# Diabetes information in cardiovascular trials published in general medical journals

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## Introduction

**Individuals with diabetes have an increased risk of developing coronary artery disease[1,2] and a poorer prognosis once coronary artery disease has developed, compared to patients without diabetes.[3] To avoid confounding, most cardiovascular trials display profiles of traditional risk factors but additional factors are also important in patients with diabetes. We examined the information provided on patients with diabetes included in cardiovascular trials published in general medical journals.**


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## Methods

Randomised controlled trials examining 'hard' cardiovascular end points or surrogates of cardiovascular disease were identified from four general medical journals (*BMJ, JAMA, The Lancet* and the *New England Journal of Medicine*) published during 2004. We assessed whether the following information pertaining to diabetes was documented, i) percentage of patients with diabetes, ii) type of diabetes, iii) duration, iv) assessment of control e.g. $HbA_{1C}$, v) presence of complications, and vi) anti-hyperglycaemic treatment.

## Results

We identified 35 suitable trials (see table 1), with a mean patient number of 3,432 (range 27–20,536), and a mean percentage of patients with diabetes of 25% (range 4.7–100%). One trial exclusively involved patients with type 2 diabetes.[4] All 35 trials documented the percentage of patients with diabetes but only one trial noted the type of diabetes. Similarly, disease duration, assessment of control and/or complications were each documented in one of the 35 trials, although in two further trials some assessment of diabetic control was made, as patients with 'poorly controlled diabetes' were excluded. Seven trials (20%) included information on current antidiabetic treatment, although this was often limited to whether insulin was required.


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## Discussion

### Type 1 versus type 2 diabetes

These results indicate that little attempt is made to distinguish between patients with diabetes recruited into trials published in general medical journals.

### Glycaemic control

The Diabetes Control and Complications Trial (DCCT)[5] and the United Kingdom Prospective Diabetes Study (UKPDS)[6] demonstrated the significance of improved glycaemic control on the incidence of microvascular complications in type 1 and 2 diabetes, respectively. There is now increasing evidence to support associated reductions in macrovascular disease.

Seventeen years following the completion of the DCCT, a highly significant reduction in cardiovascular events has now been found in the intensive treatment group. Risk of non-fatal myocardial infarction (MI), stroke or death from cardiovascular disease was reduced by 57% (p=0.02).[7] The UKPDS just failed to reach significance for reduction in MI (p=0.052) with improved glycaemic control,[6] although the difference in $HbA_{1C}$ between the two treatment groups was less impressive than for the DCCT. A recent meta-analysis, incorporating the above trials, concluded that glycaemic control is an independent risk factor for the development of macrovascular disease in both type 1 and 2 diabetes.[8]

### Microvascular complications

Microvascular complications precede the development of macrovacular disease in type 1 diabetes, whereas patients with type 2 diabetes may have complications present at the time of diagnosis. Microalbuminuria acts as a strong predictor of cardiovascular disease and mortality in patients with type 1 diabetes,[9] even in those with long-standing disease.[10] Similarly, increased urinary albumin excretion is an independent predictor of cardiovascular morbidity and mortality in type 2 diabetes, as well as in the general population,[11] since it acts as a marker of generalised endothelial dysfunction. Blockade of the renin-angiotensin system reduces both the rate of progression of renal and cardiovascular disease in patients with diabetes, which may relate to mechanisms other than blood pressure lowering.[12]

**Table 1.** Information documented on patients with diabetes included in cardiovascular trials published in four general medical journals during 2004

| Journal | *JAMA* | *N Engl J Med* | *Lancet* | *BMJ* | Total |
|---|---|---|---|---|---|
| Number of trials per journal | 14 | 10 | 8 | 3 | 35 |
| Number of trials fulfilling assessment criteria (%) | | | | | |
| - number of patients with diabetes | 14/14 (100) | 10/10 (100) | 8/8 (100) | 3/3 (100) | 36/36 (100) |
| - type of diabetes | 0/14 (0) | 0/10 (0) | 1/8 (12.5) | 0/3 (0) | 1/36 (2.8) |
| - duration | 0/14 (0) | 0/10 (0) | 1/8 (12.5) | 0/3 (0) | 1/36 (2.8) |
| - assessment of control | 0/14 (0)* | 0/10 (0) | 1/8 (12.5) | 0/3 (0) | 1/36 (2.8) |
| - assessment of complications | 0/14 (0) | 0/10 (0) | 1/8 (12.5) | 0/3 (0) | 1/36 (2.8) |
| - antidiabetic treatment | 1/14 (7.1) | 4/10 (40) | 2/8 (25) | 0/3 (0) | 7/36 (19) |

**Key:** * An exclusion criterion in two trials was poorly controlled diabetes

## Duration of diabetes

Type 1 diabetes tends to present acutely, whereas the onset of type 2 diabetes tends to be insidious. Longer duration of diabetes implies prolonged exposure to chronic hyperglycaemia, and an increased risk of developing hypertension, dyslipidaemia and microalbuminuria, and has been shown to influence cardiovascular risk in both type 1 and type 2 diabetes.[13-15]

## Antidiabetic treatment

There is increasing evidence of cardiovascular benefits with insulin sensitisation. In the UKPDS, a cohort of 342 obese patients receiving metformin monotherapy had a 39% risk reduction for MI (p=0.01) and a 36% reduction in all-cause mortality (p=0.011), which could not be explained by improved glycaemic control alone.[16] Furthermore, the recently published Prospective Pioglitazone Clinical Trial in Macrovascular Events Study (PROactive) was a large, placebo-controlled trial of pioglitazone 'add on' therapy in high-risk patients with type 2 diabetes. The primary end point was not achieved but a significant reduction in the pre-specified secondary composite end point of all-cause mortality, non-fatal MI and stroke was observed.[17]

## Conclusions

Our results confirm that large numbers of patients entered into cardiovascular trials have diabetes (approximately 25%), but suggest that insufficient information regarding them is provided. Possible explanations include space limitations, insufficient patient numbers to be relevant or, more simply, these factors may not be considered when designing the trial. Alternatively, there may be plans to publish the subset of data for patients with diabetes separately.

Given the increasing prevalence[18] and associated burden of cardiovascular disease, the number of patients with diabetes recruited into cardiovascular trials can be expected to increase. Additional risk factors contribute to cardiovascular risk in diabetes, and these should be assessed in trials including significant numbers of patients with diabetes.

### Key messages

- Individuals with diabetes have increased cardiovascular risk and have a poorer prognosis once cardiovascular disease has developed
- Large numbers of patients with diabetes are recruited into cardiovascular trials but insufficient information is published on this subgroup
- Additional risk factors contribute to cardiovascular risk in diabetes



## Conflict of interest

MF has received fees for speaking and advisory panels from Takeda. DM and KP report no conflict of interest.

## References


1. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA* 1979;**241**:2035-8.
2. Laing SP, Swerdlow AJ, Slater SD *et al*. The British Diabetic Association Cohort Study II: cause-specific mortality in patients with insulin-treated diabetes mellitus. *Diabet Med* 1999;**16**:466-71.
3. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993;**16**:434-4.
4. Colhoun HM, Betteridge DJ, Durrington PN *et al*. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;**364**:685-96.
5. The Diabetes Control and Complications Trial (DCCT) Research Group. Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. *Am J Cardiol* 1995;**75**:894-903.
6. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;**352**:837-53.
7. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;**353**:2643-53.

8. Selvin E, Marinopoulos S, Berkenblit G *et al*. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Int Med* 2004;**141**:421-31.
9. Deckert TH, Yokoyama E, Mathiesen B *et al*. Cohort study of predictive value of urinary albumin excretion for atherosclerotic vascular disease in patients with insulin dependent diabetes. *BMJ* 1996;**312**:871-4.
10. Arun CS, Stoddart J, Mackin P, MacLeod JM, New JP, Marshall SM. Significance of microalbuminuria in long-duration type 1 diabetes. *Diabetes Care* 2003;**26**:2144-9.
11. Hillege HL, Fidler V, Diercks GF *et al*. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 2002;**106**:1777-82.
12. Lindholm LH, Ibsen H, Dahlof B *et al*. for the LIFE study group. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;**359**:1004-10.
13. Fox CS, Sullivan L, D'Agostino Sr RB, Wilson PWF. The significant effect of diabetes duration on coronary heart disease mortality: The Framingham Heart Study. *Diabetes Care* 2004:**27**:704-08.
14. Spijkerman AMW, Dekker JM, Nijpels G *et al.* Impact of diabetes duration and cardiovascular risk factors on mortality in type 2 diabetes: The Hoorn Study. *Eur J Clin Invest* 2002;**32**:924-30.
15. Weis U, Turner B, Gibney J *et al*. Long-term predictors of coronary artery disease and mortality in type 1 diabetes. *Q J Med* 2001;**94**:623-30.
16. UK Prospective Diabetes Study (UKPDS) Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;**352**:854-65.
17. Dormandy JA, Charbonnel B, Eckland DJA *et al*. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005;**366**: 1279-89.
18. Wild S, Roglic G, Green A, Sicree R, King H. Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004;**27**:1047-53.