.8 mmol/mol] with 600 mg [P<0.0001]).

5 Aleglitazar did not appear to reach its maximum effect on HbA_{1c} after 16 weeks based on the trend of changes in data over time.

6 In the aleglitazar 300 µg group, there were no congestive heart failures, frequency of oedema was similar to placebo (and fewer than with pioglitazone), and weight gain was less than with pioglitazone (0.52 kg at 150 µg vs. 1.06 kg).

7 The authors concluded that the safety and efficacy profile of aleglitazar was favourably balanced and suggests that this drug can move into phase III investigation.

Henry RR, Lincoff AM, Mudaliar S et al (2009) Effect of the dual peroxisome proliferator-activated receptor-alpha/gamma agonist aleglitazar on risk of cardiovascular disease in patients with type 2 diabetes (SYNCHRONY): a phase II, randomised, dose-ranging study. *Lancet* **374**: 126–3

ANNALS OF INTERNAL MEDICINE

Risk-scoring system to predict diabetes

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

1 This study aimed to develop and validate simple scoring systems to predict people at risk of diabetes.

2 Participants of the Atherosclerosis Risk in Communities study formed the sample (12 729 US adults were followed for 14.9 years).

3 Anthropometry, blood pressure, pulse and a fasting blood specimen were analysed and assigned points to help assess risk (for example, 10–35 points were assigned for waist circumference).

4 Limitations included no information about previous gestational diabetes, and that knowledge of parental diabetes may be uncertain.

5 Basic information did identify those at risk of diabetes, and including blood sample data better predicted those at risk.

Kahn HS, Cheng YJ, Thompson TJ et al (2009) Two risk-scoring systems for predicting incident diabetes mellitus in US adults age 45 to 64 years. *Ann Intern Med* **150**: 741–51

LANCET

Blood glucose changes detected 3 years prior to diagnosis

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

1 The authors of this study sought to find out more about the trajectories of glycaemia, insulin sensitivity, and insulin secretion before type 2 diabetes is diagnosed.

2 Data from participants of the Whitehall II study were analysed (n=6538; 71% male; civil servants without diabetes).

3 A total of 505 cases of diabetes were diagnosed over a median follow-up period of 9.7 years.

4 In the group with diabetes, fasting glucose increased in a linear pattern followed by a steep quadratic increase (from 5.79 mmol/L to 7.40 mmol/L) starting 3 years before diagnosis.

5 Results from a 2-hour glucose tolerance test began to rapidly increase 3 years prior to diagnosis (from 7.60 mmol/L to 11.90 mmol/L).

6 This study detected changes in fasting blood glucose levels and glucose tolerance 3 years before diagnosis. This evidence could contribute to more accurate risk prediction models.

Tabák AG, Jokela M, Akbaraly T et al (2009) Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. *Lancet* **373**: 2215–21

ANNALS OF INTERNAL MEDICINE

Telmisartan does not affect long-term renal outcomes

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

1 This multicentre, multinational study examined the long-term renal effects of telmisartan compared with placebo in 5927 adults with cardiovascular disease or diabetes.

2 Participants were randomised to receive either telmisartan 80 mg once-daily (n=2954) or a placebo (n=2972) plus standard treatment for a mean of 56 months.

3 No difference was found between groups in the composite outcome (dialysis or doubling of serum creatinine, changes in estimated glomerular filtration rate [eGFR] and changes in albuminuria) (P=0.20).

4 Decreases in eGFR were greater with telmisartan than placebo (P<0.001).

5 In this sample, telmisartan had similar effects on major renal outcomes as placebo.

Mann JF, Schmieder RE, Dyal L et al (2009) Effect of telmisartan on renal outcomes: a randomized trial. *Ann Intern Med* **151**: 1–10