Key studies in diabetes and coronary heart disease research

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Introduction

Much research has been conducted in the last decade providing the rationale for the management of patients with diabetes and coronary heart disease. This article offers a brief synopsis of some of the more important clinical trials, both completed and ongoing, looking at the who, why, when, where and how the evidence was obtained that underpins current medical research.

Evidence based is a term that trips off the tongues of all healthcare professionals but how often do we give a passing thought to the source of our evidence? What is the evidence that shapes our decisions? Why, where, when and how was it obtained? If you are a hard pushed GP or nurse in primary care who has hardly enough time to read weekly journals let alone lengthy, academic and often obscure study reports, then read on. I am going to provide a brief overview of some of the major studies, completed and current, that have provided us with the evidence to make changes to the way we treat and care for people with diabetes and coronary heart disease.

The United Kingdom Prospective Diabetes Study (UKPDS)

In the UKPDS, 5000 people who had been newly diagnosed with type 2 diabetes were monitored for 10 years (UKPDS, 1998a; 1998b; 1998c). This study was a 20 year longitudinal study – the largest ever conducted – in 23 centres across England, Scotland and Northern Ireland. The purpose of the study was many fold, but one objective was to ascertain if microvascular and macrovascular complications could be reduced by appropriate treatment. People who had been newly diagnosed with type 2 diabetes were divided into two groups: intensive treatment and conventional treatment. Results showed conclusively that intensive glycaemic control reduced eye complications by 25% and early renal complications by a third. Tight blood pressure control reduced risk of death from vascular complications, i.e. myocardial infarction (MI)/stroke by a third.

The outcome of the UKPDS has had a big impact on our attitude to type 2 diabetes. It has demonstrated that appropriate treatment can reduce the incidence of life threatening complications. The UKPDS has also shown that blood pressure and glycaemic control from the time of diagnosis is of paramount importance. Type 2 diabetes should not be thought of as mild, but as a progressive condition requiring close monitoring and follow-up.

The increased importance and emphasis on good diabetes care has fallen to a great extent in the lap of the primary care team, from the setting up of the diabetic 'mini' clinics of yore through to the NSF of today. There have been many offshoots along the way, such as specialised diabetes training for practice nurses and patient-led services. According to the UKPDS, blood pressure control is at least as important as glycaemic control in prevention of complications. The recommended blood pressure level is 140/80 mmHg or below. An HbA_{1c} level of 7.0% and a preprandial blood glucose of 4–7 mmol/l is the aim of glycaemic control.

Diabetes Prevention Program

The Diabetes Prevention Program (1994-2001) studied 3234 people with impaired glucose tolerance (IGT), but who did not have diabetes (Knowler et al, 2002).

ARTICLE POINTS

1 This article attempts to clarify what the evidence is that shapes our decisions and why, where, when and how this evidence is obtained.

2 An overview of the major studies that have provided us with evidence to make changes in the way we treat diabetes is presented.

3 The work of NICE and the standardisation of care under the umbrella of the National Service Frameworks would not be possible without the evidence base that is underpinned by the studies.

4 These landmark studies have had a profound effect on the prevention and treatment of diabetes and coronary heart disease.

5 Clinical trials are crucial to our future health and well-being.

KEY WORDS

- **Evidence based**
- **Major studies**
- **Coronary heart disease**
- **Myocardial infarction**
- **ACE inhibitors**

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PAGE POINTS

1 The Diabetes Prevention Program demonstrated the importance of lifestyle changes, exercise and weight control for people with diabetes.

2 Exercise and weight control has become the cornerstone of advice given by practice nurses and GPs to help prevent type 2 diabetes and coronary heart disease in at-risk groups.

3 Treatment with a statin is now mandatory post MI, in the absence of contraindications, in accordance with guidelines from the National Institute of Clinical Excellence.

4 The CARE study confirmed the place of statins in secondary prevention even in patients who do not have raised serum cholesterol.

Participants ranged in ages from 25–85 years, and 50% of participants were from non-Caucasian ethnic groups. There were 27 participating centres across the USA.

The trial finished early, having answered the main research question which was: would modifying lifestyle or administration of metformin delay or prevent the development of diabetes? Participants were randomly allocated to intensive lifestyle modification, 1.7 g of metformin daily or placebo. The results showed that both interventions were successful. Lifestyle intervention and metformin reduced the risk of diabetes by 58% and 31%, respectively.

The Diabetes Prevention Program demonstrated the importance of lifestyle changes, exercise and weight control for people with diabetes; this has become the cornerstone of advice given by practice nurses and GPs to help prevent type 2 diabetes and coronary heart disease in at-risk groups. Close collaboration with leisure centres and health centres running activity events and 'exercise on prescription' has been introduced in some areas.

Studies on the effects of lipids

The following studies looked at the use of statins with view to secondary and primary prevention.

Scandinavian Simvastatin Survival Study (4S)

The 4S study investigated 4444 men, aged between 35 and 70 years, with a history of angina or MI and with serum baseline cholesterol levels > 5.5 mmol/l (The Scandinavian Simvastatin Study Group, 1994). It ran from 1988–94 in 94 centres across Scandinavia. The 4S study was groundbreaking in that it was the first study of its kind to show a positive outcome.

The study was designed to test the hypothesis that raised serum cholesterol is associated with coronary atherosclerosis and consequent sequelae, and that treatment with a statin to lower cholesterol would improve survival rates in patients with coronary heart disease. Participants were randomly assigned to 40 mg simvastatin or placebo. The doses were adjusted with the aim of achieving the target serum lipid level (3.5–5.2 mmol/l). There was intensive follow-up for 18 months and 6 monthly thereafter for an average of 5 years.

The results showed a reduction in overall mortality by 30%, coronary heart disease mortality by 42%, and non-fatal MI by 37% in comparison with placebo. This was clear evidence for the benefit of lowering cholesterol in patients with previous MI/angina, i.e. the benefits of secondary prevention. The benefits on mortality rates were also shown to be cumulative over time.

Treatment with a statin is now mandatory post MI, in the absence of contraindications, in accordance with guidelines from the National Institute of Clinical Excellence (NICE, 2001).

Cholesterol and Recurrent Events Trial (CARE)

Another important lipid trial studied 4159 patients aged 21–75 years with a previous MI and average low density lipoprotein (LDL) levels of 3.0–4.5 mmol/l (Sacks et al, 1996). The CARE study was carried out at 80 centres in Canada and the USA (between 1989 and 1996) to test the hypothesis that high levels of LDL are a predictor of recurrent coronary events in patients with coronary heart disease and to look at the benefit of lowering cholesterol in patients with normal cholesterol levels.

This double-blind randomised placebo-controlled trial tested 40 mg pravastatin daily versus placebo. In the group treated with pravastain there was: a 28% reduction in LDL; a 25% relative risk reduction of having another coronary event; a 32% relative risk reduction of the need for angioplasty or coronary artery bypass grafting; and a 31% reduced risk of a stroke. The benefit was greater in women than men. This study confirmed the place of statins in secondary prevention even in patients who do not have raised serum cholesterol.

The Heart Protection Study

The Heart Protection Study assessed 20 000 people aged between 40 and 80 years of age who were at increased risk of heart disease in 69 UK hospitals between 1994 and 1997 (The Heart Protection Study Collaborative Group, 2002). Researchers studied the impact of cholesterol lowering therapy and

antioxidant vitamin supplements in patients at high risk. In this randomised placebo controlled trial, the effects of 40 mg simvastatin versus placebo were compared. Within each group, half received antioxidant vitamins (vitamin E, C and ß-carotene) and half were given placebo.

Results showed that 5 years of treatment with the statin prevented major vascular events in 100 of every 1000 people with previous MI and 70 out of every 100 people with diabetes There was no significant benefit in the group given vitamins.

The Heart Protection Study demonstrated that cholesterol lowering with a statin reduces risk of MI and stroke by a third as well as reducing need for angioplasty, arterial surgery and amputation. Statin use significantly reduces risk of major vascular events in men and women, the elderly, people with a previous stroke, people with diabetes and those with known heart disease.

Statins are now widely prescribed to these groups. The Heart Protection Study also showed a benefit for people with a normal cholesterol level, and that prior measurement before giving a statin is redundant, although adequate liver function should be established.

West of Scotland Coronary Prevention Study (WOSCOPS)

Close on the heels of the 4S study, the WOSCOPS investigated 6595 men between the ages of 45 and 64 years with moderately elevated LDL, who had not had a previous MI, but who were at risk (Shepherd et al, 1995). It was based in the West Coast of Scotland in a population, mostly served by centralised primary care from 1989–96.

The purpose of this study was to look at the effect of a cholesterol lowering medication on the risk of cardiovascular death in people with no history of cardiovascular disease. This 5 year follow-up study compared 40 mg pravastatin and placebo in a randomised double blind trial.

The study showed that in the group treated with pravastatin, those with high cholesterol had a 31% risk reduction of a first MI, and a 22% reduction in all-cause mortality. There was also a 20% reduction in total cholesterol, a 26% reduction in LDL and a 12% reduction in triglycerides. Overall, pravastatin reduced the incidence of a first MI in men who were at risk by almost a third, and gave compelling evidence for the use of statins in the primary prevention of MI in at-risk patients in general practice.

Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)

In the PROSPER study, 5804 elderly people, between the ages of 75 and 82 years who had or who were at risk of pre-existing vascular disease, and with an average baseline total cholesterol of 5.4 mmol/l were monitored for a mean duration of 3.2 years, in centres in Scotland, Ireland and Holland (Shepherd et al, 2002).

This study was devised to test the hypothesis that treatment with pravastatin can reduce the risk of coronary heart disease death, MI or stroke in high-risk elderly people. All patients were given dietary and smoking advice, and randomly allocated to groups either receiving 40 mg pravastatin or placebo. This was the first study of this kind to include a majority of women in the cohort. The findings showed a relative risk reduction of morbidity and mortality from coronary heart disease and strokes by 15%.

Thus, the benefits gained by the use of a statin, previously observed in the younger age group, can be extended to the elderly population.

Studies with ACE inhibitors

The following two studies look at primary prevention with angiotensin converting enzyme (ACE) inhibitors.

Heart Outcomes Prevention Evaluation Study (HOPE)

The HOPE trial recruited 9297 high-risk patients aged 55 years or over with vascular disease or diabetes plus at least one other cardiovascular risk factor (The HOPE study investigators, 2000). It was a 5-year study at 267 centres in 19 countries, although it was stopped a year early due to the evidence strongly supporting a favourable outcome in the group treated with ramipril. The researchers wanted to know if ACE inhibitors and/or vitamin E can reduce the incidence of death, MI and stroke in a broad range of high-risk patients. Clinical observations had indicated that there was such an effect in patients who had been treated with ramipril

PAGE POINTS

1 The Heart Protection Study demonstrated that cholesterol lowering with a statin reduces risk of MI and stroke by a third as well as reducing need for angioplasty.

2 The WOSCOPS gave compelling evidence for the use of statins in the primary prevention of MI in at-risk patients in general practice.

3 The PROSPER study was the first study of this kind to include a majority of women in the cohort.

4 The benefits gained by the use of a statin, previously observed in the younger age group, can be extended to the elderly population.

for hypertension.

The randomised double-blind placebo controlled trial used 10 mg ramipril daily versus placebo. Both groups were also assigned to 400 IU vitamin E daily or placebo. The outcome was a 22% reduction in incidence of non-fatal MI, stroke and death from coronary heart disease in the ramipril group. Individually, this was a 32% risk reduction for stroke, a 20% reduction for MI and a 26% reduction in risk of death from coronary heart disease that could not be explained by the hypotensive effect alone. Vitamin E, however, had no significant effect. Ramipril significantly reduced mortality and morbidity in people at high risk of cardiovascular events.

An interesting ad hoc finding, which needs to be investigated prospectively is that there was a lower incidence (33%) of the development in those with type 2 diabetes and who received ramipril (see DREAM study). So convincing were the results that an ACE inhibitor is now prescribed for people in high-risk groups, such as those with diabetes who otherwise have no confirmed history of cardiovascular disease.

Studies currently in progress

The two studies outlined below are typical of the trend to study more than one treatment concurrently with placebo.

Diabetes Reduction Approaches with Medications Study (DREAM)

Recruitment for the DREAM study commenced in July 2001 and will end in 2003. A total of 4000 people with impaired glucose tolerance will be followed for 3 years. In the wake of the HOPE study, researchers want to test the hypothesis that ramipril can prevent type 2 diabetes in high-risk groups. Rosiglitazone had previously been shown to be beneficial in reducing insulin resistance, an underlying cause of type 2 diabetes. The treatment groups are: ramipril versus placebo and rosiglitazone versus placebo in a 2 x 2 factorial way. There will be 6 monthly follow-up to monitor glucose intolerance and the development of diabetes.

The possibility of pharmacological prevention of type 2 diabetes in at-risk patients will have a huge impact on a disease that is dramatically increasing each year to an estimated 221 million people worldwide by 2010 (Amos et al, 1997).

Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR)

Recruitment for the NAVIGATOR study is in progress across 40 countries, involving 7500 people with impaired glucose tolerance and at increased risk of cardiovascular disease. It is a double-blind placebo controlled trial with 60 mg nateglinide before meals versus placebo and 160 mg valsartan daily versus placebo in a 4-way mix to see if either can prevent or delay the onset of type 2 diabetes/ coronary heart disease. Recent early studies have shown that nateglinide enhances early insulin secretion and reduces postprandial blood glucose levels. This in turn may normalise glucose tolerance and prevent the onset of diabetes.

Again, like the DREAM study a positive outcome may have huge benefits for the prevention of these diseases in the future.

Conclusion

These landmark studies have had profound effect on the prevention and treatment of diabetes and coronary heart disease, and the results of those in progress are eagerly awaited. Such large-scale studies have spin off sub studies for many years afterwards, providing more evidence to further our knowledge of prevention and refine our treatments.

The work of NICE and the standardisation of care under the umbrella of the National Service Frameworks would not be possible without the evidence base that is underpinned by these studies. Increasingly, more sophisticated studies and meta-analyses of previous studies are adding weight to our already large body of evidence. Such time and effort on the part of the investigators and the patients who are willing to participate in clinical trials are crucial to the future economy as well as the health and well-being of our patients. ■

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