Improved survival of diabetic foot ulcer patients 1995-2008, possible impact of aggressive cardiovascular risk management

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Objectives: To determine if a strategy of aggressive cardiovascular risk management reduced the mortality associated with diabetic foot ulceration.

Research design and methods: Following an initial audit of outcomes demonstrating a high mortality rate in 404 diabetic foot ulceration patients with first ulceration developing between 1995 and 1999, a new aggressive cardiovascular risk policy was introduced as standard practice at the Diabetic Foot Clinic, Royal Infirmary of Edinburgh in 2001. 251 patients were screened and identified in the first three years of this policy. The audit cycle was then closed by re-auditing the five year mortality for a second group of foot ulcer patients in 2008.

Results: Overall five-year mortality reduced from 48.0% in cohort 1 to 26.8% in cohort 2 (p<0.001). Improvement in survival was seen for both neuroischaemic patients (five year mortality 58% to 36% relative reduction 38%) and neuropathic patients (36% to 19%, relative reduction 47%), both p<0.001. Patients were more likely to die if they were older at time of ulceration or had type 2 diabetes, renal impairment, pre-existing cardiovascular disease or were already on aspirin. Prior statin use, current or ex smoking, blood pressure, HbA1c or total cholesterol were not significantly different between survivors and those who died in the follow up periods.

Conclusions: Diabetic foot ulcer patients are at high risk of death. Survival has improved over the past 13 years. The adoption of an aggressive cardiovascular risk management policy in diabetic foot ulcer clinics is recommended for these patients.
Lower limb amputation in diabetic patients is associated with a significant excess mortality (1). Foot ulceration is also believed to be associated with increased deaths due to related cardiovascular disease (2, 3). In addition, patients with foot ulceration often have advanced diabetes complications (4). Cardiovascular risk reduction has, over the last 10 years, become a major part of diabetes care, particularly for type 2 patients. However, it is only since 2004 that the United Kingdom General Medical Services contract has made the treatment of cardiovascular risk a remunerated part of diabetes management in primary care (5). This initiative is driven by target glycated haemoglobin, blood pressure and cholesterol levels rather than absolute or calculated risk as in the past and has increased prescribing of therapies aimed to reduce cardiovascular risk (6). Patients without established risk factors might not receive adequate treatment if they are not above target.

It is likely that the peripheral arterial disease and microvascular sclerosis associated with diabetic foot ulceration will reflect established arterial disease elsewhere in the body (3). Therefore, cardiovascular risk factor intervention might be expected to be effective in this setting. However, there are no studies of aggressive risk factor modification in diabetic foot ulcer patients to determine if such a strategy improves survival.

METHODS

The specialist diabetic foot clinic of the Royal Infirmary of Edinburgh was started, in its current form, in March 1995. As part of the structure of the clinic, separate notes, a database, and robust audit procedures were put in place. The healing rates and other outcome results of the first four years of care in the clinic have been published elsewhere (7), but it was the mortality following foot ulceration in this group of patients that prompted this audit.

This audit was designed to determine if a new policy of standard care, optimising cardiovascular risk reduction, in an identified high risk population would influence mortality. There were two cohorts of patients studied. The first cohort were those patients referred with new ulceration between March 1st 1995 and 28th February 1999. The second cohort included those patients referred between July 2001 and March 2004. All follow up was until 31st July 2008.

In each group survival was measured from the time of first ulceration to death even if the first ulcer occurred before referral to the clinic. Ulcer type was determined in the following manner. Patients with both pedal pulses present without a history of revascularisation were deemed to be primarily neuropathic, patients with absent pulses or a prior history of revascularisation were deemed neuroischaemic.

When the mortality rate for the first cohort was identified, the initial therapy history on first attendance to the clinic and all clinic notes and primary care referrals for this group, were examined for drugs known to reduce cardiovascular risk. These were statin therapy, anti-platelet agents, ACE inhibitors and beta-blockers (8).

The care of the second cohort was adapted from the results of the initial audit. All patients were screened for known cardiovascular risk factors including blood pressure and serum cholesterol. Glycated haemoglobin, total cholesterol and serum creatinine results were taken from the year of ulceration. The normal range for HbA1c in the Royal Infirmary of Edinburgh is up to 6.5%. Where multiple values existed then the mean value in the year of first ulceration was used. Blood pressures in cohort 2 were taken at clinic during the cardiovascular risk assessment process. Sufficient blood pressure data for analysis of cohort 1 were unavailable.
A cardiovascular risk score for patients in cohort 2 was derived using the UKPDS risk engine for primary prevention patients (9). Patients with known cardiovascular disease (ischaemic heart disease or stroke) were deemed to be secondary prevention patients.

A detailed drug history was taken and the following recommendations were made. All foot ulcer patients referred after 2001 were recommended to be on an anti-platelet agent (10, 11), aspirin 75mg, or clopidogrel 75mg if they were aspirin intolerant. The only contraindications to anti-platelet therapy were known intolerance, a recent history of gastrointestinal bleeding or unexplained anaemia. Warfarin was a relative contraindication. Statin therapy was recommended for all patients without a history of statin intolerance and, if patients were already on a statin, the dose was recommended to be optimised to pravastatin or simvastatin at a minimum dose of 40mg (11-16).

ACE inhibitors or angiotensin receptor blockers (ARB) were recommended for all patients with hypertension, previous cardiovascular disease and, or, microalbuminuria, unless there was known reno-vascular disease (11). Again doses were maximised if possible. In addition beta-blockers were recommended for all patients with existing cardiovascular disease or where blood pressure was still uncontrolled despite ACE inhibition. This was normal practice in 2001 in line with the findings of the UKPDS study and the expected high levels of cardiovascular disease and, despite recent controversy, is still recommended for secondary prevention of cardiovascular events in the 2006 ADA standards of diabetes care (11, 17, 18). Peripheral vascular disease was not an absolute contra-indication for beta-blockade. Letters were sent to the primary care team for every patient informing them of the clinic policy, screening process and the reasons underlying it, whether changes were thought to be required or not.

In 2004 and 2005 second letters were sent to ensure that the first had been received and that the recommended therapy changes had been made. In addition, the causes of death for the first cohort and any deaths up that point in the second cohort were determined. The primary care physician for each patient was sent a letter asking what cause of death was registered on the death certificate. Death certificates are unreliable but are the best available information for cause of death in the absence of post mortem examinations (19). Any causes of deaths after 2005 have been sought prospectively.

Statistical analyses—All statistical analyses were performed using SPSS for Windows 11.0. Between group comparisons were performed using t-tests and Chi-squared tests with Yates correction depending on the nature of the comparison and the distribution of the variables. Statistical significance was taken as two-tailed at the 0.05 level.

RESULTS
There were 404 foot ulceration patients in the first cohort, 251 in the second. Their characteristics are detailed in table 1. There were no significant differences in the available data between the groups other than initial total cholesterol. Over the thirteen years of follow up only six patients from the first cohort have been completely lost to follow up with no outcome data available due to a loss of case notes during a change in hospital location and a later change in hospital computer systems. At least three of these are known to have died but the date and cause of death could not be determined as no primary care contact details were available. No patients were lost to follow up in cohort 2.

Major amputations have been performed on 11.3% of the first cohort to date. Survival was not different between those with and without a major amputation,
five year mortality without amputation 48%, with amputation 47.8%, p=NS. Therefore amputation was not used to sub-divide the groups in subsequent analyses. Patients in cohort one with peripheral vascular disease (PVD) had a higher five year mortality than those with mainly neuropathic ulcers (58% versus 36%, p<0.001).

Calculated five-year cardiovascular mortality in cohort 2 was significantly lower then the actual mortality in cohort 2. Neuropathic patients 7.5% versus 19% and Neuroischaemic patients 9.0% versus 36% (both p<0.01).

Prescribing of cardiovascular risk reducing drugs improved significantly by 2003 (table 2). However further changes were recommended for more than half the patients. Analysis of the actions by primary care teams after recommendations showed that these were acted upon in around 80% of occasions (p=0.02). The final level of prescribing of statins and anti-platelet therapy increased to nearly 90% after a second letter was sent to follow up the recommendations (table 2).

All 251 cohort 2 patients were followed to four years. The relative risk of death at four years was 49.4% lower in cohort 2. Overall mortality at 4 years cohort 1 43.3% and cohort 2 21.9% (p<0.001). One-hundred and sixty patients in cohort 2 ulcerated prior to 1st August 2003 and were compared with the five year survival for cohort 1. Overall five-year mortality reduced from 48.0% in cohort 1 to 26.8% in cohort 2 (p<0.001) (figure 1). Improvement in survival was seen for both neuroischaemic patients (five year mortality 58% to 36%) and neuropathic patients (36% to 19%), both p<0.001.

Patients in cohort 2 who died were older at time of first ulceration (70.6 ± 10.4 vs 57.5 ± 15.0 years p<0.01), and were more likely to have type 2 diabetes (OR 3.21 95% CI 1.53 to 6.74, p<0.01), renal impairment (creatinine >130 umol / l) (OR 3.04 95% CI 1.57 to 5.87), pre-existing cardiovascular disease (OR 3.25 95% CI 1.87 to 5.67) or already be on aspirin (OR 3.52 95% CI 1.93 TO 6.42). Similar results were seen in cohort 1. In both groups gender, prior statin use, current or ex smoking, blood pressure (cohort 2 only), HbAlc or total cholesterol were not significantly different between survivors and those who died in the follow up periods.

The largest single recorded cause of death in both cohorts was ischaemic heart disease. Ischaemic heart disease was the recorded cause of death in 61% of cohort 1 and 65% of cohort 2 patients, with all vascular causes, including stroke, comprising 74 and 81% of deaths respectively. Cancer, 7%, chronic airways disease, 6% and end stage renal failure, 5%, were the next three most prevalent causes.

The patients in cohort 2 were on average 1.3 years younger at presentation (95% CI: -3.5823 - 0.9823 p=0.26). However, the patients in cohort two who died in the first five years after presentation (63 of 87 total deaths to date) were on average 3.5 years older at death than the cohort one patients who died in the same period (194 of 285 total deaths to date). Average age at death cohort two 73.9 ± 10.1 years versus cohort one 70.4 ± 11.8 years, p=0.025.

**DISCUSSION**

This study has demonstrated improved survival for diabetic foot patients over the past 13 years. The marked improvement in mortality in our patients occurred at a time when greater attention was given to glycaemic control, blood pressure and lipid management following the publication of the UKPDS studies and the main lipid studies of the 1990’s (6, 10-17, 20). However, of the available data only total cholesterol, was significantly lower at the time of ulceration in these two groups. Given the higher levels of blood pressure therapy in cohort two it is
likely that blood pressure would also be lower in this group. However, extrapolating from the major statin trials, and the UKPDS blood pressure study, where the relative risk reductions for cardiovascular events have been in the order of 25% and absolute overall mortality reductions in single figures, these differences alone are probably not enough to explain the difference in mortality between the groups (12-17). Even the recent study by Charlton et al (6), which shows impressive relative reductions of around 37% in early mortality from type 2 diabetes, reports overall absolute reductions in mortality of less than 2%. Other contemporaneous foot ulcer and amputation mortality studies still show mortality rates of around 50% at five years in a similar diabetes and cardiovascular management climate (1-3). It is therefore likely that the introduction of the aggressive cardiovascular risk management policy has contributed to the improvement in mortality observed in these patients.

The levels of therapy prescription in cohort one were derived from hospital case notes and referral letters and may be an underestimate of the true levels of prescribing, perhaps exaggerating the effect of the new treatment policy. However they are in line with reported aspirin, statin, and ACE inhibitor use in Type 2 diabetes patients in 1996 and 2004 (6, 10). Despite the landmark studies of the 1990s there were still significant gaps in the prescription of proven cardiovascular risk lowering medications in cohort two. This finding is also in keeping with the gaps in prescribing in similar studies of therapies for cardiovascular risk reduction in diabetic patients (6, 10, 21, 22). The gaps in prescribing might be partly explained because this group of patients was not widely recognised as being one with a proven high mortality outside of diabetic foot care centres nor one in which there was an evidence base for successful cardiovascular risk reduction. Even the most accurate cardiovascular risk modelling would have seriously underestimated mortality and therefore, prior to universal treatment recommendations in type 2 diabetic patients only those with true secondary prevention needs would have been treated and then often incompletely (6, 9, 10). The eventual levels of statin and anti-platelet are significantly higher than those achieved by national guidelines alone in other studies (6, 10, 21, 22). This is likely to reflect the fact that the diabetes foot clinic, by focussing the care for this high risk group of patients, and by regular review and follow up, is in the best position to ensure that cardiovascular risk reducing therapies are prescribed and used.

The significant benefits in mortality were seen despite blood pressure and total cholesterol measurements that would not have merited blanket treatment for cardiovascular risk according to QOF or other target driven guidelines (5). This may be due to additional anti-platelet effects, ACE inhibition, and the non-cholesterol related benefits of statin treatment (11, 23).

The association of older age, but not duration of diabetes, with risk of dying would be in keeping with the known higher mortality in Type 2 patients (17, 20). Pre-existing vascular disease and secondary prevention measures explain the higher initial levels of aspirin use in those who died (6, 10, 11). Risk reduction therapy was similar between the dead and surviving patients after the changes imposed by the new prescribing policy. Smoking rates were high in both groups and either the overall numbers in the study were too small to determine a difference in outcome or diabetes and other factors had a greater effect. The lack of a difference in HbA1c between survivors and those who died is unsurprising in a population of only 650 patients. In the UKPDS study a difference of 0.9% in HbA1c did not significantly alter mortality (20).

The absence of an increase in mortality following major lower limb
amputation is reassuring and has been reported previously (24). It is likely to be the underlying vascular disease in neuroischaemic and neuropathic patients and not the procedure that influences outcomes. The decision to group all foot ulcer patients together was taken on the basis of similar characteristics for the two cohorts and a high mortality for neuropathic ulcer patients in this study and in other prospective studies (25). The benefits in reduction of cardiovascular mortality were seen equally in both ulcer types suggesting that even neuropathic diabetic patients have a degree of underlying macrovascular disease.

The relative risk of death within five years of foot ulceration was 48.5% lower in cohort 2 than in cohort one. The size of the improvement in mortality, and the observation that this was also associated with an older age at death, suggests that cardiovascular risk reduction treatment does prolong survival in this population. The large effect seen in this population is in keeping with previous studies which suggest that absolute risk reduction is greater in high risk groups (12-16, 22, 23).

The findings of this study are based on actual outcomes from a clinic population and not a study population. The advantages of specialist multi-disciplinary foot clinics in improving healing rates for diabetes foot ulceration and reducing amputation rates and hospital admissions have been described previously, and they are accepted as the best model of foot ulcer care (7). This study adds another justification for concentrating foot ulcer care in specialist centres. It would suggest that specialist diabetes foot clinics should adopt a policy of aggressive cardiovascular risk management, prescribing secondary prevention therapies not just for those with previously known cardiovascular events, or cholesterol or blood pressure levels above target, but for all foot ulcer patients.

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Table 1  Demographic characteristics of the two cohorts shown as mean (SD) unless otherwise stated.

|                                | Cohort 1 | Cohort 2 |
|--------------------------------|----------|----------|
| Number                         | 404      | 251      |
| Male                           | 62%      | 66%      |
| Type 2                         | 70%      | 77%      |
| Age at first ulcer             | 63.2 (13.8) years | 61.9 (14.9) years |
| Mean duration diabetes         | 13.4 (11.2) years | 13.8 (10.8) years |
| Ischaemic ulcers               | 52%      | 48%      |
| Previous cardiovascular disease| 39%      | 36%      |
| Current smoker                 | 24%      | 24%      |
| Systolic blood pressure mmHg   | -        | 139.1 (23.7) |
| Diastolic blood pressure mmHg  | -        | 81.7 (13.6) |
| HbA1c                          | 8.6 (1.6) | 8.4 (1.8) |
| Creatinine >130 umol / l       | 22%      | 19%      |
| Total Cholesterol mmol / l     | 5.21 (1.01) | 4.77 (1.30)* |

*p<0.05 Cohort 1 versus Cohort 2

Table 2. Percentage levels of prescribing for major cardiovascular and diabetes drug therapies on first clinic visit in each cohort.

|                   | Cohort 1 | Cohort 2 Initial | Cohort 2 After letter |
|--------------------|----------|------------------|-----------------------|
| Anti-platelet      | 19       | 56*              | 84†                   |
| Statin             | 9.6      | 54*              | 88†                   |
| ACE inhibitor      | 8.9      | 45*              | 55                    |
| Angiotensin receptor blocker | 0 | 5*   | 6                     |
| Beta-blocker       | 7        | 26*              | 35                    |
| Diuretic           | -        | 46               | -                     |
| Insulin            | -        | 50               | -                     |
| Metformin          | -        | 36               | -                     |
| Sulphonylurea      | -        | 12               | -                     |

*All p>0.05 cohort 2 versus cohort 1.
†p<0.05 after follow up letter versus on presentation to the clinic.
Figure 1. Survival graphs for cohort 1 (▲) and cohort 2 (●). Five year survival 52.0% in cohort 1 improved to 73.2% in cohort 2 (p<0.001)