Diabetes journals

Pioglitazone use and heart failure in people with type 2 diabetes and pre-existing CVD

Marc Evans, Consultant Physician, Llandough Hospital, Cardiff

Heart failure is a common co-morbidity in type 2 diabetes, with an occurrence rate of 8–20 %. Aggressive risk factor management confers a reduced risk for heart failure; while factors such as ischaemic heart disease, diabetes duration and elevated serum creatinine levels are recognised predetermining factors. The Prospective pioglitAzone Clinical Trial In macroVascular Events (ProActive) enrolled people with type 2 diabetes and CVD and thus at high risk of heart failure. Heart failure has been recognised as a potential adverse effect of glitazone therapy, thus any therapeutic benefit of pioglitazone may have been offset by a higher incidence of heart failure.

The study summarised alongside (Erdmann et al, 2007) analysed the heart failure cases reported during ProActive and evaluated the effect of pioglitazone treatment on morbidity and mortality. 5238 patients were enrolled in ProActive, with New York Heart Association grade II–IV heart failure being an exclusion criterion. A serious heart failure event occurring during the study was defined as heart failure requiring hospitalisation, prolonged hospital stay, was fatal/life threatening or resulted in persistent incapacity.

More people on pioglitazone (5.7 % versus 4.1 %; *P*=0.007) experienced such an event during the study, mortality was, however, similar for both groups (0.96 % versus 0.84 %; *P*=0.64). All-cause mortality was lower for those individuals receiving pioglitazone (26.8 % versus 34.3 %), while fewer of the pioglitazone group also went on to have a primary (47.7 % versus 57.4 %; *P*=0.059) or main secondary end point (34.9 % versus 47.2 %; *P*=0.025).

The results show that while there was an increase in serious heart failure associated with pioglitazone therapy, this did not appear to result in an increase in morbidity and mortality. Indeed, the subsequent event rate that included the most serious outcomes associated with heart failure – all cause mortality, MI and stroke – was lower in pioglitazone-treated individuals with heart failure. The mechanisms behind the heart failure associated with pioglitazone, and indeed all glitazone therapy, is unclear but may be due to PPAR-gamma mediated renal tubular sodium and fluid retention, rather than a direct detrimental effect on myocardial function.

The results of this analysis suggest that while pioglitazone may exacerbate heart failure in susceptible individuals, this did not translate into increased cardiovascular morbidity and mortality and did not diminish the potential CV benefits associated with pioglitazone therapy seen in the ProActive study. Therefore when considering pioglitazone therapy in routine clinical practice optimising the risk–benefit profile for such an intervention requires an assessment of a person's heart failure risk prior to initiating therapy.

DIABETES CARE

Mortality is not increased in serious heart failure with pioglitazone

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

1 The ProActive was a multicentre double-blind placebo-controlled trial in 5238 people with type 2 diabetes randomised to placebo or pioglitazone. This study looked at the serious heart failure cases reported during ProActive and examined the effects of pioglitazone on morbidity and mortality.

2 Serious heart failure was defined as heart failure requiring hospitalisation, prolonged hospital stay, was fatal/life threatening or resulted in persistent incapacity.

3 During the study more individuals taking pioglitazone suffered serious heart failure than those on placebo (5.7% versus 4.1%; *P*=0.007). However, mortality due to heart failure was similar for both groups.

4 All-cause mortality was lower in the pioglitazone group and fewer of those taking the drug went on to have a primary or main secondary end point (*P*=0.1338; *P*=0.593; *P*=0.025; respectively.

5 The proportion of individuals who had non-serious heart failure was significantly higher in the pioglitazone group (*P*=0.0007).

6 The results of this investigation show that while pioglitazone can cause serious heart failure in those using the agent, the level of morbidity and mortality was comparable with placebo.

Erdmann E, Charbonnel B, Wilcox RG et al (2007) Pioglitazone use and heart failure in patients with type 2 diabetes and preexisting cardiovascular disease: data from the PROactive study (PROactive 08). *Diabetes Care* **30**: 2773–8

'Intensified use of statins, ACE inhibitors and aspirin was significantly more common in those with resolution than those who developed new MI.'

'Multi-intervention and structured care are necessary to reach treatment goals and reduce CV risk.'

DIABETES CARE

Intensive treatment of cardiovascular risk factors resolves MI

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

1 This study was undertaken to investigate the prevalence of inducible myocardial ischaemia (MI) over 3 years.

2 Repeat adenosine stress myocardial perfusion imaging showed that 71 of 358 (20 %) people with type 2 diabetes had ischaemia at enrollment.

3 Of these, 56 (79 %) had resolved MI and 15 (21 %) remained abnormal during the study.

4 Of the 287 without MI at baseline, 28 (10 %) developed it.

5 Intensified use of statins, ACE inhibitors and aspirin was significantly more common in those with resolution than those who developed new MI (P = 0.04).

Wackers FJ, Chyun DA, Young LH et al (2007) Resolution of asymptomatic myocardial ischemia in patients with type 2 diabetes in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study. *Diabetes Care* **30**: 2892–8

DIABETIC MEDICINE

Compared with standard care, structured multi-interventional care improves CHD risk

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

1 Over 2 years, 106 people with type 2 diabetes of a median 4-year duration were randomised to standard care (GP follow up) or structured care at a hospital outpatient clinic (6-month lifestyle programme followed by intensified pharmacological treatment).

2 Greater improvements were seen in the structured care group for systolic BP, triglycerides, glucose and HbA_{1c} ($P < 0.05$).

3 Estimated 10-year CHD risk was lowered from 17.9 % to 14.5 % with intensified treatment but increased from 18.3 % to 19.6 % with standard follow up.

4 Prevalence of CHD risk >20 % improved for structured care (38 % to 22 %) but increased with standard treatment (39 % to 45 %).

5 Multi-intervention and structured care are necessary to reach treatment goals and reduce CV risk.

Johansen OE, Gullestad L, Blaasaas KG et al (2007) Effects of structured hospital-based care compared with standard care for Type 2 diabetes-The Asker and Baerum Cardiovascular Diabetes Study, a randomized trial. *Diabetic Medicine* **24**: 1019–27

JOURNAL OF DIABETES AND ITS COMPLICATIONS

ACE-i/ARB treatment reduces risk of coronory artery calcification progression

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

1 Over a period of 2.5 ± 0.4 years, coronary artery calcification (CAC) progression was assessed in 478 people with type 1 diabetes with no history of coronary artery disease.

2 At baseline, 157 (33 %) were on ACE-i treatment and 83 (17 %) had albuminuria. At follow up, 114 (24 %) had CAC progression.

3 Albuminuria at baseline predicted CAC in people not treated with ACE-i/ARBs (OR: 4.06; 95 % CI: 1.45–11.35; $P = 0.008$).

4 Those treated with ACE-i/ARBs were 62 % less likely to exhibit CAC progression ($P = 0.106$).

Maahs DM, Snell-Bergeon JK, Kinney GL et al (2007) ACE-I/ARB treatment in type 1 diabetes patients with albuminuria is associated with lower odds of progression of coronary artery calcification. *Journal of Diabetes and its Complications* **21**: 273–9

DIABETIC MEDICINE

Revascularisation could reduce mortality in asymptomatic CAD

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

1 The authors of this Korean investigation looked at the clinical outcomes and clinical and angiographic characteristics of people with asymptomatic and symptomatic coronary artery disease (CAD).

2 From March 1997–April 2001, 310 individuals who underwent coronary angiography at the authors' institution met the inclusion criteria for the study.

3 These people were divided into two groups according to presence of angina or angina-like chest pain at the time of angiography: asymptomatic (n=56) and symptomatic (167 with unstable angina, 87 with chronic stable angina).

4 Despite the severity of coronary atherosclerosis being similar in asymptomatic and symptomatic individuals, revascularisation was performed significantly less frequently in asymptomatic people ($P<0.001$).

5 Asyptomatic individuals had a similar number of major cardiac adverse events (death, non-fatal MI, revascularisation) as symptomatic people, but had higher cardiac mortality (26 % versus 9 %; $P<0.001$).

6 In those who underwent revascularisation therapy on diagnosis of CAD the rates of major adverse cardiac events and cardiac mortality were similar in both groups ($P<0.05$).

7 The authors conclude that lack of revascularisation may be responsible for the higer cardiac mortality rate in those with asymptomatic CAD.

Choi EK, Koo BK, Kim HS et al (2007) Prognostic significance of asymptomatic coronary artery disease in patients with diabetes and need for early revascularization therapy. *Diabetic Medicine* **24**: 1003–11