Cardiovascular journals

STROKE

Pioglitazone reduces recurrent stroke risk but may increase risk of heart failure

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

1 This subgroup analysis was undertaken to evaluate the effect of pioglitazone on recurrent stroke and other cardiovascular outcomes in people with and without prior stroke.

2 The PROactive study randomised 5238 people with type 2 diabetes and a history of macrovascular disease to either pioglitazone 45mg or placebo. Of these, 984 had a previous history of stroke.

3 The primary end point of the PROactive trial was all-cause death, nonfatal myocardial infarction, acute coronary syndrome, cardiac intervention (including coronary artery bypass graft or percutaneous coronary intervention), stroke, major leg amputation, or bypass surgery or leg revascularisation. Cardiovascular end points were judged independently.

4 The results appear to show a beneficial trend for the primary end point for those with prior stroke with pioglitazone, although it was non-significant (event rate = 20.2% pioglitazone versus 25.3% placebo; P=0.067).

5 Pioglitazone significantly reduced fatal or nonfatal stroke (P=0.0085) and cardiovascular death, nonfatal myocardial infarction and stroke (P=0.0467).

6 There were significantly more individuals hospitalised through heart failure in the pioglitazone group than in the placebo group (118 versus 88; P=0.0279).

Wilcox R, Bousser MG, Betteridge DJ et al (2007) Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). *Stroke* **38**:865–73

PROactive stroke data is encouraging, but must be used with care

Vinod Patel, Consultant Physician at the George Eliot Hospital, Nuneaton, and Associate Professor at the University of Warwick

There has recently been considerable coverage in the press in relation to the safety of the use of thiazolidinediones. We all have considerable experience with this class of drugs and need reassurance of their long-term safety profiles. I have therefore chosen to review the stroke data from the PROactive study (Wilcox et al, 2007; summarised on right).

PROactive was a large prospective, randomised, double-blind study that lasted for a mean of 34.5 months. Participants with type 2 diabetes and a history of macrovascular disease were randomised to pioglitazone (titrated to 45mg) or placebo in addition to their current diabetes and cardiovascular medications. The primary end point was all-cause death, nonfatal MI, acute coronary syndrome, cardiac intervention (including coronary artery bypass graft or percutaneous coronary intervention), stroke, major leg amputation, cardiac bypass surgery or leg revascularisation.

This subgroup analysis (summarised on right) evaluated the risk of stroke and other cardiovascular outcomes in people with and without prior stroke.

In people with previous stroke (n=486 in the pioglitazone group and n=498 in the placebo group), there was a trend of benefit with pioglitazone for both primary and secondary end points. Although these are non-significant trends with wide confidence levels, they may be clinically reassuring.

The stroke data were significant and interesting. Pioglitazone reduced fatal or nonfatal stroke by 47%. Higher event rates were observed in those with prior stroke compared with those without prior stroke as we would expect. In people without prior stroke, no treatment effect was observed for a first stroke.

It must be stressed that the above 'reassuring' data were against the background of a distinct and significant increase in cardiac failure. However, the study by Erdmann et al (summarised on the next page), showed a significant reduction in the occurrence of fatal and non-fatal MI and acute coronary syndrome in those with diabetes and MI in another PROactive sub-group analysis. It is only possible to conclude that the glitazones should be used with care and that definitive data on long-term effects of cardiovascular safety are awaited.

INTERNATIONAL JOURNAL OF CARDIOLOGY

Admission glycaemia affects mortality

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

1 This study looked at admission glycaemia and mortality risk in those presenting with acute coronary syndrome (ACS).

2 Of the 1957 followed up for this study, 22% had diabetes. The authors looked at short-term (≤30 day) and long-term (>30 day) mortality over a 45-month period.

3 The investigation showed that among those presenting with ACS and no history of diabetes, those who had hyperglycaemia had a higher short- and long-term mortality risk (P<0.0001 and P=0.007, respectively).

4 The authors also found that of those presenting with hyperglycaemia, people without diabetes had a higher short-term mortality than those with diabetes (P=0.002).

5 This paper concludes that admission hyperglycaemia is a strong risk factor for mortality in people with ACS and may be stronger than a previous history of diabetes.

Petursson P, Herlitz J, Caidahl K et al (2007) Admission glycaemia and outcome after acute coronary syndrome. *International Journal of Cardiology* **116**: 315–20

"The risk of stroke in people with newly treated diabetes is more than double the rate for the general population"

"Pioglitazone significantly reduced the occurrence of fatal and nonfatal MI and ACS in people with type 2 diabetes"

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Pioglitazone reduces occurrence of MI and ACS but may increase risk of heart failure

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

1 This subgroup analysis from the PROactive study was undertaken to evaluate the effects of pioglitazone on stroke and other cardiovascular outcomes in people with and without prior stroke.

2 This was a prospective, randomised, double-blind study involving 5238 people with type 2 diabetes and a history of macrovascular disease who were randomised to pioglitazone (45mg) or placebo.

3 There was a history of MI in 2445 individuals. Of these, 1230 were in the pioglitazone group and 1215 in the placebo group.

4 Pioglitazone showed a statistically significant risk reduction of 28% for fatal and nonfatal MI (P=0.045) and a reduction of 37% for acute coronary syndrome (ACS; P=0.035). There was a 19% risk reduction in the cardiac composite end point of nonfatal MI, coronary revascularisation, ACS and cardiac death (P=0.033).

5 The rates of heart failure requiring hospitalisation were higher (7.5%) in the pioglitazone group than in the placebo group (5.2%).

6 The authors found that there was an increased risk of 75% for heart failure leading to hospitalisation among those who had a previous MI compared with those who had no history of MI (P≤0.0001).

7 The results suggest that pioglitazone significantly reduced the occurrence of fatal and nonfatal MI and ACS in people with type 2 diabetes.

Erdmann E, Dormandy JA, Charbonnel B et al (2007) The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive (PROactive 05) Study. *Journal of the American College of Cardiology* **49**: 1772–80

STROKE

Stroke risk is doubled in the newly treated

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

1 The authors conducted this inception cohort study to determine the short-term risk for stroke in people with newly treated type 2 diabetes compared with the general population.

2 The diabetes cohort was made up of 12272 individuals with diabetes who had received either metformin or a sulfonylurea in the period 1991–1996. People were defined as newly treated if they had not received a prescription for medication in the year prior to the study period.

3 During the 5-year follow-up period, 9.1% of the diabetes cohort had a stroke. This is equivalent to 642 per 100000 person-years in those with diabetes, compared with 313 per 100 000 person-years in the general population.

4 The authors conclude that the risk of stroke in people with newly treated diabetes is more than double the rate for the general population.

Jeerakathil T, Johnson JA, Simpson SH, Majumdar SR (2007) Short-term risk for stroke is doubled in persons with newly treated type 2 diabetes compared with persons without diabetes: a population-based cohort study. *Stroke* **38**: 1739–43

AMERICAN HEART JOURNAL

Intensive intervention improves risk factors

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

1 The DANish StUdy of impaired glucose metabolism in the settings of cardiac rehabilitation (DANSUK) examined the effect of an intensified multifactorial intervention on risk factors in people with type 2 diabetes or impaired glucose tolerance (IGT).

2 Those involved in the study were randomised to usual care or comprehensive cardiac rehabilitation (CCR). There were a total of 201 participants and 104 had type 2 diabetes.

3 CCR comprises of stepwise behavioural modification and pharmacotherapy.

4 After 1 year, those with type 2 diabetes in the CCR group had significantly (P<0.05) lower HbA_{1c} (-0.65%±0.9%); lower blood pressure and a higher exercise capacity than those randomised to usual care.

Soja AM, Zwisler AD, Frederiksen M et al (2007) Use of intensified comprehensive cardiac rehabilitation to improve risk factor control in patients with type 2 diabetes mellitus or impaired glucose tolerance–the randomized DANish StUdy of impaired glucose metabolism in the settings of cardiac rehabilitation (DANSUK) study. *American Heart Journal* **153**: 621–8

AMERICAN JOURNAL OF CARDIOLOGY

High HbA_{1c} is linked to more severe PAD

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

1 The authors of this study investigated the relationship between HbA_{1c} and the severity of PAD in 224 people with diabetes and PAD, measured by ankle-brachial index (ABI).

2 Of these, 6 were treated with diet alone, 108 with metformin, 49 with sulfonylureas, 101 with insulin and 43 with thiazolidinediones.

3 The mean ABI of those with an HbA_{1c} of 7.1%±0.9% was 0.60–0.89, while the mean ABI of those with a higher HbA_{1c} (9.1±2.1%) was <0.60. This was a significant difference (P<0.0001).

4 The data presented appear to indicate that the higher the HbA_{1c} in people with diabetes and PAD, the more severe the PAD will be. The authors suggest that intensive risk modification should occur to reduce HbA_{1c} levels to below 6.5%.

Aronow WS, Ahn C, Weiss MB, Babu S (2007) Relation of increased hemoglobin A(1c) levels to severity of peripheral arterial disease in patients with diabetes mellitus. *American Journal of Cardiology* **99**: 1468–9

CIRCULATION

FPG level predicts hospitalisation for congestive heart failure

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

1 The authors carried out this study to evaluate the association between fasting plasma glucose and risk of being hospitalised due to congestive heart failure (CHF).

2 The fasting plasma glucose levels of 31 546 individuals taking part in two parallel trials (ONTARGET and TRANSCEND) were recorded at baseline.

3 The inclusion criteria were a high risk for CVD, age≥55 years, and history of diabetes or symptomatic CVD with evidence of major end-organ damage.

4 The participants were split into groups depending on their FPG result and whether or not they had diabetes, and followed up at 6 weeks, 3 months, 6 months and then every 6 months for an average of 4.5 years.

5 Of the cohort, 11 708 had known diabetes and 1006 were newly diagnosed at baseline. During the follow'up period, 668 individuals were hospitalised for CHF.

6 The investigators found that, after adjustment for age and sex, a 1 mmol/l rise in fasting plasma glucose was associated with a 1.10-fold increase in the risk of hospitalisation due to CHF ($P<0.0001$). This was still significant after adjustment for diabetes and other CVD risk factors.

7 While the authors conclude that FPG can be used to predict hospitalisation for CHF, they suggest that studies need to be conducted to determine if lowering FPG can reduce the risk of hospitalisation due to CHF.

Held C, Gerstein HC, Yusuf S et al (2007) Glucose levels predict hospitalization for congestive heart failure in patients at high cardiovascular risk. *Circulation* **115**: 1371–5

AMERICAN JOURNAL OF CARDIOLOGY

Inhibiting the renin–angiotensin system may help prevent type 2 diabetes

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

1 This meta-analysis was conducted to determine whether or not the development of diabetes can be hindered or prevented by the inhibiting the renin–angiotensin system.

2 The authors searched Medline and the Cochrane database for prospective, randomised, placebo-controlled or active-controlled trials of ACE inhibitor or ARB therapy in adults that reported rates of new-onset diabetes during follow up, and performed a meta-analysis on the results: 13 trials with a total of 93 451 individuals were identified as suitable for analysis.

3 Of these, 41 950 were randomised to renin–angiotensin system antagonists, either ACE inhibitors or ARBs.

4 Diabetes developed in 7.1 % of those treated with ACE inhibitors or ARBs compared with 9 % receiving placebo. This was a significant 26 % reduction in the odds of developing diabetes ($P<0.001$).

5 The reduction in the odds of developing diabetes were similar for ACE inhibitors (28 % reduction; $P<0.001$) and ARBs (27 % reduction; $P<0.001$).

6 The authors conclude that based on evidence accumulated up to the current point in time, inhibition of the renin–angiotensin system may be an important factor in preventing the onset of type 2 diabetes.

Andraws R, Brown DL (2007) Effect of inhibition of the renin-angiotensin system on development of type 2 diabetes mellitus (meta-analysis of randomized trials). *American Journal of Cardiology* **99**: 1006–12

'Inhibition of the renin–angiotensin system may be an important factor in preventing the onset of type 2 diabetes'

EUROPEAN HEART JOURNAL

Diabetes management post AMI needs to be more effective

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

1 This comparative analysis was undertaken to investigate whether or not people with diabetes have benefited from the advances in management of acute myocardial infarction (AMI) of the last 10 years.

2 The study compared baseline characteristics, management and survival of people with and without diabetes who suffered an AMI in 1995 (n=1762) with a group of people who sustained an AMI in 2003 (n=1642). All individuals were followed up for 18 months or until death.

3 The authors noted that there was a significant increase in diabetes prevalence in those sustaining an AMI over the study period of 4.1% ($P<0.001$).

4 Despite a significant improvement in 30-day mortality in both groups – 40% improvement in those without diabetes ($P=0.006$) and 30% in those with diabetes ($P<0.001$) – there was no significant change in 18-month mortality between 1995 and 2003 in those with diabetes.

5 These results show that despite a reduction in early post-AMI mortality, these improvements are only maintained in people without diabetes.

6 The authors suggest that more effective management strategies are required for those with diabetes following AMI.

Cubbon RM, Wheatcroft SB, Grant PJ et al (2007) Temporal trends in mortality of patients with diabetes mellitus suffering acute myocardial infarction: a comparison of over 3000 patients between 1995 and 2003. *European Heart Journal* **28**: 540–5

'More effective management strategies are required for those with diabetes following AMI'