1 Epidemiology of Vascular Disease in Diabetes

Susan Laing

1.1 Introduction

Mortality rates in people with diabetes exceed those in the general population despite many recent improvements in care. Diabetes is one of the most common chronic diseases in the young, and is a substantial cause of morbidity as well as mortality at all ages. After the introduction of insulin in 1922 it was hoped that adverse consequences of diabetes might become a thing of the past, but mortality rates are still higher than those in the general population and, in addition, the late complications of diabetes, in particular cardiovascular disease (CVD), have been unmasked (Kessler, 1971; Dorman et al., 1984; Orchard et al., 1990). The St Vincent declaration of 1989, pledged by representatives of European government health departments, patient organizations and diabetes experts, set targets for improving the outlook for people with diabetes. It urged health departments throughout Europe to work towards a reduction in the heavy burden of disease in these patients by better recognition and treatment in the early stages and reduction of long-term complications. Determining the success of these health initiatives requires accurate measurement of morbidity and mortality rates, country by country.

1.2 The Role of Epidemiological Studies

Epidemiological studies are the best means by which these outcomes, and changes in these outcomes, can be measured. Epidemiology is concerned with events that occur in populations rather than separate individuals, and it is this that differentiates epidemiology from clinical medicine. Epidemiological studies are concerned not only with people who get a disease, or in this case those people with diabetes who develop cardiovascular complications, but also with those who do not, and in particular how
the two groups differ. Initially epidemiological studies can be used to measure and
describe the occurrence of CVD in patients with diabetes and how it differs between
males and females, between different age- or socio-economic groups or between
geographical regions. Secondly, epidemiological studies are concerned with how these
measurements vary over time, or following the introduction of a new treatment. Finally,
by measuring cardiovascular risk factors as well as the disease itself, these studies can
be used to address the question ‘why?’ Why do some people with diabetes develop
serious cardiovascular complications while others do not? Is it possible to identify
factors (biological, environmental or lifestyle) that are associated with an increased
likelihood of developing cardiovascular complications?

Epidemiological studies may measure mortality, morbidity or both, but the studies
measuring mortality tend to be larger. Smaller studies are ideal for tracking morbidity
as it is possible to do frequent out-patient assessments of each patient and note the
development of complications of diabetes, or any changes in symptoms, as they occur.
Regular measurements of possible risk factors can also be made.

Patients with diabetes cannot always be identified from routine death certificates
as diabetes is frequently not recorded on the death certificate, and therefore death
certificates alone cannot be used to pick out the diabetic study group. Thus national
mortality statistics will underestimate the true death rates (Andresen et al., 1993), and
instead a cohort study is the method of choice for assessing mortality. A group or
‘cohort’ of people with diabetes is gathered together, often from a number of different
sources, and registered centrally. When the patient dies the research group is notified
and receives a copy of the death certificate. The death certificate can then be used
to indicate the fact and cause of death, independent of whether or not diabetes is
mentioned. This chapter will be mainly confined to mortality studies because it was
as a consequence of studies of this type that CVD was first recognised as the principal
complication of people with diabetes.

1.3 Cohort Studies of People with Diabetes

The Framingham study, which has provided the foundation for so much of
cardiovascular epidemiology over the past five decades, was one of the first to follow
people with diabetes over time. From 1948 onwards over 5000 residents from the town
of Framingham in Massachusetts were followed-up for mortality and morbidity. A
cohort of people with diabetes was a subgroup of this population (Garcia et al., 1974;
Kannel and McGee, 1979). About the same time a cohort of over 21 000 people with
diabetes was also being followed-up from the Joslin Clinic in Boston (Kessler, 1971).
Both of these cohort studies began within a decade or so of the introduction of insulin,
and both studies reported a significant excess risk of death from CVD in patients with
diabetes.

Early studies rarely distinguished between patients with type 1 and type 2 diabetes.
A recent meta-analysis (Kanters et al., 1999) was conducted to determine an estimate of
mortality and the incidence of CVD events. Of the 27 studies that allowed calculations
of at least one of the outcomes, only two were restricted solely to patients with type
1 diabetes, eleven to patients with type 2 diabetes and of the remainder only one
distinguished between type 1 and type 2. It is not surprising that the majority of
the studies concern patients with type 2 diabetes (Barret-Connor et al., 1991; Manson et al., 1991; Stamler et al., 1993; Muggeo et al., 1995) as this condition is the most prevalent type of diabetes and accounts for 90% of all diagnoses (Nathan et al., 1997). In addition, as it is primarily a condition of older people and is often associated with, or preceded by, the detection of CVD risk factors, it is comparatively straightforward to follow this group for subsequent CVD events. Type 1 diabetes is less frequent, occurs at an earlier age and is rarely accompanied by any co-existent CVD risk factors at the time of diagnosis.

**Type 1 diabetes**

Cohort studies of patients with type 1 diabetes are rarely large unless they are compiled from more than one centre. The earliest report of patients with type 1 diabetes alone was from Pittsburgh in 1972 (Sultz et al., 1972) and since then there have been a number of further studies published from Pittsburgh, including a cohort study of 1966 patients with type 1 diabetes in 1984 (Dorman et al., 1984; Krolewski et al., 1987; Lloyd et al., 1996a). There have also been a number of studies of a similar size from Scandinavian countries (Deckert et al., 1979; Borch-Johnsen et al., 1986; Lounamaa et al., 1991; Laakso and Kuusisto, 1996).

To date, the largest study of patients with type 1 diabetes has come from the UK (Laing et al., 1999a, 1999b). The Diabetes UK Cohort Study (formerly British Diabetic Association Cohort Study) has followed over 23 000 patients with insulin-treated diabetes, recruited from separate registers across the UK. Both prevalent and incident cases were recruited. All had been diagnosed under the age of 30 years and were treated with insulin, and were therefore presumed to have type 1 diabetes. The first patients were recruited into the study in 1972, and recruitment continued until 1993. Although insulin treatment rather than evidence of absolute insulin deficiency was the criterion for inclusion, this cohort was considered to be essentially one of patients with type 1 diabetes. From the age-specific percentages of diabetic patients with type 1 diabetes (Laakso and Pyorala, 1985) it was estimated that at least 94% will have had type 1 diabetes.

A few international studies have compared complications and outcomes between countries. A four-country comparative study run by the Diabetes Epidemiology Research International Study Group has followed patients with type 1 diabetes from the USA, Finland, Israel and Japan (Diabetes Epidemiology Research International Study Group, 1995), and the WHO Multinational Study of Vascular Disease in Diabetes (which follows patients with both type 1 and type 2 diabetes) continues to report from 10 centres worldwide (Fuller et al., 2001; Morrish et al., 2001).

As it is more usual nowadays to distinguish between the two types of diabetes rather than group them together, it is tempting to draw comparisons. However, there are a number of difficulties in comparing studies of patients with type 1 and type 2 diabetes. Factors that must be taken into consideration include the relative ages of the two groups, the calendar period during which the data were collected, the endpoint chosen, together with the measurement used, and the population from which the cohort was selected.

As the patients with type 2 diabetes are diagnosed at an older age, usually over 45 years, there are very few age-specific studies of these patients and the patients are
generally grouped together. As mortality is known to vary with age a comparison of type 1 and type 2 patients without any reference to age group would be flawed. To complicate things further, in a number of the type 1 studies there may be insufficient numbers to subdivide by age. Mortality is also known to vary with calendar period as lifestyles change or medical treatments improve and it would be difficult to draw any comparisons between results from two studies conducted 20 or 30 years apart. Studies may also differ in the type of endpoint that is measured, for example some may report mortality, others morbidity or a combination of the two. In addition these may be reported as a rate, a proportion, or a ratio relative to the underlying general population. The variation in mortality between countries further complicates international comparisons.

Despite these difficulties, it is only by drawing comparisons that the similarities and differences in CVD risk between type 1 and type 2 diabetes can be understood, which in turn might lead to a better understanding of the mechanisms by which CVD complications develop.

1.4 Cardiovascular Disease and Diabetes

Diabetes, both type 1 and type 2, is increasing in prevalence and it is estimated that three million individuals in the UK will have type 2 disease by 2010 (Gale, 2002; Fisher, 2003). Overall the numbers of people with type 2 far exceed those with type 1 and, in addition, they are usually middle aged or elderly and often present with concomitant CVD risk factors. However, comments such as ‘Diabetes mellitus, and particularly non-insulin dependent diabetes mellitus increases the risk for all manifestations of vascular disease’ (Laakso, 1998) and ‘CVD complications occur more often in patients with NIDDM than in patients with IDDM’ (Laakso and Lehto, 1997) can easily be misconstrued. Epidemiological studies measure outcome in a number of different ways. While absolute numbers can be counted, other measurements, adjusted for the size of the group, are more commonly used. For example, a rate (of an event) can be calculated as the number of such events per 100 000 people per year. Another commonly used epidemiological measure is the standardised mortality ratio (SMR), which is calculated as the number of observed deaths in the study population compared with the number of deaths that would be expected if general population rates, allowing for the size and age distribution of the study group, were applied. Once the smaller numbers and younger age distribution of people with type 1 diabetes have been taken into account, comparisons can be made.

A direct comparison of all-cause mortality, matched for age, calendar period and country, was made in the WHO Multinational Study (Head and Fuller, 1990). They studied mortality among 4740 diabetic men and women, aged 35–55 years, from 10 centres around the world and they calculated age-adjusted death rates, by centre, separately for type 1 and type 2 diabetes. Death rates for patients with type 1 diabetes were almost always higher than for the corresponding type 2 group.

Standardised mortality ratios, which take into account the underlying mortality in the general population, can also be compared. All-cause mortality in middle-aged and elderly patients with type 2 diabetes is generally 2–4 times higher than the mortality in the general population (Manson et al., 1991; Moss et al., 1991; Muggeo et al., 1995).
1.4 CARDIOVASCULAR DISEASE AND DIABETES

The Diabetes UK Cohort Study (Laing et al., 1999a), of patients with type 1 diabetes, reported an overall SMR of 2.7 for men and 4.0 for women. However, at younger ages in type 1 studies the SMRs for all cause mortality are higher, partly reflecting the much lower mortality in the general population in this age group, with SMRs for the under 40s from Pittsburgh being 5.0 for men and 9.3 for women (Dorman et al., 1984). The Diabetes UK Cohort Study reported all-cause SMRs of 3.7 for men and 4.9 for women in the 30–39 age group. In both studies the relative risk of death was higher in the women than men.

Causes of death

All-cause mortality statistics give no clue as to why mortality might be raised. As well as the acute complications of diabetes, such as hypoglycaemia and ketoacidosis, a number of chronic complications are well recognised. Almost all of these relate in some way to micro- or macrovascular disease, and include CVD, nephropathy, neuropathy and retinopathy. Some may feature largely in studies of morbidity but not be a major cause of mortality, for example peripheral arterial disease is a common condition among diabetic patients but is rarely the primary cause of death (Chapter 8). Studies of patients with type 2 diabetes, although not usually subdivided by age, indicate that CVD is the major cause of death in these patients, accounting for as much as 80% of the excess deaths (Blendea et al., 2003). In younger patients the chronic complications of diabetes develop some time after the initial diagnosis.

Data from the Diabetes UK Cohort Study illustrates how the predominant cause of death in people with type 1 diabetes changes with age (Table 1.1). Under the age of 20 the greatest single cause of death was acute complications of diabetes, which accounted for 38% of the deaths in men and 54% of the deaths in women. In males, between the ages of 20 and 39 years, acute complications remained the greatest single cause of death but in females CVD was the cause of the greatest number of deaths even at this young age. By the 40–59 age groups CVD accounted for at least half of all the deaths in patients with type 1 diabetes. This same pattern has been seen in other studies of young people with diabetes (Lounamaa et al., 1991; Moss et al., 1991), acute complications initially being responsible for the greatest number of deaths but CVD complications becoming the predominant cause of death at fairly young ages.

Table 1.1 Cause of death, expressed as a percentage of the total, by age group. Data from the Diabetes UK Cohort Study.

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
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<th>Females</th>
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<tbody>
<tr>
<td></td>
<td>1–19 years</td>
<td>20–39 years</td>
<td>40–59 years</td>
<td>1–19 years</td>
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<td></td>
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<td>20–39 years</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40–59 years</td>
</tr>
<tr>
<td>Diabetes</td>
<td>38</td>
<td>26</td>
<td>7</td>
<td>54</td>
</tr>
<tr>
<td>Renal disease</td>
<td>0</td>
<td>8</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>6</td>
<td>17</td>
<td>61</td>
<td>10</td>
</tr>
<tr>
<td>Other</td>
<td>56</td>
<td>49</td>
<td>23</td>
<td>36</td>
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<td>29</td>
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</table>
Renal disease has previously been identified as a major cause of death in patients with type 1 diabetes. From Pittsburgh (Dorman et al., 1984) it was reported that renal disease was responsible for the majority of deaths in the 20–29 age group of the Pittsburgh morbidity and mortality study, and studies from Denmark suggested that the high relative mortality after 20–30 years’ duration of diabetes was due to the development of proteinuria (Borch-Johnsen et al., 1986). In the Diabetes UK Cohort Study the proportion of deaths due to renal disease was lower than the proportion due to CVD at all ages.

Clearly if mortality and morbidity are to be reduced then the prevention and treatment of CVD must be addressed. Cardiovascular disease itself is a generic term, encompassing many specific components, and can be further divided into peripheral arterial disease, cerebrovascular disease and heart disease as well as other types of vascular disease such as venous disease and aneurysms. Even within these groups further divisions can be made, for example the term ‘heart disease’ includes not only ischaemic heart disease, but also valve disorders, hypertensive heart disease, cardiomyopathy, dysrhythmias and heart failure. Large cohort studies are necessary if separate statistics are to be calculated for the individual components of CVD. A number of studies of patients with type 2 diabetes have calculated these separate statistics, although the results are rarely reported by specific age group, but among the studies of patients with type 1 diabetes the Diabetes UK Cohort Study is alone in being of sufficient size and having sufficient follow-up to examine some of the CVD outcomes separately by age (Laing et al., 2003a, 2003b).

1.5 Mortality from Coronary Heart Disease

Heart disease is well recognised as a chronic complication of diabetes, and is the major cause of morbidity and mortality in patients from middle-age onwards. Type 2 diabetes is associated at the onset with risk factors for heart disease such as hypertension and obesity, raising the question of whether diabetes per se is an independent risk factor for heart disease. Type 1 diabetes is not associated with risk factors for heart disease at the time of diagnosis although these develop later. Both types of diabetes are also characterised by hyperglycaemia and abnormal protein and lipid metabolism (Chapter 2).

The majority of cardiovascular deaths are specifically due to heart disease (Morrish et al., 2001) and it is becoming apparent that heart disease is the major cause of morbidity and mortality at young as well as older ages. Heart disease, however, is such a broad term that unless the conditions included are made clear it is difficult to interpret the results. A number of studies have now specifically reported mortality from coronary heart disease (CHD) using codes according to the International Classification of Diseases.

There is a paucity of age- and sex-specific data for mortality from CHD in patients with type 1 diabetes as most studies are too small for such subdivisions. The Diabetes UK Cohort Study has recently published rates and SMRs for mortality from ischaemic heart disease (IHD) in 10-year age groups and the results are shown for the age groups between 20 and 59 years (Table 1.2). Within each age group the mortality rates for the patients with type 1 diabetes were higher than the corresponding rates for subjects in the general population. The mortality rates in the females were not only higher than
Table 1.2  Mortality from ischaemic heart disease in patients with type 1 diabetes. Data from the Diabetes UK Cohort Study.

<table>
<thead>
<tr>
<th>Age at death (years)</th>
<th>Rate (per 100,000 person-years)</th>
<th>SMR (95% CI)</th>
<th>Rate (per 100,000 person-years)</th>
<th>SMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>20–29</td>
<td>12</td>
<td>11.8 (5.4–22.4)</td>
<td>14</td>
<td>44.8 (20.5–85.0)</td>
</tr>
<tr>
<td>30–39</td>
<td>69</td>
<td>8.0 (5.1–11.9)</td>
<td>84</td>
<td>41.6 (26.7–61.9)</td>
</tr>
<tr>
<td>40–49</td>
<td>537</td>
<td>7.5 (5.6–9.7)</td>
<td>282</td>
<td>18.3 (11.4–27.6)</td>
</tr>
<tr>
<td>50–59</td>
<td>1273</td>
<td>4.4 (3.4–5.7)</td>
<td>551</td>
<td>7.2 (4.5–10.9)</td>
</tr>
<tr>
<td>1–84</td>
<td>107</td>
<td>4.5 (3.9–5.1)</td>
<td>73</td>
<td>8.8 (7.4–10.3)</td>
</tr>
</tbody>
</table>

Figure 1.1  Ischaemic heart disease mortality in patients with type 1 diabetes. Data from the Diabetes UK Cohort Study.

For women without diabetes but were also considerably higher than for men without diabetes (Figure 1.1). In the general population mortality from CHD is higher for men than women at all ages but in the patients with type 1 diabetes there was no difference in mortality under the age of 40 years. The increased vulnerability of the young women is shown by the SMRs. At all ages the SMRs were higher for women than men, and under the age of 40 years the risk of mortality from CHD in women was increased 40-fold. This reflects both the mortality from CHD in these women and the low mortality rates, at younger ages, among women in the general population.

Although there are no age-specific results to compare with the findings reported here, a few studies of patients with type 1 diabetes have reported overall morbidity or mortality from CHD (Manson et al., 1991). The most direct comparison can be made with the results from the population-based study from Wisconsin that recorded SMRs for CHD mortality in a group of 1200 patients diagnosed with diabetes under the age of 30 years, but the results were not subdivided by age (Moss et al., 1991). They reported SMRs for IHD mortality at ages under 60 years of 9.1 for men and 15.4 for women. The exceptionally high SMRs for women in the Diabetes UK Cohort Study were only apparent after finer stratification by age.
In all reports of patients with type 2 diabetes, mortality from CHD was raised compared to the general population, and the relative risks were generally higher in women than men (Manson et al., 1991; Stamler et al., 1993). The data were not usually stratified by age, but there was one study from Scotland that enabled a comparison with the Diabetes UK data (Wong et al., 1991). Not only was this a geographical area covered by the Diabetes UK Cohort Study, but it also specified the age at which the patients died. The SMRs for CHD mortality in the 45–64 age group were 3.7 for men and 5.4 for women. Values for the same age group from the Diabetes UK Cohort Study were 4.7 for men and 7.9 for women. In the absence of epidemiological studies of CHD in young patients with type 2 diabetes, direct comparisons cannot be made for the younger age groups, but it is of interest to note that the relative risk of death from CHD in the type 1 group was much higher at younger ages than at older ages, although the absolute risk remains low at this age.

In some cases it is possible that the high cardiovascular risk is mediated by renal disease, and in the Pittsburgh study there were more deaths certified to renal disease than to CVD among the young patients (Dorman et al., 1984). It has been suggested that ‘in IDDM macrovascular disease usually occurs in the presence of renal complications’ (Laakso, 1998) and data from the American Diabetes Association (1989) suggest that the risk of overall CVD is much higher in type 1 patients with renal disease than in those without. Clearly the interrelationship between nephropathy and CVD is complicated.

As has already been discussed there are many more cases of CVD in patients with type 2 diabetes as it is the most prevalent type of disease and develops at an older age. However, it seems probable from the results shown above that type 1 diabetes confers the greater relative risk of a CVD event in an individual.

1.6 Mortality from Cerebrovascular Disease

Type 1 diabetes

Clinical aspects of stroke disease in people with diabetes are described in Chapter 7. Mortality from cerebrovascular disease is barely mentioned in epidemiological studies of patients with type 1 disease and usually only gets a passing mention in studies of patients with type 2 diabetes (Barrett-Connor and Khaw, 1988; Manson et al., 1991; Moss et al., 1991; Lehto et al., 1996). Cerebrovascular disease is generally manifest in later years and most cohort studies of younger patients do not continue follow-up beyond their 40s. Further, cerebrovascular disease complications are not as frequent as heart disease and many studies will therefore be too small, with too few events, to draw any conclusions. This lack of data has led some to suggest that ‘in the patient with insulin-dependent diabetes mellitus the frequency of stroke and death from stroke is less than in the patient with non-insulin dependent diabetes mellitus’ (Bell, 1994). None the less it is a significant cause of mortality in patients with both types of diabetes, and in the Diabetes UK Cohort Study accounts for 6% of all deaths overall, and 8% of deaths under the age of 40 years (Laing et al., 2003a). A similar proportion, 7% of the total mortality, was reported in a much smaller study of patients with type 1 diabetes by Deckert et al. (1979).
1.6 MORTALITY FROM CEREBROVASCULAR DISEASE

Table 1.3 Mortality from cerebrovascular disease in patients with type 1 diabetes. Data from the Diabetes UK Cohort Study.

<table>
<thead>
<tr>
<th>Age at death (years)</th>
<th>Males</th>
<th></th>
<th></th>
<th></th>
<th>Females</th>
<th></th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Rate (per 100 000 person-years)</td>
<td>SMR (95% CI)</td>
<td></td>
<td></td>
<td>Rate (per 100 000 person-years)</td>
<td>SMR (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–19</td>
<td>2.3</td>
<td>4.6 (0.6–16.5)</td>
<td></td>
<td></td>
<td>2.5</td>
<td>6.1 (0.7–21.9)</td>
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</tr>
<tr>
<td>20–30</td>
<td>10.2</td>
<td>5.2 (2.6–9.2)*</td>
<td></td>
<td></td>
<td>13.8</td>
<td>7.6 (4.0–12.9)*</td>
<td></td>
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</tr>
<tr>
<td>40–59</td>
<td>100.3</td>
<td>4.6 (2.6–7.5)*</td>
<td></td>
<td></td>
<td>101.7</td>
<td>5.1 (2.6–8.9)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–84</td>
<td>458.7</td>
<td>1.7 (0.9–3.0)</td>
<td></td>
<td></td>
<td>548.4</td>
<td>2.8 (1.5–4.7)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–84</td>
<td>18.7</td>
<td>3.1 (2.2–4.3)*</td>
<td></td>
<td></td>
<td>21.1</td>
<td>4.4 (3.1–6.0)*</td>
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</table>

*p < 0.05.

The Diabetes UK Cohort Study of type 1 diabetes has recently published rates and SMRs for mortality from cerebrovascular disease and these are shown in Table 1.3. During the follow-up (an average of 17 years per person) there was a total of 1437 deaths, 80 of which were from cerebrovascular disease. The rates were comparable for men and women at all ages. Overall the rates were raised compared with the general population, though not significantly so at ages 1–19, or in the men aged 60–84 years. In the 20–39 age group the risk of cerebrovascular mortality was increased more than fivefold in men and more than sevenfold in women. There are no other studies of cerebrovascular mortality rates by age and sex in patients with type 1 diabetes, probably because available studies have not been large enough or had sufficient follow-up. Other studies have either calculated risks of combined fatal and non-fatal cerebrovascular events (Manson et al., 1991) or calculated risks of cerebrovascular mortality based on only a few deaths (Moss et al., 1991).

Type 2 diabetes

One of the earlier reports of the increased risk of stroke in patients with type 2 diabetes was from Framingham (Garcia et al., 1974), which indicated an increased risk for stroke of 2.4 in both men and women. Other studies, of mortality, have reported SMRs similar to those in the 60–84 age group of the Diabetes UK Cohort Study and it is interesting to note that these studies have also failed to demonstrate a significantly raised risk for men, although they have demonstrated a raised risk for women. Results from the Joslin Clinic (Kessler, 1971) reported SMRs for cerebrovascular mortality of 1.1 in men and 1.2 in women, with equivalent SMRs of 1.8 and 2.2 from the Wisconsin Study (Moss et al., 1991) and 1.7 and 2.6 from the Rancho Bernardo Study (Barrett-Connor and Khaw, 1988). Those studies that have included younger patients with type 2 diabetes have indicated higher risks, with a significant increase in risk for both men and women. The MRFIT study (Neaton et al., 1993) of men aged predominantly under 60 reported an SMR of 2.7 and the Nurses Health Study (Manson et al., 1991) of similarly aged women reported an SMR of 5.0.
Table 1.4 Risk of mortality from haemorrhagic and non-haemorrhagic stroke. Data from the Diabetes UK Cohort Study.

<table>
<thead>
<tr>
<th>Age at death</th>
<th>Haemorrhagic</th>
<th>Non-haemorrhagic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of deaths</td>
<td>SMR (95%CI)</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–39</td>
<td>5</td>
<td>2.3 (0.7–5.3)</td>
</tr>
<tr>
<td>40–84</td>
<td>3</td>
<td>1.1 (0.2–3.2)</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–39</td>
<td>4</td>
<td>2.4 (0.6–6.0)</td>
</tr>
<tr>
<td>40–84</td>
<td>6</td>
<td>2.5 (0.9–5.4)</td>
</tr>
</tbody>
</table>

*P < 0.05.

The risk of mortality from cerebrovascular disease has been shown in the MRFIT study to be only associated with ischaemic, non-haemorrhagic stroke, but there was no increased risk of death from subarachnoid or intracranial haemorrhage (Neaton et al., 1993). Similar findings have now been shown for type 1 diabetes. The death certificates for those people who had died from cerebrovascular disease in the Diabetes UK Cohort Study were examined further to determine whether the death had occurred as a result of a haemorrhagic or non-haemorrhagic incident. Of the 80 deaths, 50 could be classified as non-haemorrhagic, 18 as haemorrhagic and the remaining 10 were excluded as there was not sufficient information on the death certificate for classification. These groups were analysed separately (Table 1.4). The risk of death from non-haemorrhagic stroke was high, especially in the under 40 age group where it was increased 18-fold in men and 35-fold in women. The risk of mortality from haemorrhagic stroke, whilst higher than for the general population, was not significantly increased but the numbers were too small to draw any firm conclusions. Although it was not possible to be certain about the exact nature of the non-haemorrhagic deaths from the death certificates, it seems probable that many of these deaths were ischaemic in origin.

As we have already noted for CVD in general, the absolute number of people with diabetes dying from cerebrovascular disease will always be higher in type 2 diabetes because this is the predominant form of diabetes among older people and cerebrovascular disease is related to age. However, at younger ages the Diabetes UK Cohort Study has demonstrated that risks of cerebrovascular mortality, relative to the general population, are raised, especially for those deaths likely to be ischaemic in origin, and although the risks are not so high in the older age groups they remain very comparable to the risks seen in patients with type 2 diabetes.

1.7 Discussion

Appraisal of epidemiological studies

Since the early days of Framingham, epidemiological studies have played an essential role in the recognition of cardiovascular complications in diabetes. Not long after the introduction of insulin, just as it was hoped that diabetes could be ‘cured’, the
first epidemiological studies indicated that a significant excess mortality was still a feature of these patients. Subsequently, specific pathologies accounting for this raised mortality have been identified, although for the less frequent outcomes these can only be identified by very large studies – even in the Diabetes UK cohort there were still only 80 deaths from cerebrovascular disease from a cohort of over 23,000 patients with type 1 diabetes during a lengthy follow-up.

Epidemiological studies have provided quantification of these deaths, expressing mortality as an absolute number, but also expressing mortality as a rate or a rate ratio (such as an SMR) using a different, usually non-diabetic, group as the denominator. Once mortality is described and quantified, changes over time or between populations can be measured. The larger studies have also been able to report these measures according to specific age groups and gender, and measurements of mortality have been shown to vary with age and sex as well as the type of disease.

The large studies have highlighted not only the increased risk of death from CVD, but more specifically indicated that these deaths are usually atherosclerotic in origin. For example, while it was noted that there was an association between diabetes and mortality from ischaemic, non-haemorrhagic stroke it was also noted that there was no such association with subarachnoid or intracranial haemorrhage in patients with type 2 diabetes, and this has subsequently been shown to be the case in patients with type 1 diabetes as well. Similarly, for heart disease the mortality rates and SMRs are much higher for death from IHD alone than from all types of heart disease grouped together. These observations are relevant because they indicate where treatment and early detection might help reduce mortality.

### Gender and cardiovascular risk in diabetes

One of the features of CVD complications in patients with diabetes that has been highlighted by epidemiological studies, and is of particular interest, is the relationship between CVD risk and gender. Mortality from cerebrovascular disease in the general population does not vary between the sexes. Although the rates are higher in the patients with type 1 diabetes these also do not differ between men and women except in the oldest age group where mortality from stroke appears to be a bit higher in women. Similar studies of patients with type 2 diabetes have also suggested that the stroke rate or the increased risk of stroke might be slightly higher for women at older ages.

In contrast mortality from heart disease in the general population is higher in men than women at all ages, and premenopausal women have a degree of cardioprotection as CHD rates remain low at this age. This premenopausal protection appears to be completely lost in young women with type 1 diabetes and CHD mortality rates are the same as for men. This accords with incidence data from Pittsburgh (Lloyd et al., 1996b), in which similar rates of new coronary artery disease events were found in males and females under 40 years, and from the WHO study (Morrish et al., 2001), which showed similar incidence rates for new myocardial infarctions in men and women. Even though the rates fall behind those of men in the older age groups, at all ages the rates in women with type 1 diabetes are higher than those for men in the general population. Women with type 2 diabetes appear to fare only slightly better and studies suggest that some of this survival advantage may also be lost. Data from
the Rancho Bernardo Study show that survival rates in females with type 2 diabetes are similar to those in men without diabetes, and considerably worse than those for women without diabetes (Barrett-Connor et al., 1991).

Clearly, although it may be convenient to do so, in reality it is impossible to generalise about the effects of diabetes on CVD risk. Not only do the rates and risks differ between the two types of diabetes but there are also considerable differences in mortality according to pathology, age group and sex. Unless the cohort is a particularly large one, it may not be possible to subdivide the deaths by age group or specific cause, but without some subdivision important differences may be overlooked and high-risk groups fail to be identified.

Although this chapter has largely concentrated on mortality, epidemiological studies that have been able to provide more detailed information, although on a smaller population, have also proved invaluable. An example of this type of study is the DARTS/MEMO Study, an electronic record linkage of multiple data sources to create a diabetes register from Tayside in Scotland (Morris et al., 1997). The advantages of these studies can be illustrated by considering peripheral arterial disease. Intermittent claudication, an early symptom, is very common in patients with diabetes and is highlighted as a major problem in morbidity studies but hardly features in studies of mortality, and the incidence of below knee amputations, a more serious consequence of peripheral arterial disease, can only be determined by local audit (Morris et al., 1998) (Chapter 8). A further advantage of smaller studies is that it is possible to measure cardiovascular risk factors in individuals (EURODIAB IDDM Complications Study Group, 1994; Fuller et al., 2001) and it turn establish which risk factors appear to be relevant to which outcomes.

Following on from the epidemiological studies that measure risk factors come clinical trials. These trials are intervention studies that assess the best method of treatment in order to reduce the complications of diabetes. Some of these concentrate on achieving tight control of diabetes in order to reduce the adverse consequences (Diabetes Control and Complications Trial Research Group, 1995; UK Prospective Diabetes Study (UKPDS) Group, 1998) whereas others put more emphasis on treating the CVD risk factors directly (Colhoun et al., 2004) (Chapter 9). These and other methods of treatment to prevent or alleviate the consequences of CVD in patients with diabetes are discussed in the subsequent chapters in this book.

References


REFERENCES


