Dialysis Treatment Is an Independent Risk Factor for Foot Ulceration in Patients With Diabetes and Stage 4 or 5 Chronic Kidney Disease

AGBOR NDIP, MD[1,2]
MARTIN K. RUTTER, MD, FRCP[1,2]
LORETTA VILEIKYTE, MD, PHD[1,2]
ANAND VARDHAN, MD, MRCP[3]
ASHWINBHAI ASARI, MD, MRCP[3]
MEHREEN JAMEEL, MBCHB[4]
HASSAN A. TAHIR, MBCHB[4]
LAWRENCE A. LAVERY, DPM, MPH[5]
ANDREW J.M. BOULTON, MD, FRCP[1,2]

OBJECTIVE — To determine whether dialysis treatment is an independent risk factor for foot ulceration in patients with diabetes and renal impairment.

RESEARCH DESIGN AND METHODS — We performed a cross-sectional study of consecutive patients with diabetes and stage 4 or 5 chronic kidney disease (CKD) attending clinics in Manchester (U.K.). Patients were classified as either receiving dialysis therapy (dialysis) or not (no dialysis). Foot assessment included diabetic peripheral neuropathy (DPN), peripheral arterial disease (PAD), prior foot ulceration and amputation, and foot self-care. Risk factors for prevalent foot ulceration were assessed by logistic regression.

RESULTS — We studied 326 patients with diabetes and CKD (mean age 64 years; 61% male; 78% type 2 diabetes; 11% prevalent foot ulceration). Compared with no dialysis patients, dialysis patients had a higher prevalence of DPN (79 vs. 65%), PAD (64 vs. 43%), prior amputations (15 vs. 6.4%), prior foot ulceration (32 vs. 20%), and prevalent foot ulceration (21 vs. 5%, all $P < 0.05$). In univariate analyses, foot ulceration was related to wearing bespoke footwear (odds ratio 5.6 [95% CI 2.5–13]) dialysis treatment (5.1 [2.3–11]), prior foot ulceration (4.8 [2.3–9.8], PAD (2.8 [1.3–6.0], and years of diabetes (1.0 [1.0–1.1], all $P < 0.01$). In multivariate logistic regression, only dialysis treatment (4.2 [1.7–10], $P = 0.002$) and prior foot ulceration (3.1 [1.3–7.1], $P = 0.008$) were associated with prevalent foot ulceration.

CONCLUSIONS — Dialysis treatment was independently associated with foot ulceration. Guidelines should highlight dialysis as an important risk factor for foot ulceration requiring intensive foot care.

Diabetes Care 33:1811–1816, 2010

The lifetime risk of an individual with diabetes developing foot ulceration has been estimated to be 25% (1). Foot ulceration is a serious problem for people with diabetes, which also results in huge economic costs (2).

Causal pathways to foot ulceration are multifactorial and involve combinations of physiological and mechanical factors, self-care, and treatment factors. Diabetic nephropathy has been identified to be an important risk factor for foot ulceration and amputation (3,4). Retrospective studies in patients with diabetes have shown that incident foot ulceration increases with progressive renal impairment (5), and one study reported a close temporal relation among the onset of dialysis, foot ulceration, and amputations (6).

Studies reporting an association between renal failure and foot ulceration have failed to separate dialysis-treated patients from those not receiving dialysis (5,7). We therefore aimed to determine whether dialysis treatment is an independent risk factor for foot ulceration among diabetic patients with stage 4 or 5 chronic kidney disease (CKD). We hypothesized that dialysis treatment would be associated with a higher prevalence of foot ulceration after adjustment for potential confounders.

RESEARCH DESIGN AND METHODS

— Study participants were consecutive patients with diabetes and stage 4 or 5 CKD attending either Manchester Diabetes Centre, the renal and dialysis units of Manchester Royal Infirmary, or one of the satellite dialysis units in the area between October 2006 and March 2008. Stage 4 or 5 CKD was defined as average Modification of Diet in Renal Disease (MDRD) estimated glomerular filtration rate (eGFR) <30 ml/min over the preceding year (8). These patients were classified according to dialysis status into the following two groups. *1*) The no dialysis group included patients with MDRD eGFR values <30 ml/min who were not receiving dialysis treatment. This group included some patients who were considered to be unsuitable for dialysis treatment for medical reasons or because of patient preference. *2*) The dialysis group included patients with end-stage renal disease (ESRD) currently receiving either hemodialysis or peritoneal dialysis treatment.

At clinic visits, using a routine data entry form, the study clinician collected data both from patients and from the medical notes. Data included the following variables: diabetes type, duration, and treatment, previous foot ulcers and am-

From the [1]Manchester Diabetes Centre, Manchester Academic Health Science Centre, Manchester National Institute Health Research Biomedical Research Centre, Central Manchester University Hospitals NHS Foundation Trust, Manchester, U.K.; the [2]Cardiovascular Medicine Research Group, School of Biomedicine, University of Manchester, Manchester, U.K.; the [3]Department of Renal Services, Manchester Royal Infirmary, Manchester, U.K.; the [4]School of Medicine, Faculty of Medical and Human Sciences, University of Manchester, Manchester, U.K.; and the [5]Department of Surgery, Texas A&M Health Science Center College of Medicine and Scott and White Hospital, Temple, Texas.
Corresponding author: Agbor Ndip, Agbor.Ako@manchester.ac.uk.
Received 8 February 2010 and accepted 10 May 2010. Published ahead of print at http://care.diabetesjournals.org on 18 May 2010. DOI: 10.2337/dc10-0255.

putations, bypass surgery, angioplasty, history of retinopathy, and the onset and current modality of dialysis (hemodialysis or peritoneal dialysis). Foot self-care was assessed by patient self-report with four items using the following format: *Do you: Currently use bespoke footwear or insoles? Attend regular podiatry? Walk barefoot at home? Inspect your feet daily?* Responses to these questions were recorded as yes/no.

Diabetic peripheral neuropathy (DPN) was assessed by measuring the vibration perception threshold (VPT) with a neurothesiometer (Horwell Scientific, Wilford, Nottingham, U.K.) over the distal hallux as described previously (9) and clinical examination using the modified neuropathy disability score (NDS). DPN was defined as VPT >25 V and/or a modified NDS >3 (10). Peripheral arterial disease (PAD) was assessed through palpation of the posterior tibial and dorsalis pedis pulses bilaterally, determination of the ankle brachial pressure index (ABPI) using a Doppler ultrasound probe in both legs. In addition, records were reviewed for documented evidence of angiographically confirmed PAD and/or revascularization. PAD was defined as at least one of the following: ABPI <0.9 (11), a history of a peripheral artery revascularization procedure or angiography confirming PAD, noncompressible arteries (defined as ABPI >1.4), abnormal waveforms (monophasic or biphasic) with ABPIs of 0.9–1.4 (12), or absence of two or more pedal pulses on palpation (13). Major amputations were defined as amputations proximal to the ankle joint, and minor amputations were defined as those through or distal to the ankle joint. Foot deformity was ascertained by the examining physician and was defined as any one of the following: hallux valgus deformity, claw/hammer toes, prominent metatarsal heads, dislocated metatarsophalangeal joints, pes cavus (high plantar arch), or pes planus (flat foot). All of these assessments are routinely performed in our combined diabetes-renal clinics.

The International Working Group on the Diabetic Foot (IWGDF) risk classification was used to assign patients into four levels of increasing risk of foot problems (13): *1*) risk 0, no recognizable risk factor; *2*) risk 1, neuropathy and no other risk factors; *3*) risk 2, PAD with or without neuropathy; and *4*) risk 3, current foot ulcer, a history of foot ulcer, or prior amputation. Patients in risk category 0 where considered to be at "low risk" for foot ulceration, whereas those in risk categories 1–3 were considered to be at "high risk." This study was performed as an audit that required no formal ethics permission. As mentioned above, data collected are part of routine care provided to patients in the study centers. However, all subjects gave informed verbal consent before inclusion.

Pearson χ^2 and Fisher exact tests were used to compare categorical data between study groups. The 95% CIs for proportions and percentages were estimated using the modified Wald formula. The Student *t* test was used to compare continuous data. Risk factors for foot ulceration were assessed by univariate logistic regression. Risk factors significantly associated with prevalent foot ulceration in univariate analysis ($P < 0.1$) were then included in the multivariable logistic regression analysis. Peripheral neuropathy was "forced" in this model because of its known association with foot ulceration. Risk estimates were presented as odds ratios (ORs) with 95% CIs, and $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS (version 16.0; SPSS, Chicago, IL).

Table 1—*Clinical characteristics of no dialysis and dialysis-treated patients*

Characteristic	No dialysis	Dialysis	*P* value
n	139	187	
Ethnicity: African/Southeast Asian/white (%)	11/20/69	10/24/66	0.70
Male sex (%)	56	64	0.09
Age (years)	67 ± 12	59 ± 14	<0.0001
Diabetes type: 1:2 and others (%)	17:83	25:75	0.041
Known diabetes duration (years)	19 ± 11	20 ± 11	0.51
A1C (% units)	7.8 ± 1.6	8.0 ± 1.7	0.29
Serum albumin (g/l)	40 ± 5	36 ± 6	<0.0001
Hemoglobin (g/dl)	11.8 ± 1.5	11.5 ± 1.7	0.07
Retinopathy (%)	69	70	0.43

Data are *n*, %, or means ± SD.

RESULTS — We assessed 326 patients (139 dialysis-treated and 187 no dialysis). Within the dialysis group, 85 patients (61%) were treated with hemodialysis, and the remainder were treated by peritoneal dialysis. The median (interquartile range) time between clinical assessment and the start of dialysis was 16 (6–30) months. Clinical characteristics were similar in dialysis-treated and no dialysis patients except that dialysis-treated patients were ~8 years younger and were more likely to have type 1diabetes and a lower serum albumin concentration (Table 1).

The overall prevalence of foot ulcers was 11% (36 patients). Ten percent of all patients had a prior lower limb amputation. Eight patients in the dialysis group were bilateral amputees; only those 131 patients with at least one lower limb were included in the prevalence analyses. There were no patients with bilateral amputations in the no dialysis group.

Thirteen of the 20 amputees (65%) in the dialysis group had undergone major amputation. Although this result was higher, it was not significantly different from the 7 major amputations of 12 amputees (58%) in the no dialysis group ($P = 0.50$).

Of the 27 patients in the dialysis group who had at least one current ulcer, the ulcers were located on metatarsal heads ($n = 2$), plantar midfoot ($n = 2$), heel ($n = 3$), distal toes ($n = 18$), multiple sites ($n = 1$), and unspecified (i.e., not recorded) location ($n = 1$). Among the 9 patients with ulcers in the no dialysis group, the sites of ulceration were toes ($n = 2$), metatarsal head ($n = 1$), midfoot ($n = 1$), dorsal foot ($n = 1$), heel ($n = 2$), and multiple sites ($n = 2$).

Dialysis treatment was associated with a fivefold higher prevalence of prevalent foot ulceration, a twofold higher risk of prior amputation, prior foot ulceration, DPN, and PAD, and a lower prevalence of foot deformity compared with no dialysis treatment (Table 2). Based on the IWGDF classification, dialysis-treated patients were ~3 times more likely to be classified as having a high risk of diabetic foot ulcers compared with no dialysis patients ($P = 0.015$). Preventative foot care behavior was better in the predialysis than in the dialysis group except for the use of bespoke footwear.

When the dialysis and no dialysis groups were combined, univariate logistic regression showed that prevalent foot ulceration was significantly related to wearing bespoke footwear, dialysis therapy,

Table 2—*ORs (95% CI) for prevalent foot complications and associated risk factors comparing dialysis-treated patients and no dialysis patients*

	No dialysis*	Dialysis*	OR (95% CI)	*P* value
n	187	139		
Lower limb complications				
Prevalent foot ulcer (%)	4.8	21	5.1 (2.3–11)	<0.0001
Prior amputation (%)	6.4	15	2.6 (1.2–5.6)	0.008
PAD (%)	43	64	2.4 (1.5–3.8)	<0.0001
Neuropathy (%)	65	79	2.0 (1.2–3.3)	0.006
Prior foot ulcer (%)	20	32	1.9 (1.1–3.1)	0.011
Deformity (%)	33	22	0.6 (0.4–1.0)	0.019
IWGDF risk categories (%)				
Low-risk category 0	16	7		
High-risk category 1	12	17		
High-risk category 2	43	39		
High-risk category 3	29	37		
Low-risk vs. high-risk category	16 vs. 85	7 vs. 94	2.7 (1.2–5.8)	0.015
Patient care				
Use of bespoke footwear (%)	8	16	2.6 (1.2–4.3)	0.026
Walking barefoot at home (%)	28	43	2.0 (1.2–3.1)	0.004
Routine podiatry clinic attendance (%)	70	44	0.3 (0.2–0.5)	<0.0001
Daily inspection of feet (%)	70	29	0.2 (0.1–0.3)	<0.0001

Data are proportions as % unless otherwise indicated. *Values of *n* for individual factors may differ slightly because of missing data. Maximum missing data were for PAD involving 6 patients overall (1.8%). The referent group for calculation of ORs was the no dialysis patient group.

PAD, duration of known diabetes, and attendance at a podiatry clinic (Table 3). In multivariable analysis prevalent foot ulceration was significantly and independently related to dialysis therapy and history of foot ulceration (Table 3).

In the combined dialysis and no dialysis patient groups, prevalent and prior foot ulceration and prior amputation did not vary by ethnic group using ANOVA and when whites were compared with other individual ethnic groups. There was a suggestion that whites were more likely than nonwhites to have a prevalent foot ulcer (OR 2.5 [95% CI 1.1–6.0] $P = 0.051$).

The proportion of patients classified as being at high risk, based on the IWGDF risk categories was equally high in all ethnic groups (NS). All Africans (14 patients), all Asians (33 patients) and 83 of 92 white patients in the dialysis group were classified as being at high risk, whereas similarly, 18 of 20 Africans, 32 of 37 Asians, and 108 of 130 white patients in the no-dialysis group were classified as being at high risk for foot ulceration. The rest of the patients were classified as low risk.

Within the white subgroup, prevalent foot ulceration was more common in dialysis-treated patients than no dialysis patients (OR 6.0 [95% CI 2.4–14.7], $P < 0.0001$) and those who were dialysis-treated were also more likely to have had an amputation (2.4 [1.0–5.9], $P = 0.04$). The numbers of patients with a foot ulceration or amputation in the African or Asian ethnic groups were too small to be analyzed by dialysis/no dialysis subgroup.

Among the no dialysis patients, DPN, PAD, past and current foot ulcers, and prior amputation did not vary by ethnicity (ANOVA). When whites were used as the referent group, Asians were less likely

Table 3—*Univariate and multivariable-adjusted ORs (95% CI) for risk factors associated with prevalent foot ulceration in patients with diabetes and renal impairment*

	Prevalent foot ulcer		Univariate analysis		Multivariable-adjusted analysis	
Risk factor	Yes	No	OR (95% CI)	*P* value	OR (95% CI)	*P* value
n	36	281				
Wearing bespoke footwear	33	8.3	5.6 (2.5–13)	<0.0001	2.2 (0.8–6.0)	0.129
Dialysis treatment	75	37	5.1 (2.3–11)	<0.0001	4.2 (1.7–10)	0.002
History of foot ulcer	56	21	4.8 (2.3–9.8)	<0.0001	3.1 (1.3–7.1)	0.008
PAD	72	48	2.8 (1.3–6.0)	0.009	1.6 (0.7–3.9)	0.257
White ethnicity	83	67	2.5 (1.0–6.1)	0.051	1.8 (0.7–4.9)	0.229
Retinopathy	81	69	1.9 (0.8–4.5)	0.144		
Neuropathy	81	71	1.5 (0.7–4.0)	0.245	0.7 (0.3–2.0)	0.542
Male sex	64	59	1.2 (0.6–2.6)	0.553		
Walking barefoot at home	36	34	1.1 (0.5–2.2)	0.840		
Known diabetes duration (years)*	24 ± 13	19 ± 11	1.0 (1.0–1.1)	0.009	1.0 (0.9–1.1)	0.121
Duration of dialysis (months)†	24 (28)	15 (22)	1.0 (0.9–1.1)	0.345		
Age (years)*	61 ± 12	64 ± 14	1.0 (0.9–1.1)	0.120		
Deformity	28	30	0.9 (0.4–2.0)	0.827		
A1C (%)	7.7 ± 1.3	7.9 ± 1.7	0.9 (0.7–1.1)	0.385		
Routine podiatry clinic attendance	44	62	0.5 (0.3–1.0)	0.055	0.9 (0.4–2.0)	0.707

Data are proportions as %, means ±SD, or median (IQR) unless otherwise indicated. Variables with $P < 0.1$ in univariate analysis were included in the multivariable analysis. In univariate analysis, duration of dialysis excluded no dialysis patients. The referent group for calculation of the OR was the no foot ulcer group. *OR calculated per year of exposure variable. †OR calculated per month of exposure variable.

to have PAD (OR 0.4 [95% CI 0.2–0.9], $P = 0.03$) and Africans were less likely to have DPN (0.3 [0.1–0.8], $P = 0.011$). We have recently reported the influence of ethnicity on diabetic foot ulcers in dialysis-treated patients.

The proportion of patients with prevalent foot ulceration in the group receiving hemodialysis was similar to that of those receiving peritoneal dialysis (22 [95% CI 15–32] vs. 17 [9–31]%, $P = 0.33$). The prevalence of prior amputation was higher in patients receiving hemodialysis than in those receiving peritoneal dialysis (21 [13–30] vs. 6 [2–17]%, OR 3.9 [1.1–14], $P = 0.02$).

CONCLUSIONS — We have shown that in patients with diabetes and stage 4 or 5 CKD, prevalent foot ulceration was fivefold higher in dialysis-treated patients than in predialysis patients. We also report that the prevalence of other lower limb complications (amputation, PAD, prior ulcer, and neuropathy) was ~2-fold higher in patients receiving dialysis. The strong association between prevalent foot ulceration and dialysis therapy remained significant after adjustment for potential confounders (neuropathy, PAD, ethnicity, known duration of diabetes, and use of footwear).

We performed a detailed, systematic foot assessment on a relatively large cohort of well-characterized patients with diabetes and CKD. Our ascertainment of risk factors for foot ulceration and our prevalence estimates for lower limb complications are therefore likely to be accurate. We made foot ulceration our primary outcome because it can be ascertained cross-sectionally, it is potentially preventable, and it usually precedes more serious foot complications such as severe infection, gangrene, or amputation. We carefully chose our no dialysis comparator group to include patients with stage 4 or 5 CKD who were not dialysis treated so that any differences compared with the dialysis group would be more likely to be due to the dialysis treatment itself. We found that dialysis-treated patients had more peripheral neuropathy, PAD, and previous foot ulceration and amputations than no dialysis patients. In our multivariable model we therefore adjusted for the markers of advanced disease because these might have confounded the relationship between dialysis therapy and foot ulceration.

This study has several limitations. The cross-sectional design limits inference about causal relationships between dialysis and prevalent foot ulceration. Our cohort was largely white, and, therefore, our conclusion may not apply to other ethnic groups. However, the inclusion of ethnicity in our final multivariable model did not attenuate the relationship between dialysis and foot ulcers. Our study sample was insufficient to reliably compare the site of foot ulceration in dialysis and no dialysis groups. We did not systematically assess the site and severity of peripheral edema and the severity of PAD, which are potential confounders of the relationship between dialysis therapy and ulceration.

McGrath and Curran (14) provided one of the first reports that dialysis is a risk factor for foot complications in patients with diabetes and CKD. This was a small retrospective study in New Zealand of 47 patients with prior amputation, 32 (68% [32/47]) of whom were Maoris. In 14 patients who were dialysis-treated, the median time between starting dialysis to having an amputation was 7 months (range 2 weeks–40 months). Subsequently, Morbach et al. (15) examined a predominantly white population of 400 patients with diabetic foot ulcers, a small proportion of whom (14 [4%]) were dialysis-treated. Although the number of events was small, the amputation rates were higher in the dialysis-treated patients (57%) than in others with (25%) or without (5%) CKD. In contrast with the studies of Morbach et al. and McGrath and Curran, our study focused on dialysis as a risk factor for foot ulceration rather than for amputation.

Game et al. (6) performed a retrospective case series analysis of 90 patients with diabetes who started dialysis and showed that the cumulative incidence of foot ulceration and amputation increased before the initiation of dialysis and then was highest during the next 2 years. Because the increase in foot complications occurred just before dialysis, it remained unclear whether the main driver of foot complications in the study cohort was ESRD or dialysis treatment itself.

Hill et al. (16) also performed a cross-sectional assessment of patients with diabetes ($n = 60$ with ESRD and $n = 72$ without ESRD) and found that ESRD was associated with a fourfold higher risk of diabetic foot complications, which were defined as current infection, ulcer, gangrene, or amputation. However, this study did not specifically relate risk to dialysis therapy. The study also had a composite outcome, and the level of renal function in those without ESRD was not defined.

A recent cross-sectional retrospective study by Wolf et al. (7) showed that the risk and severity of foot ulceration were related to the severity of renal impairment in patients with diabetes. However, the study included only 61 patients with stage 5 CKD and in this group did not differentiate dialysis-treated patients from others and made limited adjustment for confounders such as neuropathy and PAD. Our study, therefore, adds to the existing evidence that dialysis is a risk factor for foot ulceration, in addition to the impact of poor renal function.

It seems very likely that several factors explain the link between dialysis therapy and foot ulceration, only some of which we were able to address in our study. These factors include physical and psychological health, mobility, manual dexterity, visual acuity, nutrition, hypoalbuminemia, adequacy of dialysis, PAD, tissue oxygenation, neuropathy, anemia, leg edema, infection, and leg/foot support during dialysis.

The detailed etiopathogenesis of foot ulcers in relation to dialysis has been reviewed (17). Foot ulceration could be caused by lying on a dialysis couch for several hours three times a week, especially on insensate heels or with the toes impinging on the end of the bed. Hemodynamic changes and large fluid shifts associated with dialysis could predispose to postural dizziness, falls, and trauma to the foot. During hemodialysis there is a reduction in skin microcirculation and tissue oxygenation that may contribute to the development of ulceration in patients with diabetes (18). Further studies are needed to assess the role of dialysis modality, including an evaluation of the adequacy of dialysis.

We found that dialysis-treated patients were less likely to inspect their feet regularly and to attend podiatry clinics. Moreover, they were more likely to engage in potentially foot-damaging behaviors such as barefoot walking. These are believed to be potentially modifiable foot self-care actions (19), and further research is needed to establish whether improvement in these behaviors results in reduction of foot ulceration in dialysis-treated patients.

The likelihood of wearing bespoke shoes was higher in the dialysis group compared with the no dialysis group. This could be explained by the fact that a larger

proportion of dialysis-treated patients had prevalent (active) foot ulcers at the time of this cross-sectional investigation. It is also conceivable that patients might follow some behavioral recommendations more readily than the others. For example, wearing prescribed footwear may require less of a deliberate effort on the part of an individual than attending regular podiatry clinics or checking the inside of the shoes, especially because it is known that patients with ESRD are likely to be depressed (20) and thus be in the state of behavioral disengagement.

There are some data suggesting that PAD is an independent link between CKD and foot disease (21,22). We found that PAD was not associated with prevalent foot ulceration after adjustment for other factors including dialysis therapy. This finding contrasts with our recently published data in dialysis-treated patients in whom we found an independent association between PAD and prevalent foot ulceration (23). The discrepant results may be explained by two factors: *1*) inclusion of U.K.- and U.S.-based dialysis-treated patients in our previous study; and *2*) in the current study, the influence of dialysis therapy attenuating the impact of PAD on prevalent foot ulceration when the interrelated PAD and dialysis variables were included in the same model. Furthermore, another large study in patients with diabetes showed that PAD did not explain the link between CKD and foot complications, but this study did not assess the influence of dialysis (5).

It is noteworthy that all the ethnic groups we studied displayed a high prevalence of the high-risk foot, based on the IWGDF risk categorization. In addition, the strong association between dialysis and foot ulcers was not significantly affected by ethnicity in our multivariable analysis. These findings lend support to data from previous studies (5,6,14–16) and our own work (23) suggesting that all dialysis-treated diabetic patients are at high risk for foot complications.

Our findings have important clinical implications as they alert health care practitioners that dialysis is an independent risk factor for foot ulceration, thus requiring extra vigilance and foot care. Current diabetes guidelines and recommendations fail to recognize the strength of the link between dialysis treatment and foot ulceration (11,13). Our findings suggest that in terms of foot ulcer risk, dialysis treatment should be ranked equivalent to a history of previous foot ulceration (i.e., risk category 3, IWGDF classification). This is analogous to diabetes being ranked equivalent to a history of prior myocardial infarction with respect to coronary heart disease risk (24).

We suggest that patients due to start dialysis and those receiving dialysis should have intensive education including the initiation of measures to prevent foot ulceration. The efficacy and cost effectiveness of preventive foot care in these patients needs to be evaluated in carefully designed intervention studies. While results from such studies are awaited, current foot care guidelines should emphasize the importance of dialysis therapy as a risk factor for foot ulceration.

Acknowledgments— This project was funded in part by Diabetes UK. We acknowledge support from the Manchester National Institute Health Research Biomedical Research Centre and Manchester Academic Health Science Centre. M.K.R. was supported by a Higher Education Funding Council for England Clinical Senior Lecturer Award. L.V. is supported by National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (grant R01-DK-71066-01A2).

No potential conflicts of interest relevant to this article were reported.

A.N. researched and analyzed data, wrote the manuscript, and reviewed/edited the manuscript. M.K.R., L.V., A.V. and L.A.L. were involved in the study design, contributed to the analysis plan, presentation, and interpretation of data, and reviewed/edited the manuscript. A.A. researched data, contributed to discussion, and reviewed/edited the manuscript. M.J. and H.A.T. researched data. A.J.M.B. conceived the study, contributed to the analysis plan, presentation, and interpretation of data, and reviewed/edited the manuscript.

References

1. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA 2005;293:217–228
2. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet 2005;366:1719–1724
3. Fernando DJ, Hutchison A, Veves A, Gokal R, Boulton AJ. Risk factors for non-ischaemic foot ulceration in diabetic nephropathy. Diabet Med 1991;8:223–225
4. Guerrero-Romero F, Rodríguez-Morán M. Relationship of microalbuminuria with the diabetic foot ulcers in type II diabetes. J Diabetes Complications 1998;12:193–196
5. Margolis DJ, Hofstad O, Feldman HI. Association between renal failure and foot ulcer or lower-extremity amputation in patients with diabetes. Diabetes Care 2008;31:1331–1336
6. Game FL, Chipchase SY, Hubbard R, Burden RP, Jeffcoate WJ. Temporal association between the incidence of foot ulceration and the start of dialysis in diabetes mellitus. Nephrol Dial Transplant 2006;21:3207–3210
7. Wolf G, Müller N, Busch M, Eidner G, Kloos C, Hunger-Battefeld W, Müller UA. Diabetic foot syndrome and renal function in type 1 and 2 diabetes mellitus show close association. Nephrol Dial Transplant 2009;24:1896–1901
8. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461–470
9. Boulton AJ, Malik RA, Arezzo JC, Sosenko JM. Diabetic somatic neuropathies. Diabetes Care 2004;27:1458–1486
10. Young MJ, Boulton AJ, MacLeod AF, Williams DR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia 1993;36:150–154
11. Boulton AJ, Armstrong DG, Albert SF, Frykberg RG, Hellman R, Kirkman MS, Lavery LA, Lemaster JW, Mills JL Sr, Mueller MJ, Sheehan P, Wukich DK. Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. Diabetes Care 2008;31:1679–1685
12. Aboyans V, Ho E, Denenberg JO, Ho LA, Natarajan L, Criqui MH. The association between elevated ankle systolic pressures and peripheral occlusive arterial disease in diabetic and nondiabetic subjects. J Vasc Surg 2008;48:1197–1203
13. International Working Group on the Diabetic Foot. *International Consensus on the Diabetic Foot.* Noordwijkerhout, the Netherlands, International Working Group on the Diabetic Foot, 2007
14. McGrath NM, Curran BA. Recent commencement of dialysis is a risk factor for lower-extremity amputation in a high-risk diabetic population. Diabetes Care 2000;23:432–433
15. Morbach S, Quante C, Ochs HR, Gaschler F, Pallast JM, Knevels U. Increased risk of lower-extremity amputation among Caucasian diabetic patients on dialysis. Diabetes Care 2001;24:1689–1690
16. Hill MN, Feldman HI, Hilton SC, Holechek MJ, Ylitalo M, Benedict GW. Risk of foot complications in long-term diabetic patients with

and without ESRD: a preliminary study. ANNA J 1996;23:381–388
17. Papanas N, Liakopoulos V, Maltezos E, Stefanidis I. The diabetic foot in end stage renal disease. Ren Fail 2007;29:519–528
18. Beckert S, Sundermann K, Wolf S, Königsrainer A, Coerper S. Haemodialysis is associated with changes in cutaneous microcirculation in diabetes mellitus. Diabet Med 2009;26:89–92
19. Lincoln NB, Radford KA, Game FL, Jeffcoate WJ. Education for secondary prevention of foot ulcers in people with diabetes: a randomised controlled trial. Diabetologia 2008;51:1954–1961
20. Young BA, Von Korff M, Heckbert SR, Ludman EJ, Rutter C, Lin EH, Ciechanowski PS, Oliver M, Williams L, Himmelfarb J, Katon WJ. Association of major depression and mortality in Stage 5 diabetic chronic kidney disease. Gen Hosp Psychiatry 2010;32:119–124
21. O'Hare AM, Vittinghoff E, Hsia J, Shlipak MG. Renal insufficiency and the risk of lower extremity peripheral arterial disease: results from the Heart and Estrogen/Progestin Replacement Study (HERS). J Am Soc Nephrol 2004;15:1046–1051
22. O'Hare AM, Glidden DV, Fox CS, Hsu CY. High prevalence of peripheral arterial disease in persons with renal insufficiency: results from the National Health and Nutrition Examination Survey 1999–2000. Circulation 2004;109:320–323
23. Ndip A, Lavery LA, Lafontaine J, Rutter MK, Vardhan A, Vileikyte L, Boulton AJ. High levels of foot ulceration and amputation risk in a multiracial cohort of diabetic patients on dialysis therapy. Diabetes Care 2010;33:878–880
24. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–234