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Diabetic peripheral neuropathy: advances in diagnosis and strategies for screeningand early intervention.

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ABSTRACT

Diabetic peripheral neuropathy (DPN) is common, and is a leading cause of lower limb amputation and disabling neuropathic pain. Amputations have a devastating impact not only on the quality of life but also result in an alarmingly low life-expectancy which on average is only two years from the event. It also places a substantial financial burden on healthcare systems and society in general. Whie the prevalence of blindness in working age adults in the UK is falling, diabetes-related amputations are rising not only in the UK but also globally. This article reviews new innovations that enable the early diagnosis of DPN and assesses the evidence for early multiple risk factor management strategies to improve DPN. Through this review we put forward the case for early multifactorial interventions as the best prospect for preventing/halting DPN, and it's devastating sequelae.

KEYWORDS

Diabetic peripheral neuropathy, limb amputation, multifactorial intervention, diabetes mellitus.

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INTRODUCTION

Diabetic peripheral neuropathy (DPN) is the most common complication of both type 1 and 2 diabetes and occurs in over half of affected individuals [1,2]. In the UK, diabetes remains the commonest non-traumatic cause of lower limb amputations [3]. Each week in England there are around 140 amputations in people with diabetes [4]. Amputation is not only devastating in its impact on the individual and their family, but also a leading cause for loss of independence and livelihood. In low-income countries the financial costs can be equivalent to 5.7 years of annual income, potentially resulting in financial ruin for these patients and their families [5]. It also places a substantial financial burden on healthcare systems and society in general. In the USA, the total annual cost of managing symptomatic DPN (painful) and its complications (foot ulcerations and lower limb amputations) was estimated to be between $4.6 and $13.7 billion, with up to 27% of the direct medical costs of diabetes attributed to DPN [6]. Urgent action is needed in order to address this growing global health problem. Unfortunately, only 50 per cent of people with diabetes who have an amputation survives for two years [7,8]. Moreover, the relative likelihood of death within five years following a diabetic foot ulcer is greater than for colon, prostate and breast cancer (Figure 1) [9,10]. The most shocking fact of all, however, is that most of these amputations are preventable. It is estimated that 80% of amputations could be prevented through good podiatry care which not only reduces amputation risk, but also dramatically impacts the rate of hospitalization, and indeed re-ulceration [11].

NATURAL HISTORY OF DIABETIC PERIPHERAL NEUROPATHY

Diabetic peripheral neuropathy is the key initiating factor inthe development of diabetic foot ulceration [11]. It is a predominantly sensory neuropathy with autonomic nervous system involvement although there are often motor features with advancing disease. DPN is not only the commonest cause of non-traumatic lower limb amputations, but is also a cause of impaired balance and gait [12,13] and distressing neuropathic pain that is often unresponsive to therapy [14]. The neuropathy is symmetrical and length-dependent, affecting the longest nerves, hence involves the feet first [15]. Unfortunately, the early manifestations of this insidious disease are often missed until the disease is well established, at which point it appears irreversible [15].

THE CURRENT STATE OF AFFAIRS

Nerve conduction studies are the current ‘gold’ standard for the diagnosis of DPN [16]. This robust measure also predicts foot ulceration and mortality [17]. However, they are labour intensive, timeconsuming,costly and impractical to implement in routine clinical care.

Currently, there are no simple markers for early detection in routine clinical practice for DPN. The measures we use are crude and detect the disease very late in its natural history. Even the benefits gained by standardising clinical assessment using scored clinical assessments such as the Michigan Neuropathy Screening Instrument (MNSI) [18], the Toronto Clinical Neuropathy Score (TCNS) [19] and the United Kingdom Screening Test (UKST) [20], remain subjective, heavily reliant on the examiners' interpretations [21]. Bedside tests used to aid diagnosis of neuropathy such as the 10g monofilament [22,23], the Ipswich Touch Test [24] and vibration perception threshold using the tuning fork [25] are not only reliant on patients' subjective response but are mainly utilised to identify the loss of protective foot sensation and risk of ulceration [26]. As such, these tests tend to diagnose DPN when it is already well established [27]. Late diagnosis hampers the benefits of intensive management at an early stage of disease trajectorywhich includes a focus on intensified multifactorial intervention , and the prevention of neuropathy-related sequelae [28]. Conversely, the situation is different for the detection of diabetic retinopathy using digital camera-based retinal photography or diabetic kidney disease using blood and urine tests. These developments led to the institution of a robust annual screening program in many countries that has led to significant reduction in blindness [29], such that retinopathy is no longer the commonest cause of blindness in working age adults [30,31] and reductions in end-stage renal failure [32]. Unfortunately, by the time neuropathy is detected using these crude tests, it is often very well established and consequently impossible to reverse or even to halt the inexorable neuropathic process.

RECENT DEVELOPMENTS IN STATE-OF-THE ART POINT-OF-CARE DEVICES (POCD)

Significant progress has been made to develop point-of-care devices (POCD) that are capable of diagnosing early, subclinical neuropathy. Papanas et al. have recently comprehensively reviewed these devices [33]. Therefore, we will briefly outline the following devices: the NeuroQuick [34], NeuroPAD [35], NC-Stat DPN-Check [36-38], Corneal Confocal Microscopy (CCM) [39,40] and Sudoscan [41,42].

1. DPN Check

The DPN-Check is a novel, user-friendly, handheld POCD that performs a sural nerve conduction study in three minutes. It is an acceptable proxy for standard nerve conduction studies which are time-consuming, expensive and often require patients to be seen in specialists' clinics. The DPN check has been demonstrated to have excellent reliability with an inter- and intra-observer intraclass correlation coefficients of between 0.83 and 0.97 for sensory nerve action potentials respectively [36]. It also has good validity with 95%

sensitivity and 71% specificity when compared against reference standard nerve conduction study [37] [36] for the diagnosis of DPN.

Nerve conduction studies, however, is only an assessment of large nerve fibre function. DPN, on the other hand, usually involves both small and large nerve fibres, with some evidence suggesting small nerve fibre involvement early in its natural history [43,44]. Small nerve fibres constitute 80-91% of peripheral nerve fibres and control pain perception, autonomic and sudomotor function. Although intraepidermal nerve fibre density measurement from lower limb skin biopsy is considered the gold standard for the diagnosis of small fibre neuropathy [45,46] it is invasive and hence not suitable for routine screening. However, a number of POCDs have been developed to assess small fibre dysfunction. These include:

2. NeuroQuick

Thinly myelinated Aδ and unmyelinated C-fibres are small calibre nerves that mediate thermal sensation and nociceptive stimuli. Quantitative sensory testing of thermal discrimination thresholds is a non-invasive test used to examine impaired small nerve fibre function. NeuroQuick is a handheld device for quantitative bedside testing of cold thermal perception threshold. It allows near patient assessment of small fibre dysfunction avoiding the use of time-consuming and expensive quantitative sensory testing equipment in a laboratory. To date, one published clinical validation study has been performed in a diabetic population which suggests it is a valid and reliable screening tool for the assessment of small fibre dysfunction [34]. Use of NeuroQuick was more sensitive in detecting early DPN compared to the traditional bedside screening tests such as the tuning fork or elaborate thermal testing [34]. However, it is a psychophysical test that relies on the cognition/attention of the patient. Furthermore, the coefficients of variation for repeated NeuroQuick measurements ranged between 8.5% and 20.4% [34]. Further studies are required to demonstrate whether the NeuroQuick is a useful screening tool to detect small fibre dysfunction in DPN.

3. NeuroPad

This is a 10-minute test which measures sweat production on the plantar surface of the foot. It is based on a colour change in a cobalt compound from blue to pink which produces a categorical output with a modest diagnostic performance for DPN compared to electrophysiological assessments. No training is required to administer Neuropad, nor does it require responses from the patient. Therefore, this method of assessment may be more

suitable for screening in community settings and those with cognitive or communication difficulties who have to respond to other methods of assessment. A number of clinical validation studies [47-49] have been conducted which demonstrates low sensitivity for large fibre neuropathy (50-64%) but much higher sensitivity for small fibre neuropathy (80%) [50]. Neuropad has also shown good reproducibility with intra- and inter-observer coefficient of variation between 4.1% and 5.1% [51]. The main utility of the Neuropad as a screening tool is the exclusion of DPN [52].

4. Corneal Confocal Microscopy (CCM)

Another technique that has attracted significant interest, with a large number of publications over the past 15 years, is CCM. This is a non-invasive ophthalmic application that measures various structural parameters (e.g. branch density and length) of small corneal nerve fibres [53,54]. There have been a number of clinical validation studies including one 3.5-year prospective study in T1DM which demonstrated relatively modest to high sensitivity (82%) and specificity (69%) of CCM for the incipient DPN [55]. It has good reproducibility for corneal nerve fibre length measurements with intra- and inter-observer intraclass correlation coefficients of 0.66-0.95 and 0.54-0.93 respectively [56,57]. The reproducibility improves with the automated algorithm (intraclass correlation coefficient 1.0) [58]. Currently, CCM is used in specialist centres, but would suit widespread application given its easy application for patient follow-up. However, large, multicentre, prospective studies are now required to confirm that corneal nerve changes unequivocally reflect the complex pathological processes in the peripheral nerve. Moreover, the establishment of a normative database and technical improvements in automated fibre measurements and wider-area image analysis may be useful to increase diagnostic performance.

5. Sudoscan

Sudomotor function has been proposed as a surrogate marker for the small fibre involvement in DPN [41,42,59]. Sudoscan, provides a quantitative measurement of sudomotor function within 3-minutes. Its measurement is based on an electrochemical reaction between electrodes and chloride ions, after stimulation of sweat glands by a low-voltage current (<4volts) [60]. A measurement of electrochemical skin conductance (ESC) for the hands and feet, that are rich in sweat glands, is generated from the derivative current associated with the applied voltage [60]. Sensitivity and specificity of foot ESC for classifying DPN were 87.5% and 76.2%, respectively [42]. The area under the ROC curve (AUC) was 0.85 [42]. The reproducibility was also tested in T2DM patients in feet and hands were ICC 0.95 (0.89–0.98) and 0.88 (0.74–0.96) respectively [61].

In summary, the sensitivity of POCDs are acceptable and a combination of devices assessing both small and large fibre function should be used for detecting DPN (Table 1). However, there is high heterogeneity and patient selection bias in most of the studies. Further studies are needed to evaluate the performance of each POCDs based on Wilson criteria for screening of undiagnosed DPN at the population level [62]. Prospective studies of hard endpoints (e.g. foot ulcerations and lower limb amputations) are also necessary to ensure that the benefits of screening are important for patients. The cost-effectiveness of implementing screening using these devices also needs to be carefully appraised. POCDs provide rapid, non-invasive tests that could be used as an objective screening test for DPN in busy diabetic clinics, ensuring adherence to current recommendation of annual assessment for all diabetic patients that remains unfulfilled.

RATIONALE FOR AN EARLY DETECTION AND MULTIFACTORIAL INTERVENTION

Early detection of DPN can only be advocated if there is robust evidence that early treatment or intervention results in better outcomes than at a later stage. Diabetic peripheral neuropathy is a culmination of a complex interaction of several aetiologically linked pathophysiological processes –many not fully understood. Although hyperglycaemia and duration of diabetes play an important role in DPN, other risk factors have also been identified [63,64]. The EuroDiab Prospective Complications study demonstrated that the incidence of DPN is associated with other potentially modifiable cardiovascular risk factors, including a raised triglyceride level, hypertension, obesity and smoking (Figure 2), [65].

Here we discuss potentially modifiable risk factors that could be addressed early to manage DPN effectively:

1) Hyperglycaemia

Chronic hyperglycaemia plays a key role in the pathogenesis of DPN [66,67]. Through several disturbances in the metabolic pathways, hyperglycaemia leads to abnormalities in nerve polyol, hexosamine and protein kinase C pathways [68]. This triggers the release of proinflammatory cytokines [poly ADP-ribose polymerase (PARP)], the accumulation of advanced glycation end products (AGEs) and generation of reactive oxygen species [68] [60new]. Simultaneously, microangiopathic changes of the vasa nervorum result in neuroischaemia [69]. This is further exacerbated by impaired endothelial nitric-oxide mediated vasodilatory mechanisms (nitrosative stress) [70]. Separately and in concert, these glucotoxic metabolic and ischaemic changes lead to DPN by producing nervous system oxidative stress and apoptosis of both neurons and supporting glia.

In the Diabetes Control and Complications Trial (DCCT) intensive insulin treatment in T1DM reduced the risk of DPN (78% relative risk reduction) [71,72]. In the Epidemiology of Diabetic Complications (EDIC) study, at the 14 years after DCCT closeout, although DPN progressed substantially in both treatment groups, its prevalence and incidence remained significantly lower in the former intensively treated group [73]. A recent Cochrane review, however, indicated that the evidence of the benefit of intensive glucose control in T1DM is mainly from studies in younger patients at early stages of the disease and that the effects of tight blood glucose control seem to become weaker once complications are established [74]. On the other hand, in T2DM improving glycaemic control alone does not have the same impact on reducing the incidence of DPN (5-9% relative risk reduction) [74]. Even when trials demonstrate tighter glucose control might have a beneficial impact in preventing progression of DPN in T2DM, e.g. the ACCORD study [75], confusion arises when it is reported that a self-reported history of DPN at baseline was associated with a higher risk of mortality with intensive glycaemic treatment [76]. However, in this study, neither MNSI-documented DPN nor history of amputation was associated with a differential effect on mortality between the two treatment arms. This discrepancy suggests the two methods of detecting DPN may identify different populations and merits further investigation. Similar discordance among various indices of neuropathy in their strength for predicting outcome was also apparent in the DIAD study [77]. Several other long-term studies of multi-factorial cardiovascular risk intervention in T2DM [78-81] and pre-diabetes [82] have failed to slow the progression or reduce the incidence of DPN. It must be emphasised that DPN was not a primary outcome in these trials and its inclusion appears to be an afterthought, as inconsistent and insensitive measures to detect and monitor DPN were employed.

In contrast, when appropriate DPN clinical endpoints are used the outcomes appear more promising. The first randomised controlled trial that demonstrated the benefit of intensive management on the incidence of DPN in T2DM was the Kumamoto trial [83]. This study showed significant improvement in nerve conduction parameters in the intensively treated group demonstrating the importance of choosing the most appropriate surrogate marker of DPN. Nearly 50 years ago, a smaller study also utilizing nerve conduction studies demonstrated that DPN is reversible in newly diagnosed T2DM patients with appropriate treatment [84]. Moreover, in T2DM the choice agents used to achieve targets may also be as important as the glucose targets themselves. The BARI 2D trial demonstrated that the cumulative incidence of DPN was significantly lower when insulin-sensitizing agents (metformin, thiazolidinediones) were used compared to an insulin-providing (sulphonylureas, insulin) strategy [85].

2) Dyslipidaemia

Observational and cross-sectional studies have demonstrated, to varying degrees, an association between hyperlipidaemia and DPN [86]. The strongest evidence, however, is for the association of elevated levels of triglycerides and DPN [87]. In a study of patients with T2DM there was a graded relationship between triglyceride levels and the risk of lower-limb amputations [87]. Likewise, another study demonstrated that hypertriglyceridaemia was an independent risk factor for loss of sural (myelinated) nerve fibre density and lower limb amputations [88]. In addition to hypertriglyceridemia, low-level of HDL cholesterol has been reported as an independent risk factor for DPN [86]. However, clinical studies investigating the effects of statins on the development of DPN are far from conclusive. This is partly because several large statin studies that included patients with diabetes did not report data on the development of microvascular disease [89-91] let alone DPN. The Freemantle Diabetes Study, an observational study with cross-sectional and longitudinal analysis, suggested that statin or fibrate therapy may be associated with a reduced risk of DPN in people with T2DM [92]. Two subsequent, relatively small, randomised clinical studies have reported improvements in nerve conduction parameters of DPN following 6 to 12 weeks of statin treatment [93,94]. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study has since, demonstrated that fibrates are beneficial in preventing microvascular complications including DPN [95].

3) Hypertension

An association between hypertension and DPN has been demonstrated in several observational studies in both T2DM [96,97] and T1DM [98]. There is some preliminary evidence from relatively small randomised control trials with improvements in DPN based on clinical and nerve conduction parameters following antihypertensive treatment with angiotensin converting enzyme (ACE) inhibitors [99] and calcium channel blockers [100].

4) Lifestyle

Several studies have revealed an association between obesity and DPN even in the presence of normoglycaemia [101-104]. Not surprisingly, DPN prevalence increases in obese patients with prediabetes and diabetes [105]. Subsequent studies appear to demonstrate that adopting a healthy lifestyle incorporating a balanced diet, regular aerobic and weight-resistance physical activities may reverse the process, particularly if they are undertaken at an early stage of DPN [106-108]. A randomised control study of a 2.5-hour, weekly supervised treadmill exercise and dietary intervention programme aimed at

normalising body mass index or losing 7% baseline body weight in T2DM demonstrated significant improvement in markers (intraepithelial nerve fibre density and regenerative capacity) of DPN [109]. However, once DPN is established, restoration of normal weight did not show significant improvement [109]. A variety of different dietary interventions have been examined including a low fat, low calorie diet in the DPP study [110] and a Mediterranean diet [111] but presently there is no consensus on a specific regime. Once again, these studies suggest that if the disease is identified early and the appropriate surrogate marker is used, DPN can be reversed by lifestyle intervention.

5) Multiple risk factor lowering interventions

Based on the studies above, there is some evidence to suggest targeting lifestyle and individual risk factors can improve DPN. Disappointingly, however, several large intervention studies targeting multiple risk factors (UKPDS [112], STENO-2 [113], ADDITION [114]) failed to show a reduction in DPN despite clear benefits in renal and retinal complications. The best possible explanation is that the methods used to diagnose/quantify DPN lacked the necessary sensitivity or reliability to diagnose/quantity DPN let alone examine differences between study groups. The heterogeneity in effect size estimates for DPN in these studies supports this view. Nevertheless, the STENO-2 study did show that 4 years of intensive multifactorial treatment slowed the progression of autonomic neuropathy (OR, 0.32; 0.12-0.78) [113]. More recently, publication of the 21-year follow-up showed a reduction in the progression to autonomic neuropathy (HR, 0.59; 95% CI, 0.40-0.89) in the intensive treatment arm [115]. This data suggests a long-term benefit of earlier multifactorial intervention i.e. a legacy effect. Further research is needed to re-examine the impact of multifactorial interventions upon DPN using more reliable, reproducible and sensitive measures of DPN.

In summary, although the risk factors for DPN are well recognised, to-date only small-scale intervention studies targeting these risk factors have been conducted which have used DPN measures that are ‘fit-for-purpose’. Nevertheless, most of the current evidence points to multiple risk factor intervention as the best way to prevent the development and progression of DPN. Unfortunately, despite several clinical trials [116], there has been relatively little progress in the development of disease-modifying treatments [117-119] despite some advances in the management of symptoms in painful DPN [120-122]. Hence, early identifications of subjects with incipient/sub-clinical neuropathy using validated, yet novel non-invasive POCDs will allow larger studies to determine if targeted intensified cardiometabolic risk factor control can prevent clinical DPN or halt disease progression.

FUTURE PERSPECTIVES

Ultimately, the prevention of DPN will have the greatest impact on reducing amputations dramatically as 90% of patients attending the diabetic foot clinic and virtually all diabetes amputees have DPN [11]. Clearly, in those with established DPN careful foot ulcer risk assessment (including peripheral vascular status, deformity etc.) and appropriate management (education, footwear, podiatry) and risk factor management is warranted. Currently, a robust system of an annual foot screening, yet alone multifactorial risk factor interventions, for all diabetic patients, as advocated by the American Diabetes Association and Diabetes UK has not been implemented systematically. This was confirmed by the UK National Diabetes Audit (2016) [123] and the US National Health and Nutrition Examination Surveys (NHANES) [124]. These showed that the attainment of recommended vascular risk management targets was alarmingly low between 19-40%. More worryingly, only 30% adults aged 50 years or less achieved these targets. The National Diabetes Foot Care Audit (2014-17) showed a high prevalence of diabetic foot ulcers where 30% of patients self-presented despite an 85% attendance of annual foot surveillance screening. In addition, foot surveillance screening did not identify a third of individuals who subsequently developed diabetic foot ulcers [125]. This suggests that 1) the current process of care is inadequate (involving multiple visits to different members of the clinical team who do not have specialist training to assess the level of risk and provide advice/education and signpost/refer patients to receive the appropriate interventions/treatment) [126] and 2) the methods used to screen for DPN are insensitive and/or lack reliability to accurately measure risk of developing foot ulceration.

To improve clinical outcomes in DPN as in retinopathy and nephropathy, there is an urgent need to: 1) diagnose DPN early before overt clinical signs are apparent and 2) assess disease progression accurately in order to effectively reduce morbidity and 3) reliably inform patients of their underlying risk of foot ulceration. In addition, screening tests should be safe, quick and sufficiently simple to provide objective measures in a busy clinical context. Current evidence suggests that some of the recently developed POCDs fulfil these criteria. Once DPN has reached at a stage detectable by conventional bed-side tools, it might be too advanced for any intervention to reverse/halt the process. A meta-analysis of almost all the major trials on T2DM showed that when DPN is established, no intervention is effective in reversing its progression (Figure 3). However, there is an increasing body of emerging evidence which suggests that multifactorial risk reduction strategies, including structured exercise and education on lifestyles, a healthy diet, smoking cessation and obesity

management may be effective in preventing the development and progression of DPN, particularly at the stage of pre-diabetes and early diabetes [106,107].

In the UK, since the roll-out of population-based digital retinal screening programme, diabetes is no longer the leading cause of blindness in working age adults [127]. This successful screening programme has been well received with an 81% uptake. Likewise, following the implementation of a standardised protocol for early detection and management for diabetic nephropathy, there has been a significant improvement in the renal outcomes [128,129]. Such a robust program of screening doesn't exist for DPN or the diabetic foot. The scale of morbidity and mortality attributed to DPN is not in question. Furthermore, the longitudinal examination of cohorts has established the overall course of the condition [130]. Undiagnosed DPN is common [131] and by the time symptoms and/or clinical signs develop DPN is already well-established and associated with future risk. Up to 30% of patient with diabetic foot ulcers self-present despite an 85% attendance of annual foot surveillance programme [125]. A 'One-Stop service' is needed to screen for complications in one visit. Foot screening could be performed by a specialist podiatrist to assess the level of foot ulcer risk and manage patients appropriately, in order to prevent foot ulceration and amputation. In addition, DPN screening can be performed using POCDs in patients with normal physical examination (e.g. 10g monofilament, 128hz tuning fork, Ipswich touch test, Vibratip) to identify the early sub-clinical disease. This intervention was recently piloted in retinal screening clinics in a hospital and community setting [132]. A trained podiatrist performed detailed assessments of foot ulcer risk and used combined small and large nerve fibre assessments (NC-stat DPN-check and Sudoscan) for the diagnosis of subclinical DPN. This pilot study also examined the feasibility and acceptability of a "one-stop clinic" for combined screening for all microvascular complications. Combined eye, renal, DPN and foot ulcer risk screening was found to have a high uptake, reduced clinic visits, led to an early diagnosis of DPN (93.2% sensitivity for the diagnosis of DPN, Figure 4), unmasked new painful DPN, and appeared to be an effective model for the early diagnosis of DPN and management of foot complications.

CONCLUSION

Lower limb amputations are on the rise globally in contrast to other complications of diabetes. There is emerging evidence that DPN in T2DM starts early and can even be present in pre-diabetes principally driven by vascular risk factors. There is some evidence to suggest risk factor management strategies can improve DPN. However, lack of a robust, annual foot/DPN screening program utilising sensitive measures to detect neuropathy is resulting in the late diagnosis of DPN and the development of foot complications. There is

thus a good rationale for implementing a robust annual diabetes microvascular screening program, preferably in a “one-stop” service. Early detection of microvascular complications including subclinical DPN will allow the implementation of a multi-factorial risk reduction strategy when interventions are likely to prevent disease progression. The information that is provided about the tests and its outcomes could be tailored so that it is of value and readily understood by the individual being screened to make ‘informed decisions’. This will lead to an integrated partnership model, empowering and enabling patients to self-manage their risk factors with positive lifestyle choices, supplemented by an individually-tailored, target-driven intervention with carefully selected pharmacotherapy, orthotic devices and podiatry follow-up. This is the best hope of preventing the rising tide of lower limb amputations in people with diabetes.

Figures

Figure 1: Relative 5-year survival after diabetic foot ulcer and the most common cancers. Adapted from [3].

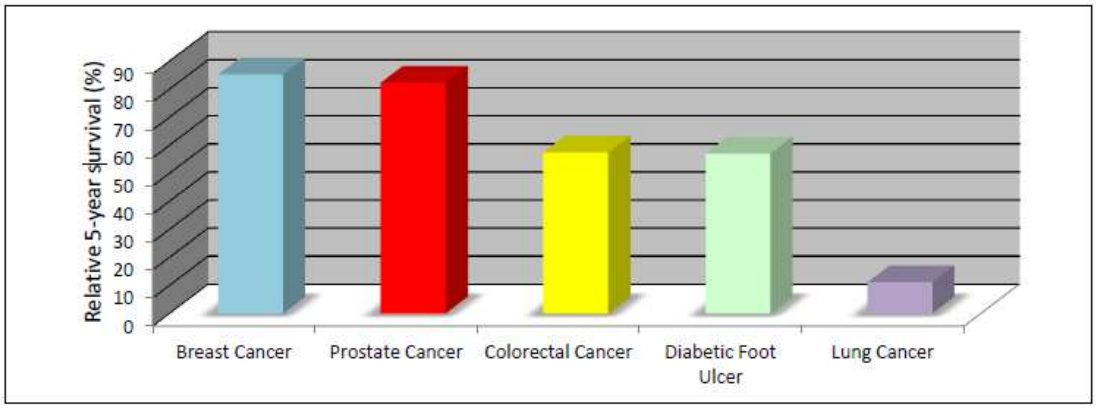


Figure 2: Odds ratios for associations between key risk factors and the incidence of diabetic neuropathy with the use of two logistic regression models. Adapted from [51].

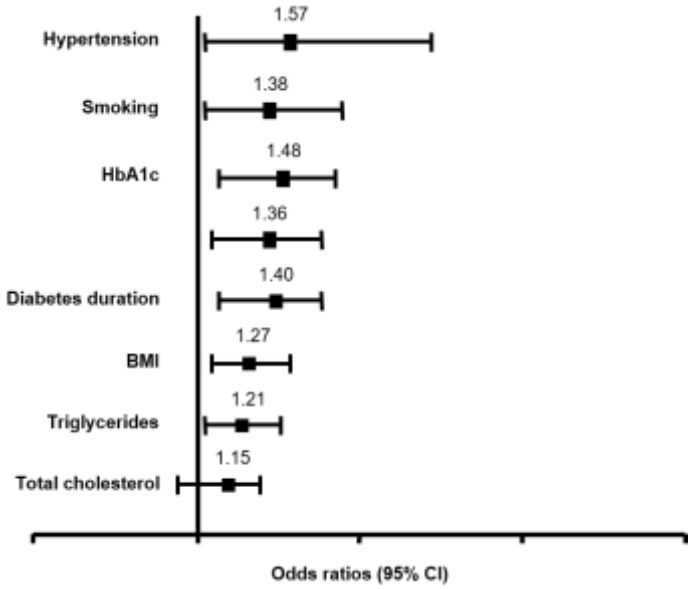
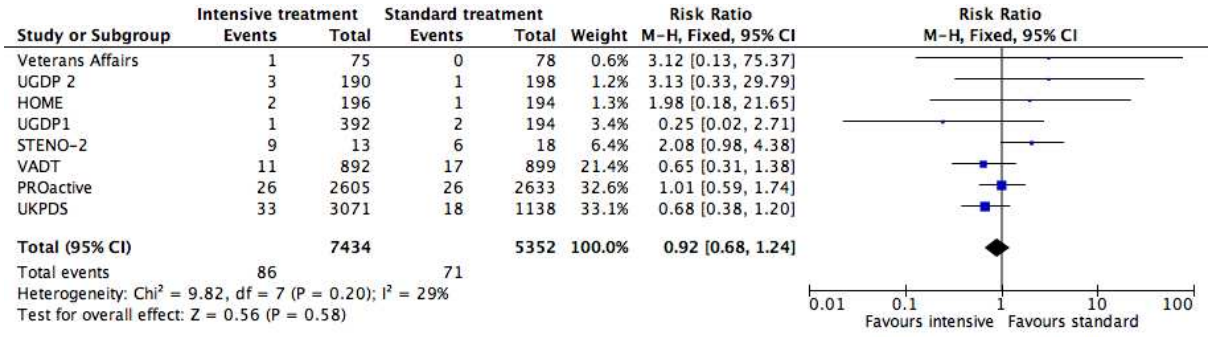


Figure 3: Forest plot showing no significant effect of intensive treatment on diabetic peripheral neuropathy event or amputation.



Study or Subgroup	Intensive treatment Events	Total	Standard treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Veterans Affairs	1	75	0	78	0.6%	3.12 [0.13, 75.37]
UGDP 2	3	190	1	198	1.2%	3.13 [0.33, 29.79]
HOME	2	196	1	194	1.3%	1.98 [0.18, 21.65]
UGDP1	1	392	2	194	3.4%	0.25 [0.02, 2.71]
STENO-2	9	13	6	18	6.4%	2.08 [0.98, 4.38]
VADT	11	892	17	899	21.4%	0.65 [0.31, 1.38]
PROactive	26	2605	26	2633	32.6%	1.01 [0.59, 1.74]
UKPDS	33	3071	18	1138	33.1%	0.68 [0.38, 1.20]
Total (95% CI)		**7434**		**5352**	**100.0%**	**0.92 [0.68, 1.24]**
Total events	86		71			

Heterogeneity: $Chi^2 = 9.82$, df = 7 (P = 0.20); $I^2 = 29\%$
Test for overall effect: Z = 0.56 (P = 0.58)

Figure 4: ROC curve for the identification of diabetic distal symmetrical polyneuropathy (DPN) using point of care devices: 10g monofilament (MF), DPN-Check [sural sensory nerve amplitude (SNAP, μV) and conduction velocity (SNCV, m/s)] and SUDOSCAN feet electrical skin conductance (ESC, μS). Symbols ◊, **ǂ and *** represent cut off points for DPN-Check SNCV, SNAP and SUDOSCAN feet ESC respectively. Adapted from [122].

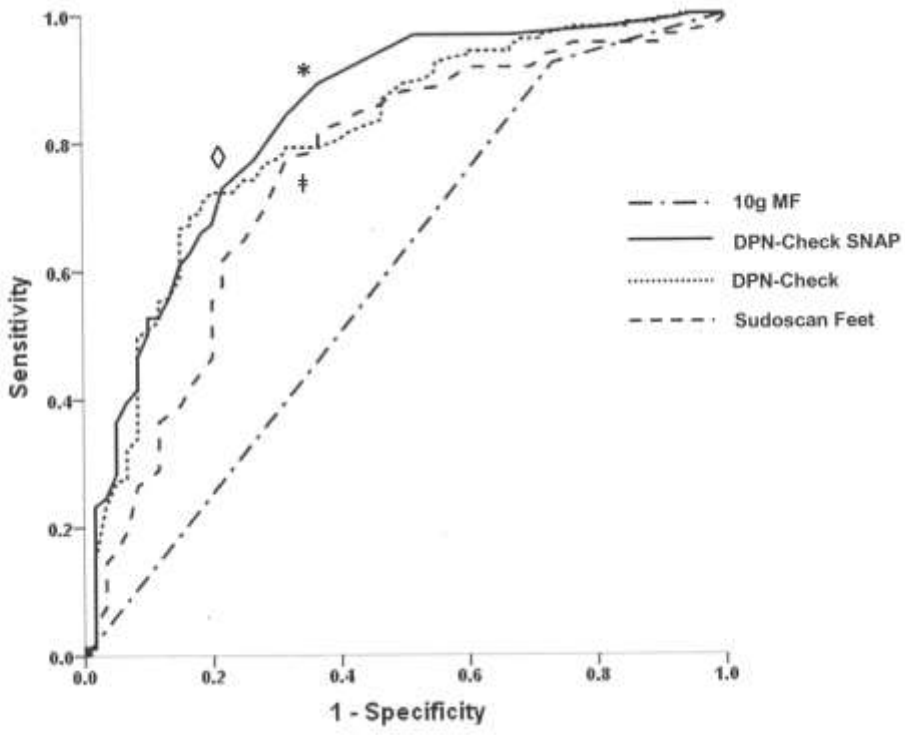


Table 1: Clinical utility of devices used for the diagnosis of DPN (adapted from Papanas et al) [33]. *Intraclass correlation coefficient using an automated algorithm; N/A not available.

Devices	Function	Fibres Assessed	Validated against	Sensitivity (%) /Specificity (%)	Intra/Inter Observer ICC	Early Diagnosis
DPN Check [37,124,133]	Sural Sensory Nerve function	Large Aα/Ab fibres	Nerve conduction studies, Standardised clinical examination, Laser Doppler LDI flare	84.3-90.5/68.3-86.1	0.94-0.97/0.79-0.83	Yes
NeuroQuick [34]	Thermal Sensory Perception	Small Aδ/C fibres	Nerve conduction studies, Standardised clinical examination, Vibration perception threshold,	N/A	0.75-0.95/N/A	Yes
NeuroPad [51,52]	Sudomotor Function	Small C fibres	Nerve conduction studies, Standardised clinical examination, Vibration perception threshold, Skin biopsy IENFD	65.1-100/32-78.5	4.1/5.1	Yes
CCM [55-58,134]	Corneal Nerve Fibre Morphometry	Small C fibres	Nerve conduction studies, Standardised clinical examination, Vibration perception threshold, Skin biopsy IENFD	82/69	0.66-0.95/0.54-0.93 1.0*	Yes
Sudoscan [41,61]	Sudomotor Function	Small C fibres	Nerve conduction studies, Standardised clinical examination, Thermal Perception Threshold	87.5/76.2	0.88/0.95	Yes

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