



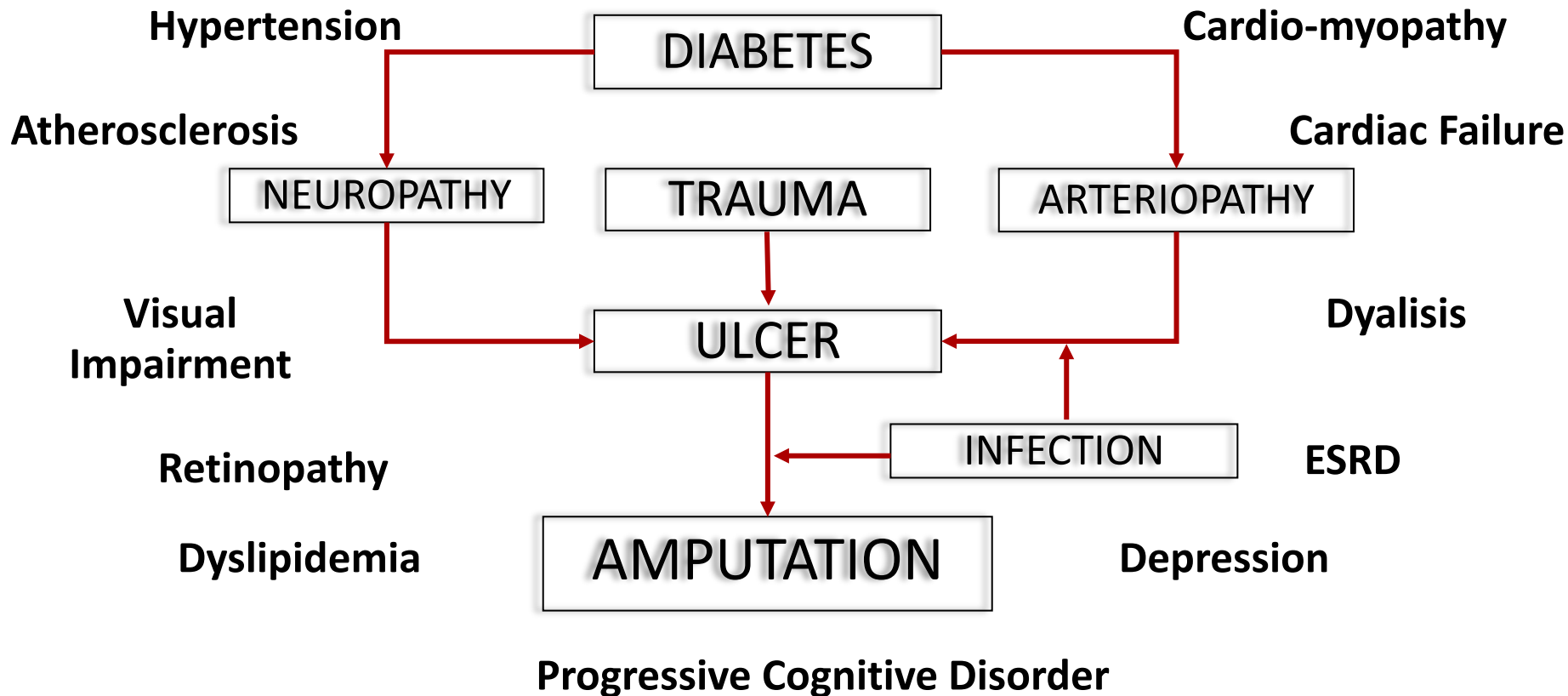
LE COMORBIDITÀ CHE “FANNO LA COMPLESSITÀ:

IL PIEDE DIABETICO COME MARKER CARDIOVASCOLARE

Dr.ssa Letizia Pieruzzi

Sezione Dipartimentale Piede Diabetico - Dipartimento di Medicina Specialistica
Azienda Ospedaliero-Universitaria Pisana

Chronic Metabolic Disturbance



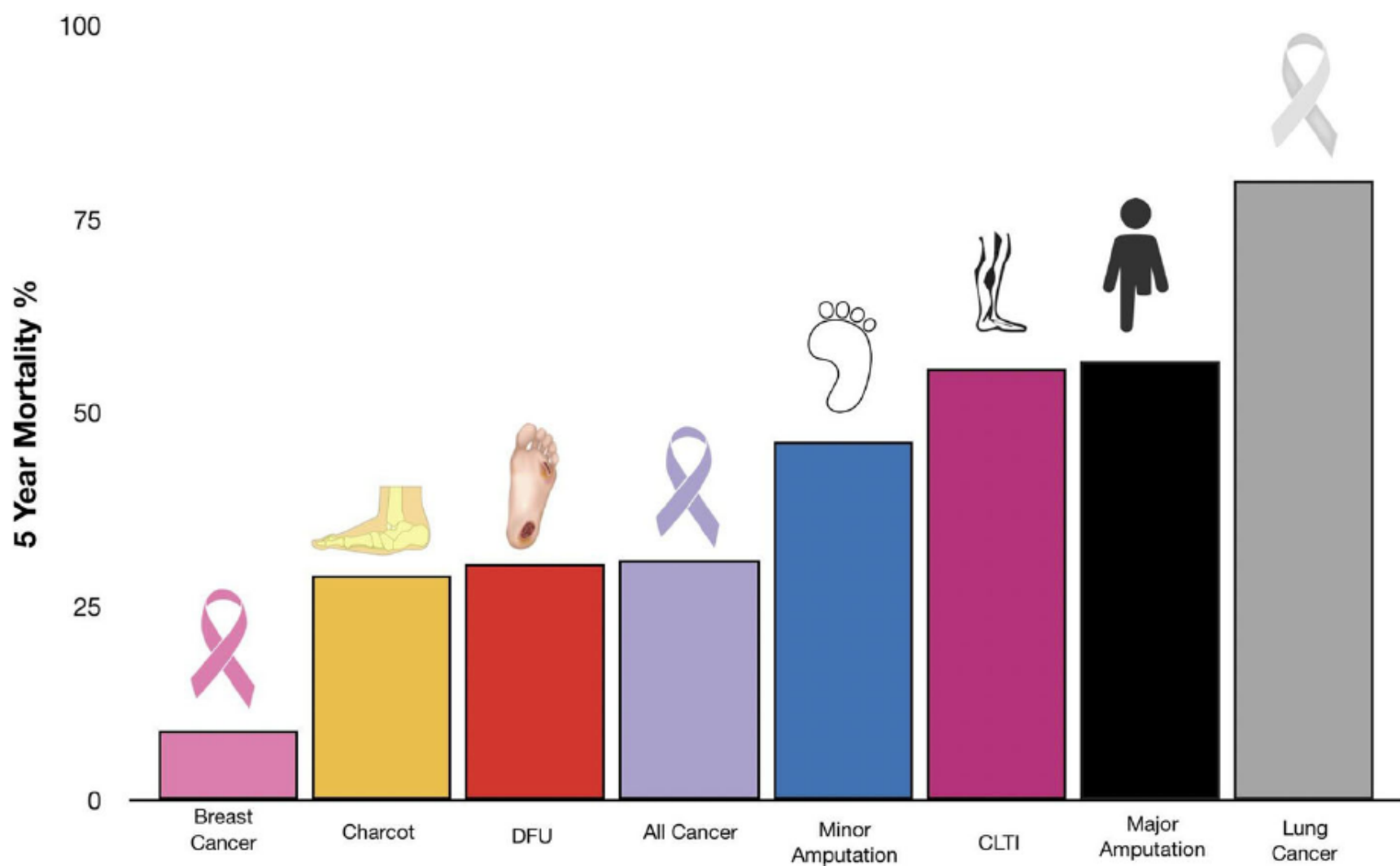
COMMENTARY

Open Access

Five year mortality and direct costs of care for people with diabetic foot complications are comparable to cancer



David G. Armstrong^{*}, Mark A. Swerdlow, Alexandria A. Armstrong, Michael S. Conte, William V. Padula and Sicco A. Bus



Review Article

Diabetic Foot Syndrome as a Possible Cardiovascular Marker in Diabetic Patients

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LIPID AND METABOLIC EFFECTS OF GASTROINTESTINAL SURGERY (R. COHEN, SECTION EDITOR)

The Diabetic Foot as a Proxy for Cardiovascular Events and Mortality Review

**Isa Dietrich^{1,2} • Gustavo Arruda Braga² • Fernanda Gomes de Melo² •
Ana Carolina Calmon da Costa Silva Silva²**

Published online: 2 October 2017

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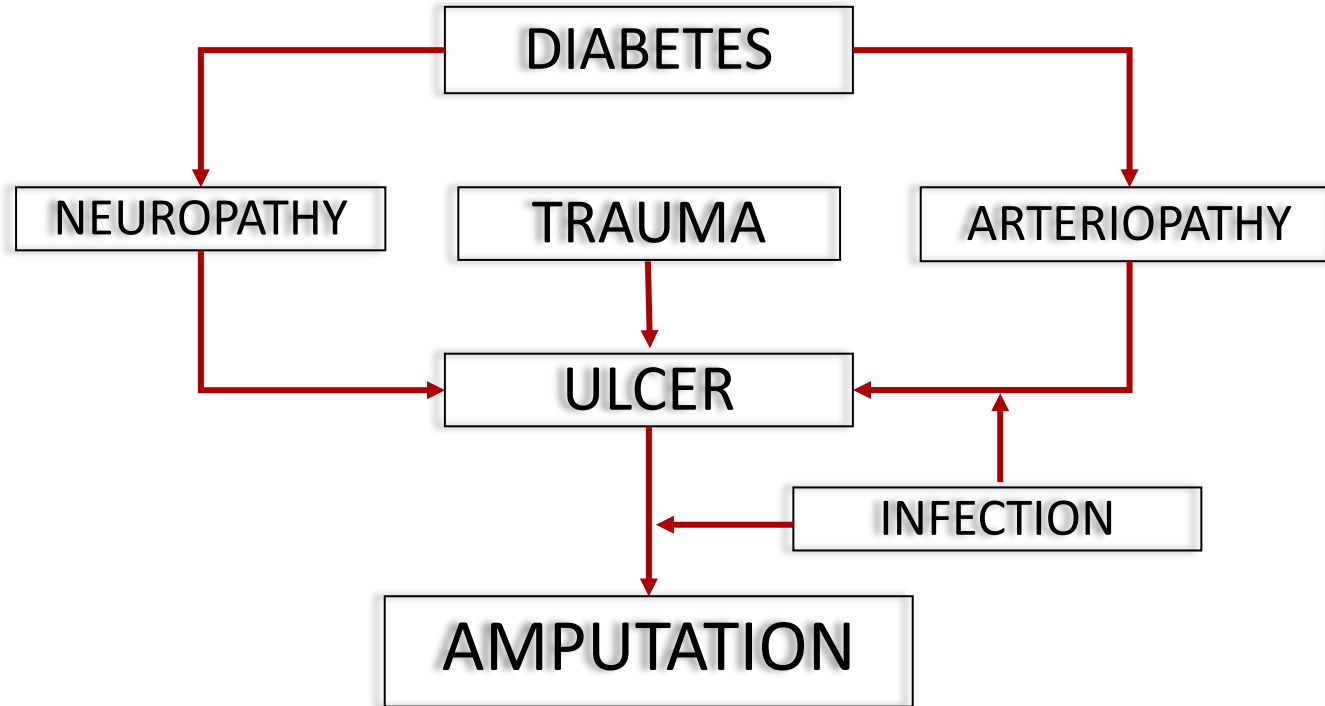
A satellite map of Italy and the surrounding Mediterranean Sea. The map shows the Italian peninsula, Sicily, and Sardinia. Overlaid on the map are four white text labels with small black square markers. The labels provide demographic and administrative statistics for Italy. The first label, '60 M abitanti', is positioned in the upper left. The second, '3 M DM', is located in the central part of the peninsula. The third, '300.000 DF', is further south. The fourth, '3.382 LEA', is in the southern part of the peninsula.

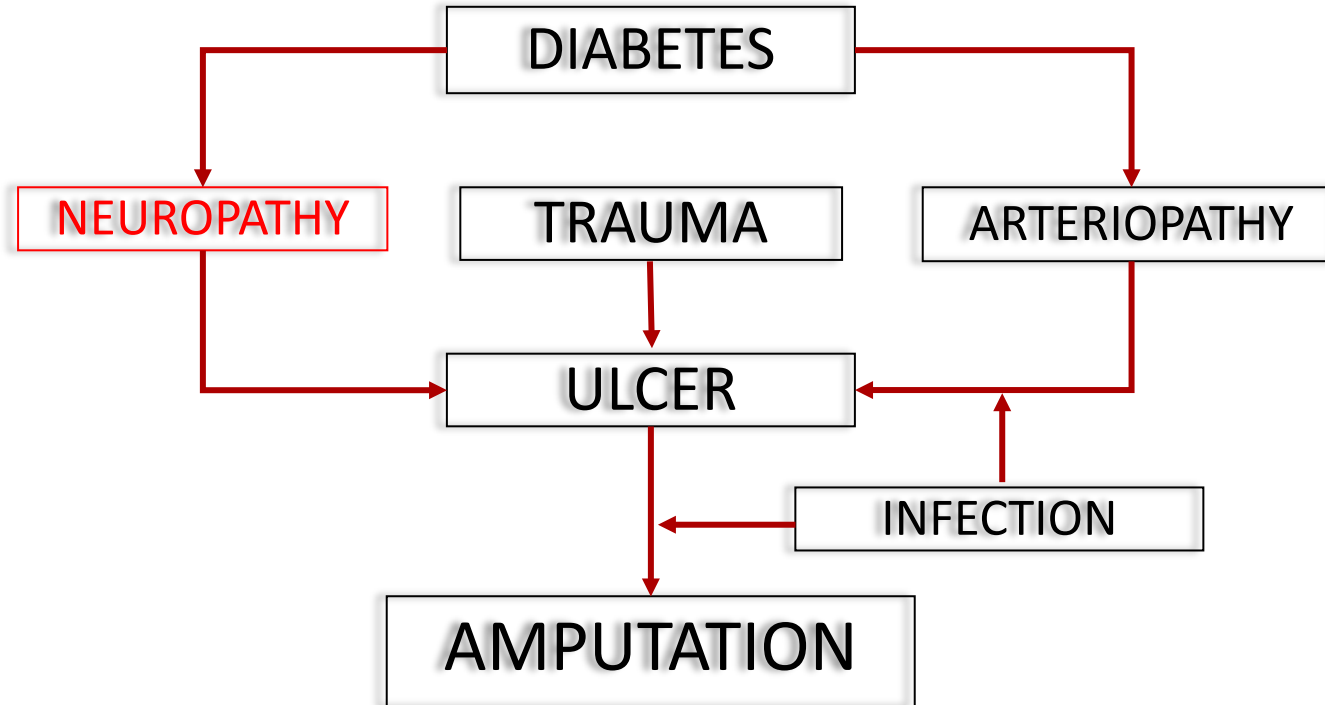
60 M abitanti

■ 3 M DM

■ 300.000 DF

■ 3.382 LEA







Mortality Associated With Acute Charcot Foot and Neuropathic Foot Ulceration

JULIETTE VAN BAAL, MSc^{1,2}
RICHARD HUBBARD, MD³

FRAN GAME, FRCP¹
WILLIAM JEFFCOATE, MRCP¹

OBJECTIVE — To compare the mortality of patients with an acute Charcot foot with a matched population with uninfected neuropathic foot ulcers (NFUs).

RESEARCH DESIGN AND METHODS — Data were extracted from a specialist departmental database, supplemented by hospital records. The findings were compared with the results of earlier populations with Charcot foot and uninfected NFUs managed from 1980. Finally, the results of all patients with acute Charcot foot and all control subjects managed between 1980 and 2007 were compared with normative mortality data for the U.K. population.

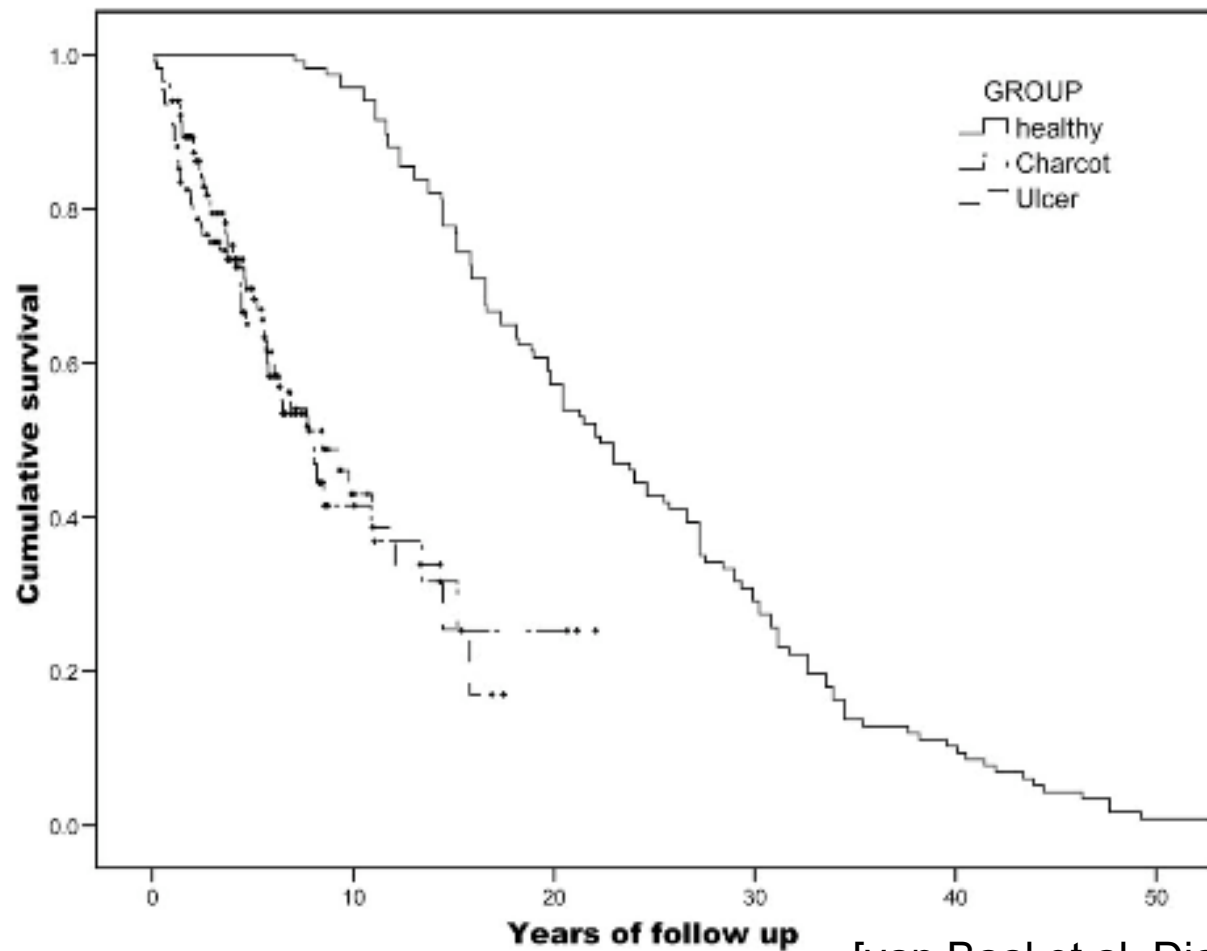
RESULTS — A total of 70 patients presented with an acute Charcot foot (mean age 57.4 ± 12.0 years; 48 male [68.6%]) between 2001 and 2007; there were 66 matched control subjects. By 1 October 2008, 13 (eight male; 18.6%) patients with a Charcot foot had died, after a median of 2.1 years (interquartile range 1.1–3.3). Twenty-two (20 male; 33.3%) control subjects had also died after a median of 1.3 years (0.6–2.5). There was no difference in survival between the two groups (log-rank $P > 0.05$). Median survival of all 117 patients with acute Charcot foot managed between 1980 and 2007 was 7.88 years (4.0–15.4) and was not significantly different from the control NFU patients (8.43 years [3.4–15.8]). When compared with normative U.K. population data, life expectancy in the two groups was reduced by 14.4 and 13.9 years, respectively.

CONCLUSIONS — These data confirm that the mortality in patients presenting to our unit with either an acute Charcot foot and an uninfected neuropathic ulcer was unexpectedly high.

RESEARCH DESIGN AND METHODS

— Data on patients with diabetes referred to the specialist multidisciplinary outpatient foot care service at the city hospital campus of Nottingham University Hospitals National Health Service Trust have been recorded since 1982. The number of referrals to the service has increased progressively, as has the completeness of the dataset. The latest version of the database dates from 2000, holds details on ~1,800 patients, and has been approved by the Caldicott Guardian of the Trust for the purposes of audit. Demographic and clinical details are recorded at the time of presentation of each new episode.

Each diabetic foot lesion is classified, according to the size (area and depth), sepsis, arteriopathy, and denervation [S(AD)SAD] system (5), in which cases of acute Charcot foot are specifically identified. The diagnosis of an acute Charcot foot was based on the presence of unexplained subacute inflammation with fracture or dislocation visible on plain X-ray. In more recent years, magnetic resonance



[van Baal et al. Diabetes Care, 2010]

Association of arterial stiffness and neuropathy in diabetes: a systematic review and meta-analysis

Angela Beros , John Sluyter , Robert Keith Rhodes Scragg 

To cite: Beros A, Sluyter J, Scragg RKR. Association of arterial stiffness and neuropathy in diabetes: a systematic review and meta-analysis. *BMJ Open Diab Res Care* 2023;**11**:e003140. doi:10.1136/bmjdr-2022-003140

ABSTRACT

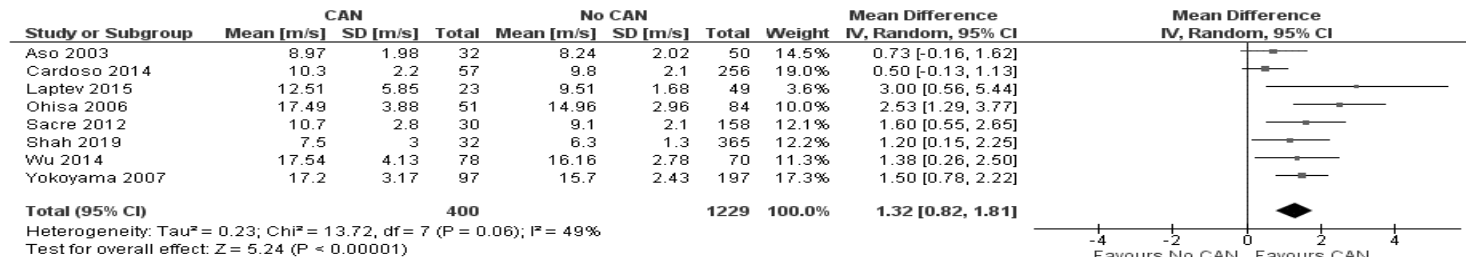
Evidence is still emerging on the relationships of arterial stiffness with cardiac autonomic neuropathy (CAN) and peripheral neuropathy (PN). To our knowledge no systematic reviews or meta-analyses of these associations have been published. The purpose of our review was to assess the association of arterial stiffness with each type of neuropathy. Medline and Embase were systematically searched for observational studies of arterial stiffness and

WHAT IS ALREADY KNOWN ON THIS TOPIC

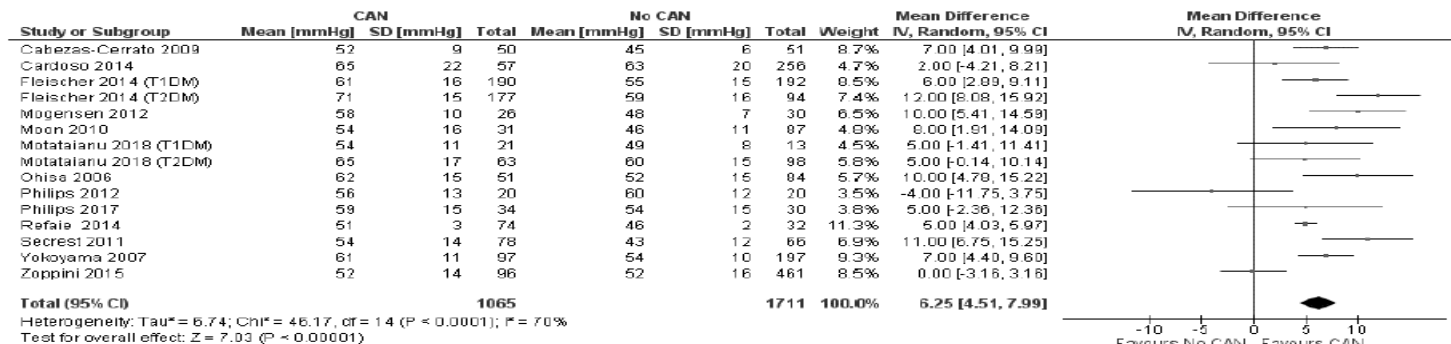
⇒ There are an increasing number of studies in people with diabetes that investigate the association of arterial stiffness with cardiac autonomic neuropathy (CAN) and peripheral neuropathy (PN). The evidence, however, as far as we are aware, has not been assessed by way of systematic review and meta-analysis.

ASSOCIATION OF CARDIAC AUTONOMIC NEUROPATHY (CAN) WITH ARTERIAL STIFFNESS

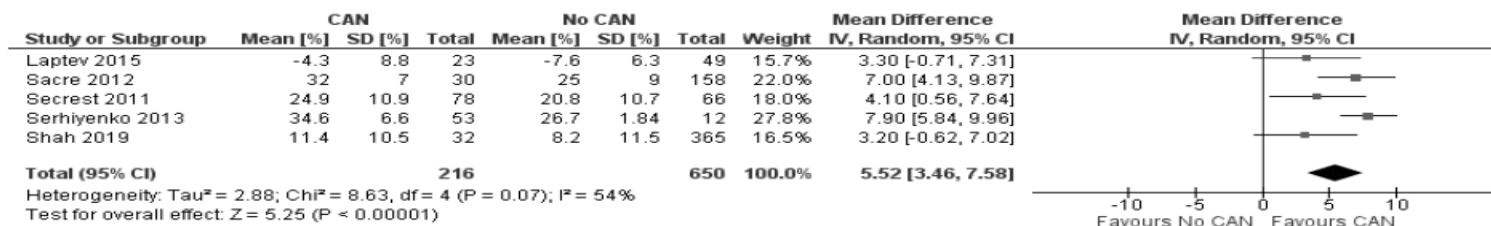
A. PWV



B. PP

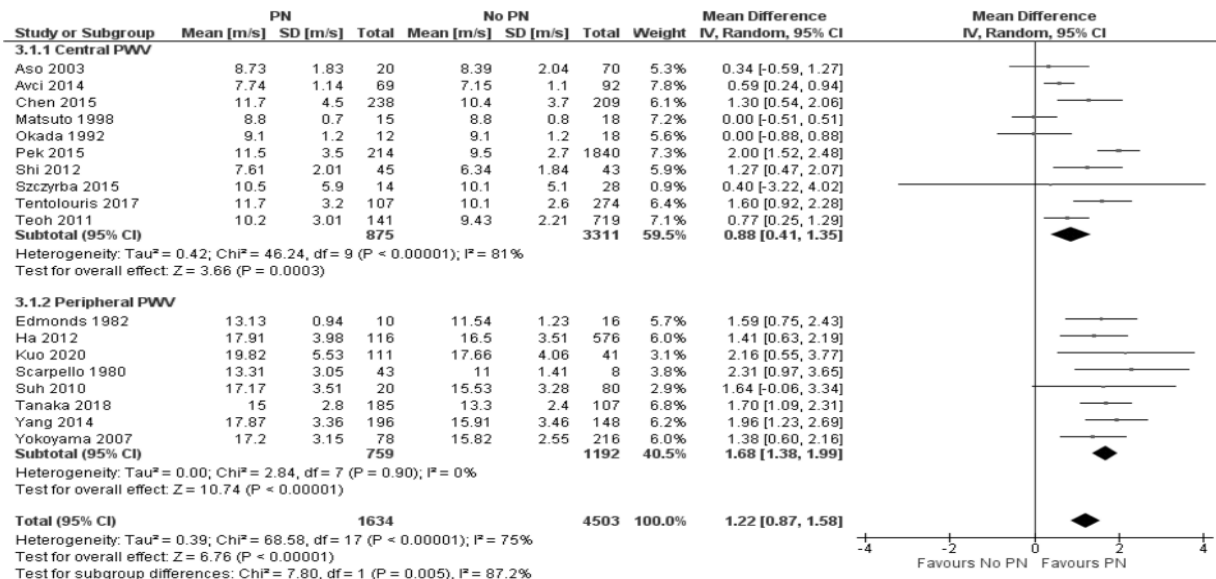


C. AIX

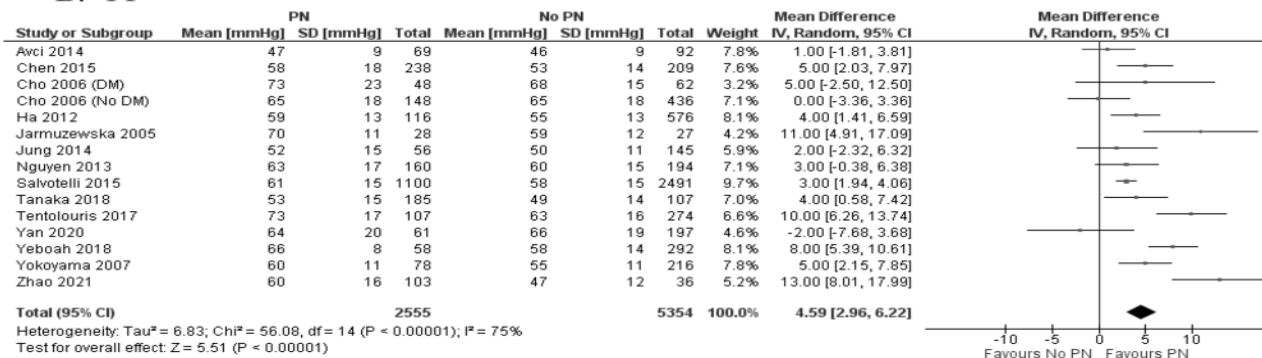


ASSOCIATION OF PERIPHERAL NEUROPATHY (PN) WITH ARTERIAL STIFFNESS

A. PWV



B. PP





The role of proinflammatory cytokines in the cause of neuropathic osteoarthropathy (acute Charcot foot) in diabetes

William J Jeffcoate, Fran Game, Peter R Cavanagh

Lancet 2005; 366: 2058–61

Published online

August 10, 2005

DOI:10.1016/S0140-6736(05)

67029-8

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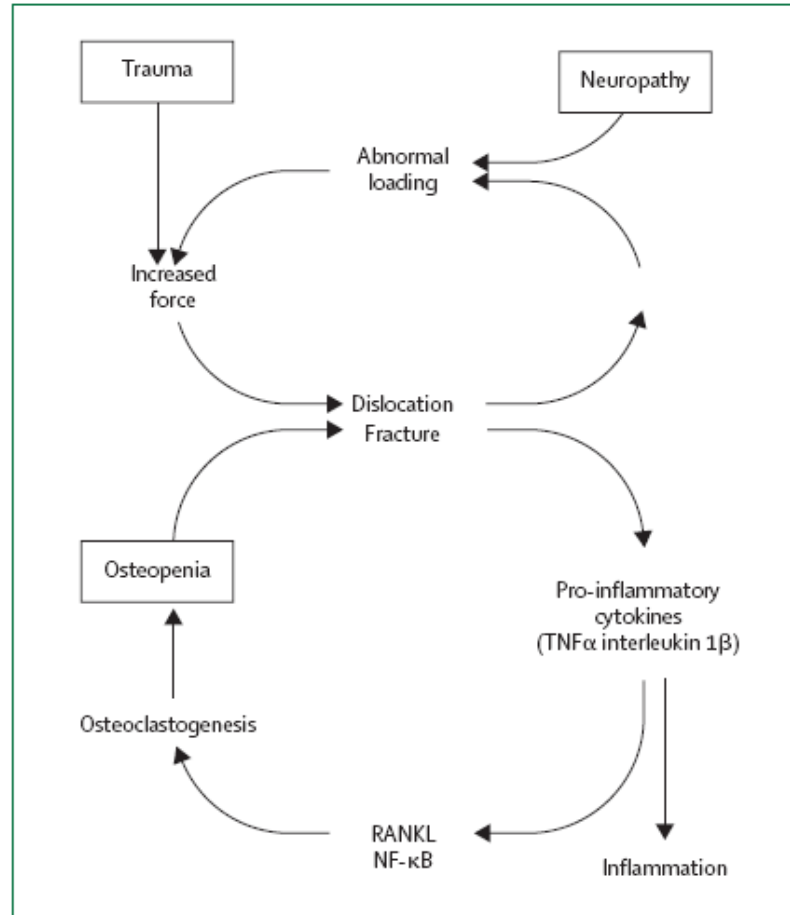
The pathogenesis of the acute Charcot foot of diabetes remains unclear. All patients with this condition have evidence of peripheral neuropathy, with loss of protective sensation and abnormal foot biomechanics. However, the acute Charcot foot is also characterised by a pronounced inflammatory reaction and the pathogenic significance of this inflammation has received little attention. We suggest that an initial insult—which may or may not be detected—is sufficient to trigger an inflammatory cascade through increased expression of proinflammatory cytokines, including $\text{TNF}\alpha$ and interleukin 1β . This cascade then leads to increased expression of the nuclear transcription factor, $\text{NF-}\kappa\text{B}$, which results in increased osteoclastogenesis. Osteoclasts cause progressive bone lysis, leading to further fracture, which in turn potentiates the inflammatory process. The potential role of proinflammatory cytokines suggests the possibility of new treatments for this sometimes devastating complication of diabetes.

Introduction

Denervation-induced destruction of joints was described by Jean-Martin Charcot in 1868,¹ although he acknowledged that the condition had been first reported by the American physician John Kearsley Mitchell (1798–1858) in 1831.² Mitchell's cases were secondary to spinal damage caused by tuberculosis, whereas Charcot's were the result of tertiary syphilis. Sir James Paget suggested

practitioners regard the condition as the simple result of continuing damage caused by loss of protective sensation in a well perfused limb. Recent attention has, however, focused on several anomalies, which together suggest a more complex cause. These anomalies include the rarity of the condition, its asymmetry, and the fact that it is usually self-limiting.^{3,4} The possible relation with reflex sympa-

[Jeffcoate et al. The Lancet, 2005]



[Jeffcoate et al. The Lancet, 2005]

CHARCOT NEURO-ARTHROPATHY



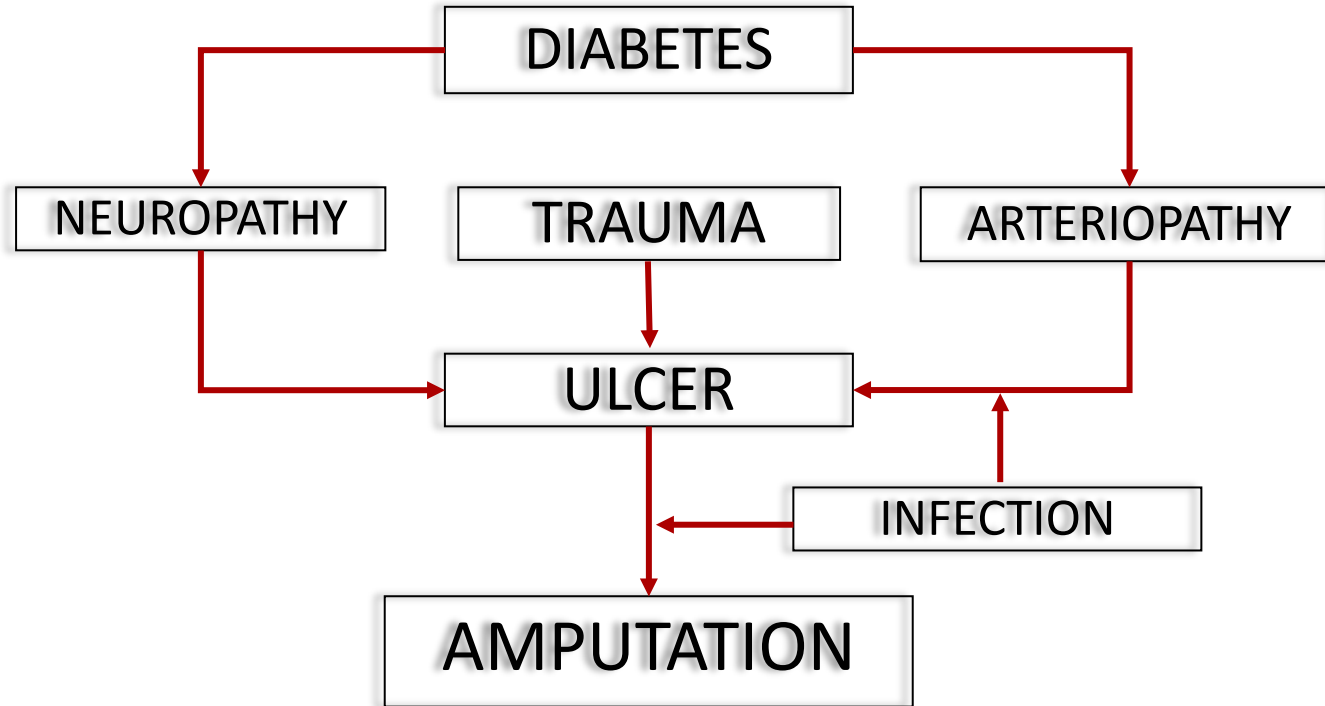
Journal of
Clinical Medicine

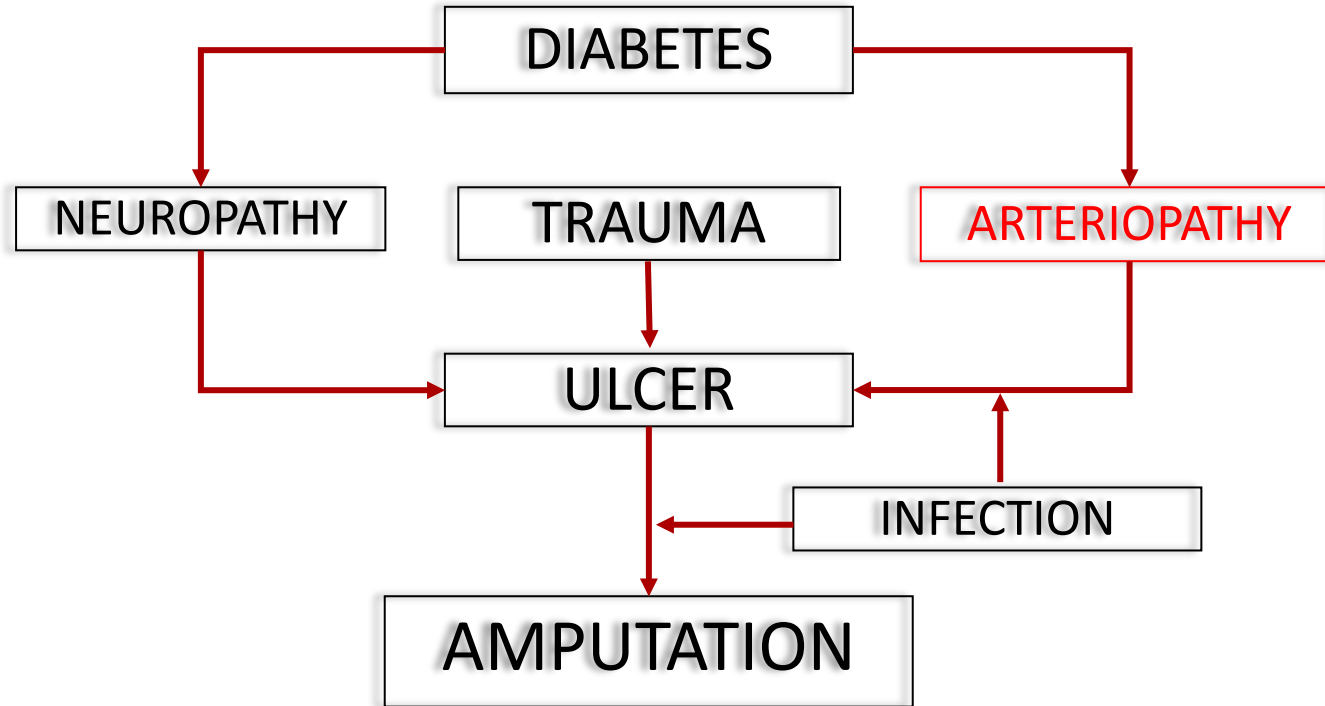
MDPI

Variable	Whole Population Included (N = 76)	PAD Yes (N = 24)	PAD No (N = 52)	<i>p</i> Value
DFU healing	46/50 (92%)	13/15 (86.7%)	33/35 (94.3%)	0.08
Minor amputation	10/76 (13.1%)	6/24 (25%)	4/52 (7.7%)	0.003
Major amputation	3/76 (3.9%)	2/24 (8.3%)	1/52 (1.9%)	0.001
Hospitalization	28/76 (36.8%)	18/24 (75%)	12/52 (23%)	0.0001

PAD: peripheral arterial disease. In the comparison between groups (CN with PAD vs CN without PAD) $p < 0.05$ was considered statistically significant.

Meloni M et al, J. Clin. Med. 2022

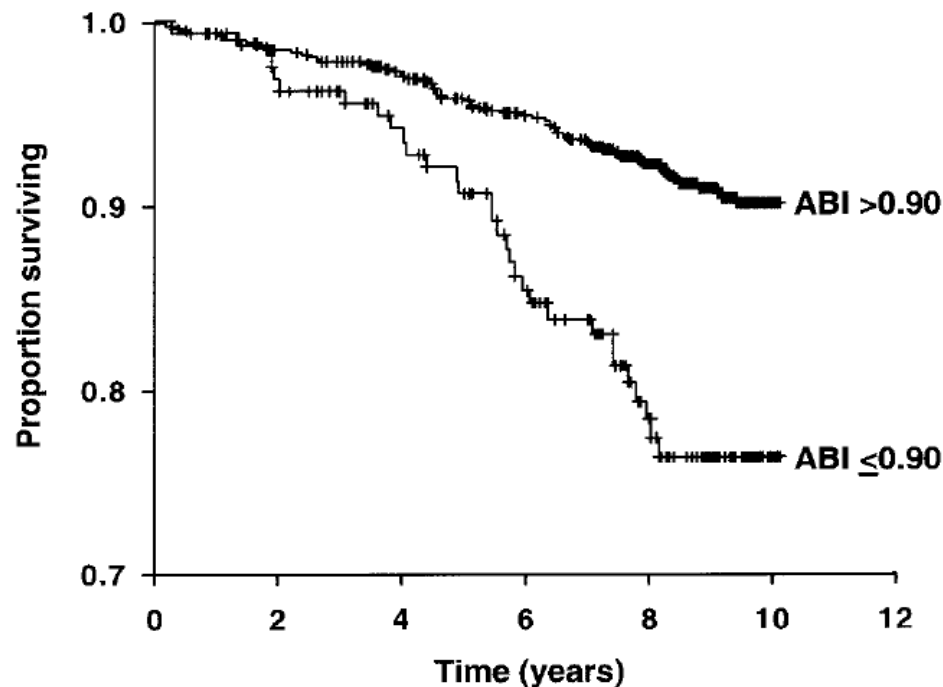




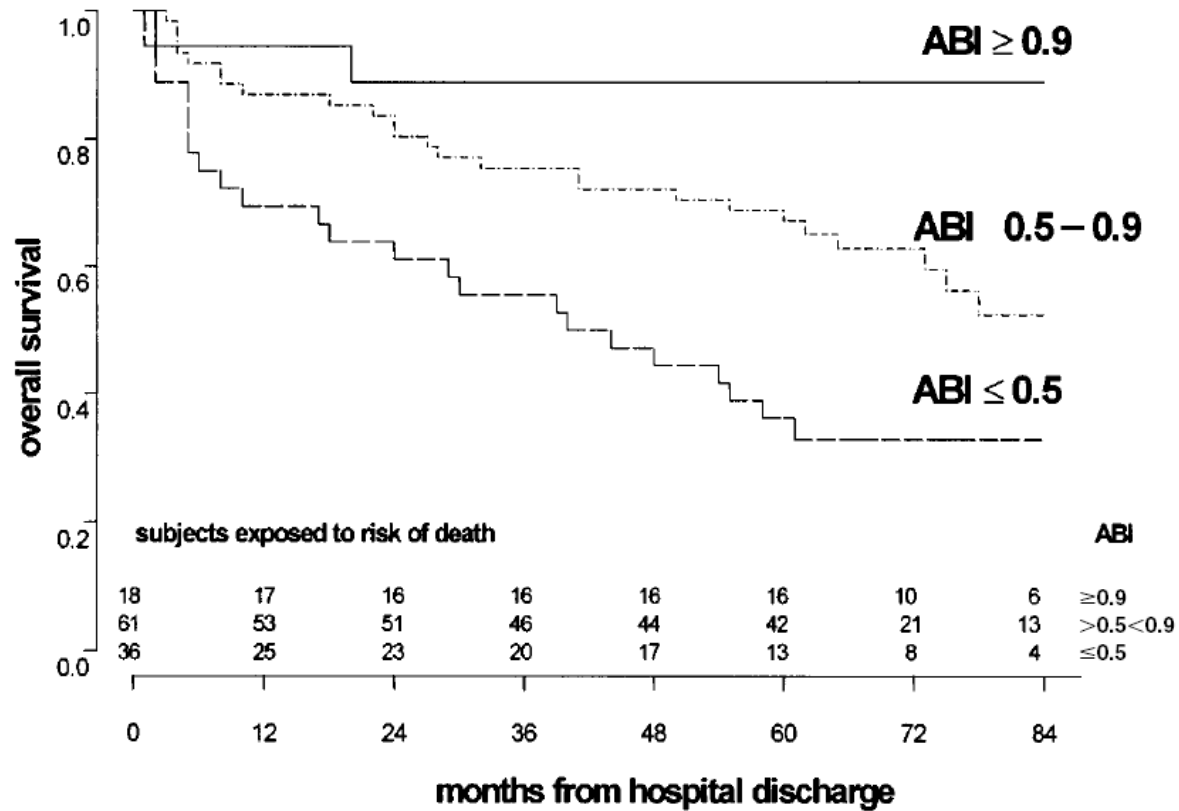


Peripheral Arterial Disease and Risk of Cardiac Death in Type 2 Diabetes

The Fremantle Diabetes Study



[Norman PE et al. Diabetes Care 2006]



[Faglia et al, Diabetes Care 2001]

ORIGINAL INVESTIGATION

Open Access



Presentations of major peripheral arterial disease and risk of major outcomes in patients with type 2 diabetes: results from the ADVANCE-ON study

Kamel Mohammedi^{1*}, Mark Woodward^{1,2,3}, Yoichiro Hirakawa¹, Sophia Zoungas^{1,4}, Stephen Colagiuri⁵, Pavel Hamet⁶, Stephen Harrap⁷, Neil Poulter⁸, David R. Matthews⁹, Michel Marre^{10,11,12}, John Chalmers¹ and on behalf of the ADVANCE Collaborative Group

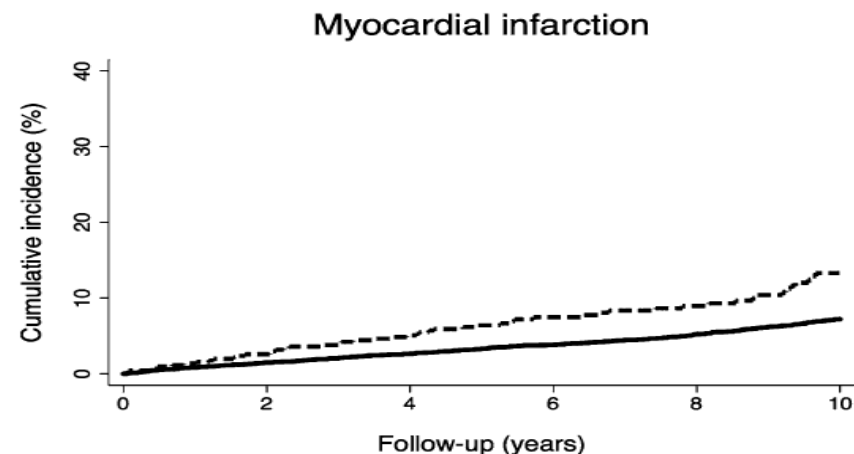
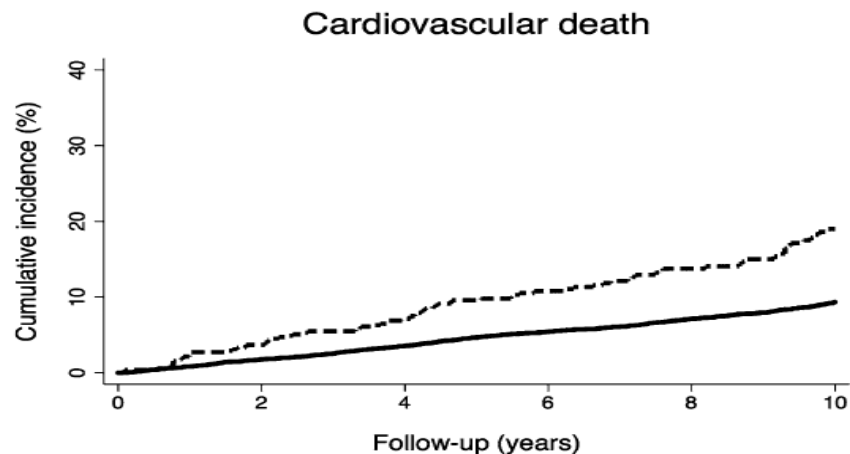
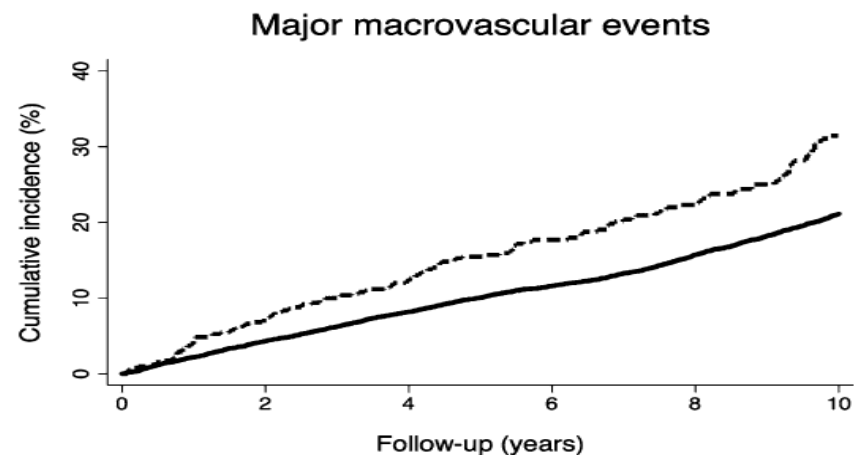
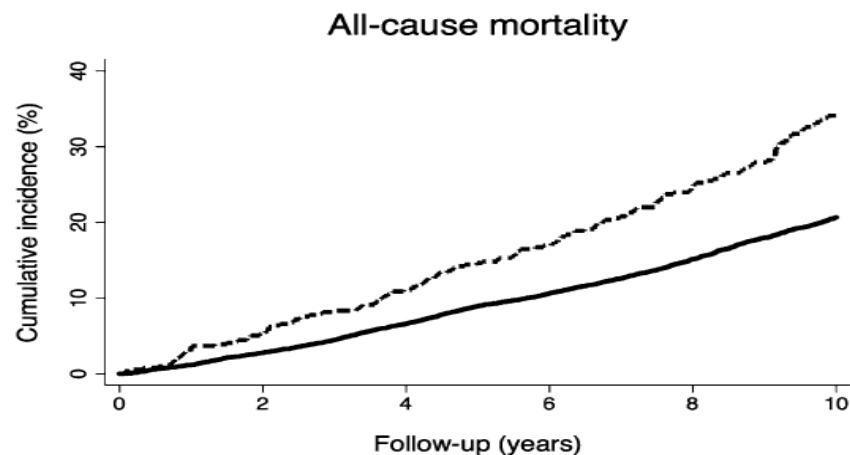
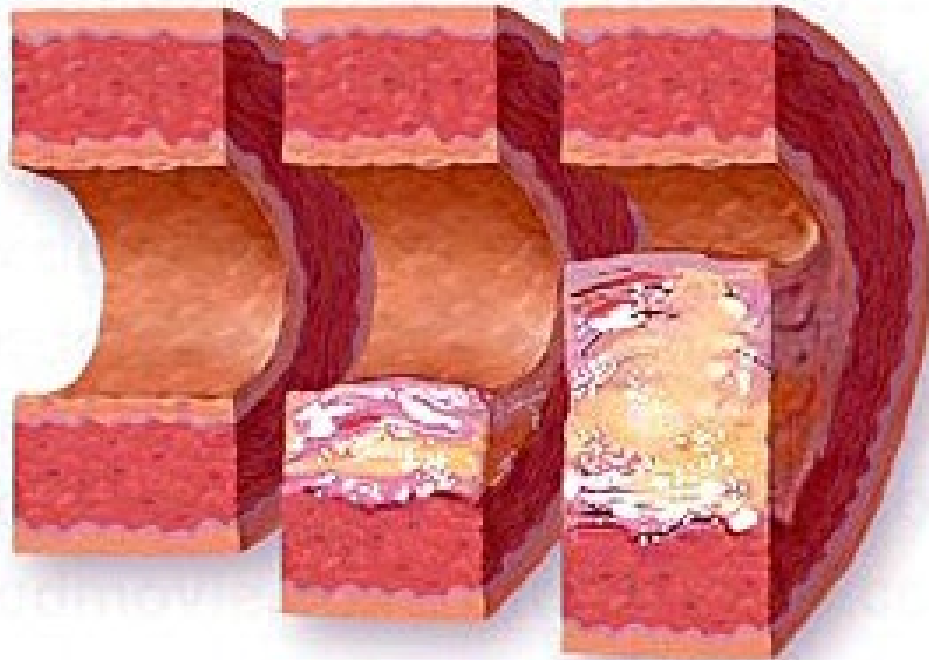
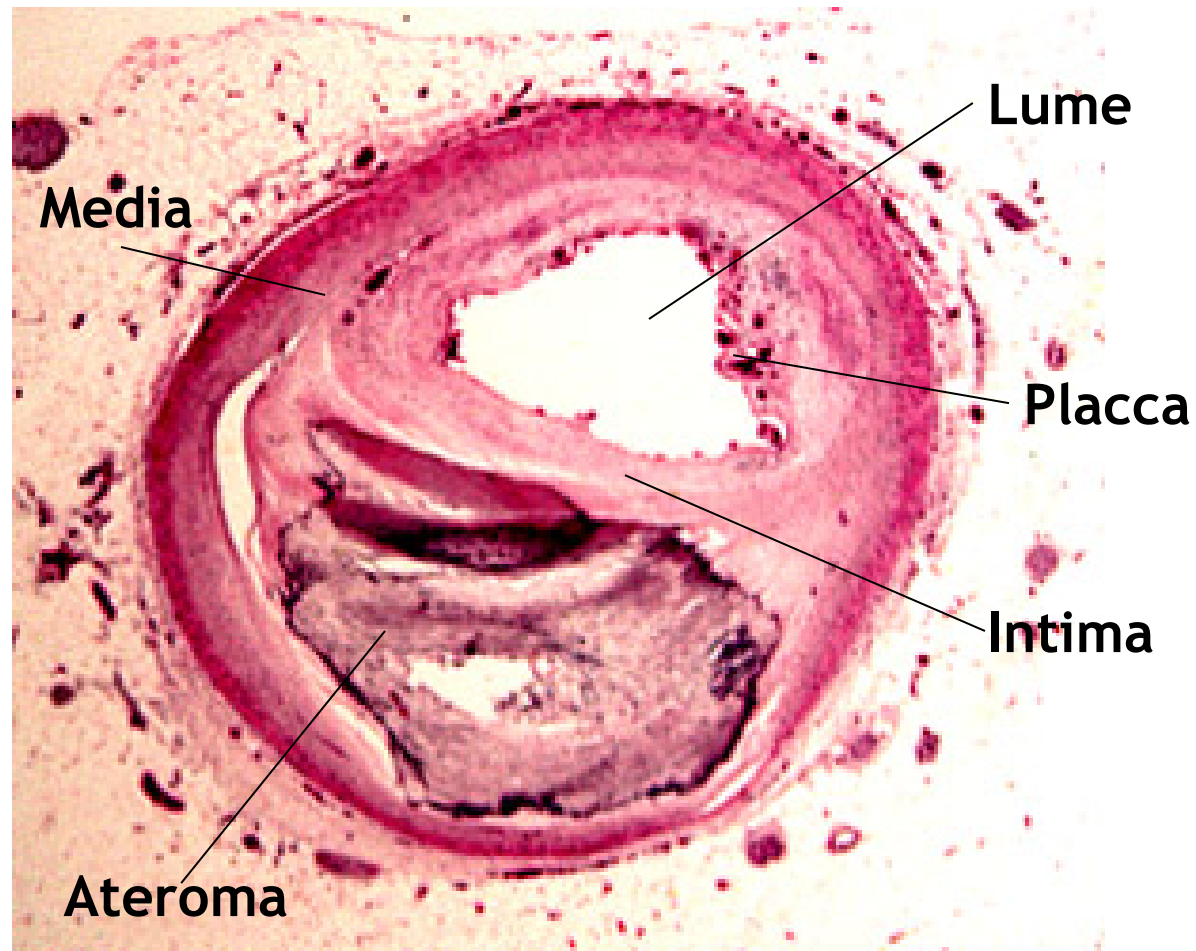
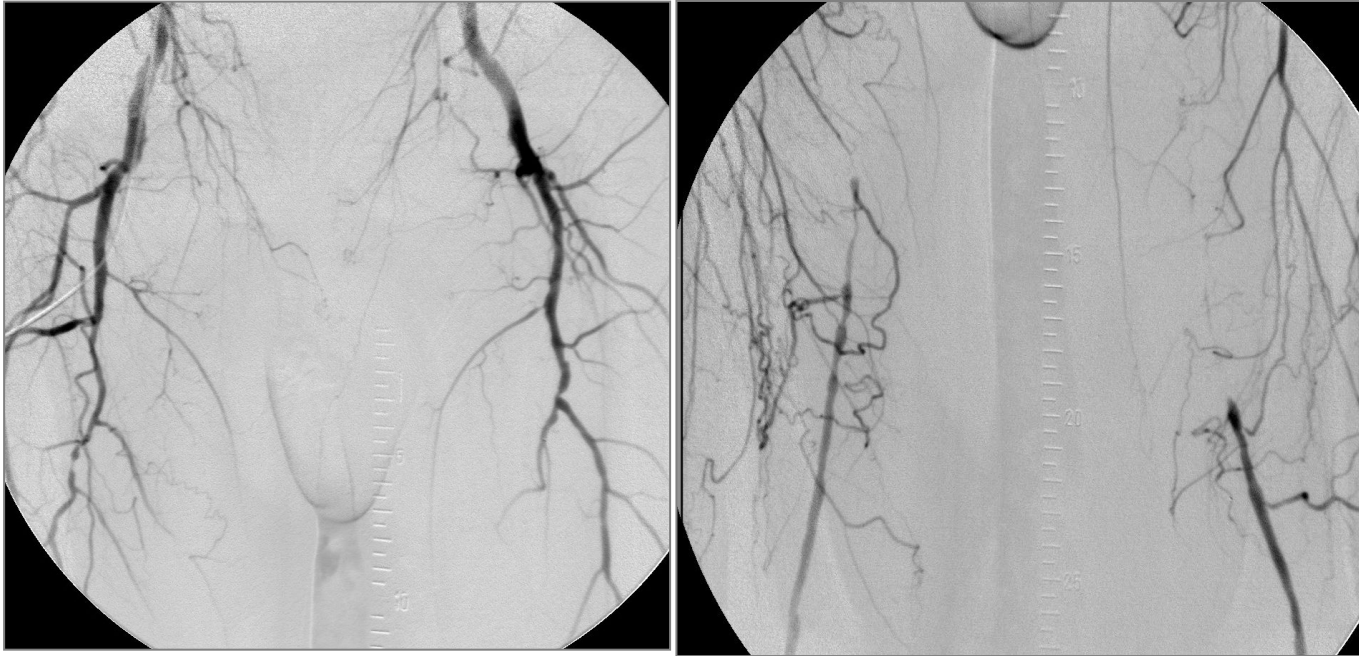


Fig. 1 Cumulative incidence of all-cause mortality, major macrovascular events, cardiovascular death, and fatal or nonfatal myocardial infarction according to the absence (*solid line*) or the presence of major PAD (*dashed line*) at baseline ($p < 0.0001$ for all)

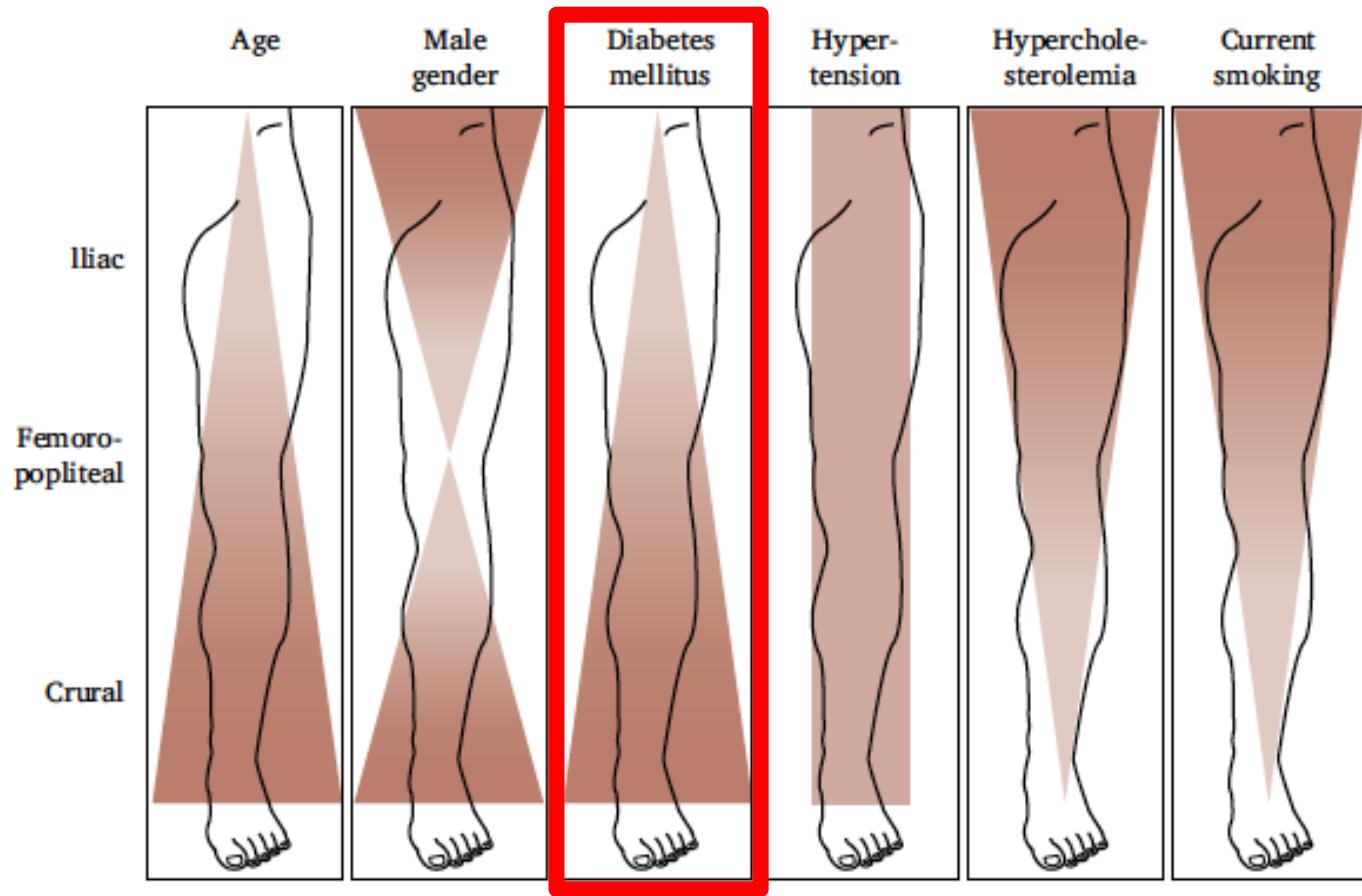




PAD IN THE ILIAC AND FEMORAL ARTERIES

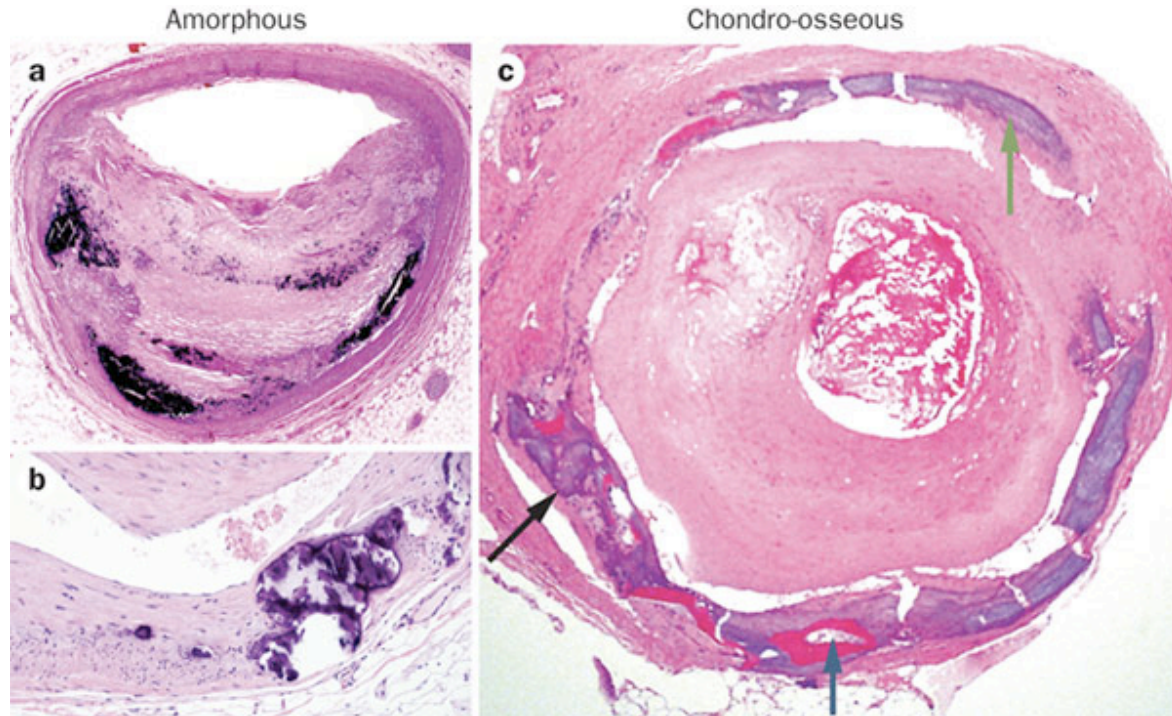








MECHANISMS OF ARTERIAL CALCIFICATION



ORIGINAL ARTICLE

RECENT DEVELOPMENTS IN THE MANAGEMENT OF THE DIABETIC FOOT

BAD transmission and SAD distribution: a new scenario for critical limb ischemia

Roberto FERRARESI ^{1 *}, Giovanni MAURI ², Fabrizio LOSURDO ³, Nicola TROISI ⁴,
Diego BRANCACCIO ⁵, Carlo CARAVAGGI ⁶, Luca NERI ⁷

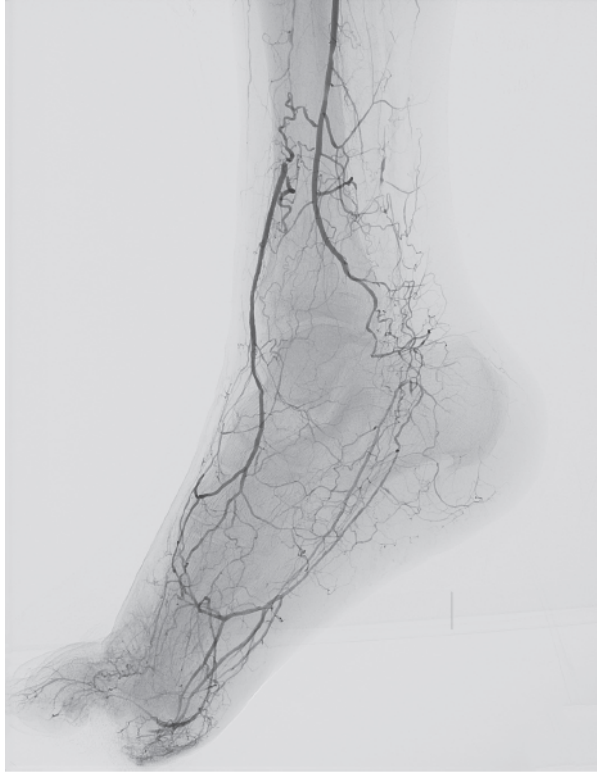
¹Peripheral Interventional Unit, Humanitas Gavazzeni Hospital, Bergamo, Italy; ²Department of Interventional Radiology, European Institute of Oncology, Milan, Italy; ³Diabetic Foot Clinic, Humanitas Gavazzeni Hospital, Bergamo, Italy; ⁴Department of Vascular and Endovascular Surgery, San Giovanni di Dio Hospital, Florence, Italy; ⁵University of Milan, Milan, Italy; ⁶Diabetic Foot Clinic, Multimedica Institute for Research and Care, Milan, Italy; ⁷Department of Clinical and Community Sciences, University of Milan, Milan, Italy

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BAD

vs

SAD



PERSPECTIVES

Vascular Calcification: A Perspective On An Imminent Disease Epidemic

Dwight A. Towler

Center for Cardiovascular Research, Department of Medicine – Bone & Mineral Diseases, Washington University in St. Louis, St. Louis, MO, USA

Abstract

Westernized societies are on the verge of an epidemic of vascular calcification. Aging, metabolic syndrome and type II diabetes (T2DM), and chronic kidney disease increasingly characterize our populace – and promote valve and arterial calcium deposition. Epidemiology, histopathology, and pathobiology define at least 5 distinct and prevalent types of vascular calcification: calcific aortic stenosis (CAS), medial artery calcification, atherosclerotic intimal calcification, vascular calcification of chronic kidney disease, and calcific uremic arteriopathy. The clinical impact of these 5 mineralization disorders is highly significant. For example, 2%-3% of individuals ≥ 65 years old have CAS, and require surgery to prevent precocious death and to improve quality of life. Valve calcium load is the best predictor of clinical progression; if unaddressed, interactions between longevity and T2DM prevalence will increase the future incidence of CAS. Reduced vascular compliance – arising in part from arterial calcification – impairs macrovascular Windkessel function and normal tissue perfusion; thus, medial artery calcification of T2DM conveys a 3-fold increased risk for lower extremity amputation, a debilitating and costly outcome. Once considered a passive process only, data from laboratories world-wide have now established that vascular calcification is an actively regulated type of biomineralization. As in bone, morphogenetic, mechanical, metabolic, endocrine, and inflammatory signals control vascular mineral deposition. Molecular and cellular mechanisms familiar to bone biologists are activated with disease initiation and progression. This *Perspective* briefly recounts the pathobiology of vascular calcification and conveys the urgent need to pursue the basic, translational, and outcomes-based research necessary to address an imminent epidemic of abnormal vascular calcium metabolism.

A Novel Scoring System for Small Artery Disease and Medial Arterial Calcification Is Strongly Associated With Major Adverse Limb Events in Patients With Chronic Limb-Threatening Ischemia

Journal of Endovascular Therapy

1–14

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**Roberto Ferraresi, MD¹, Alessandro Ucci, MD² , Alessandra Pizzuto, MD³,
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Andrea Casini, MD⁵, Giacomo Clerici, MD⁴, Miguel Montero-Baker, MD⁶,
and Joseph Mills, MD⁶**



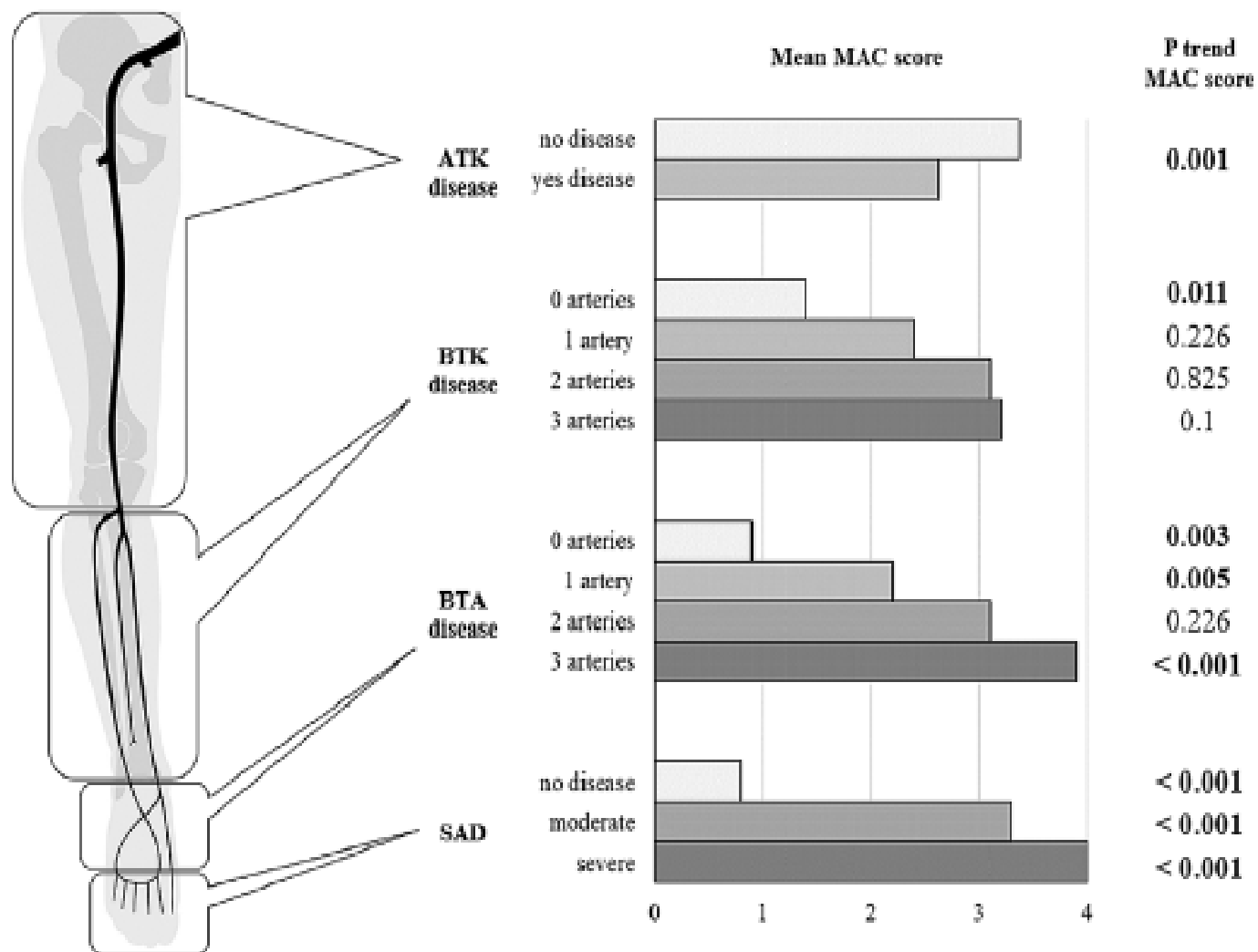
1	≥ 2 cm?	yes = 1 or no = 0
2		yes = 1 or no = 0
3		yes = 1 or no = 0
4	≥ 1 cm?	yes = 1 or no = 0
5		yes = 1 or no = 0

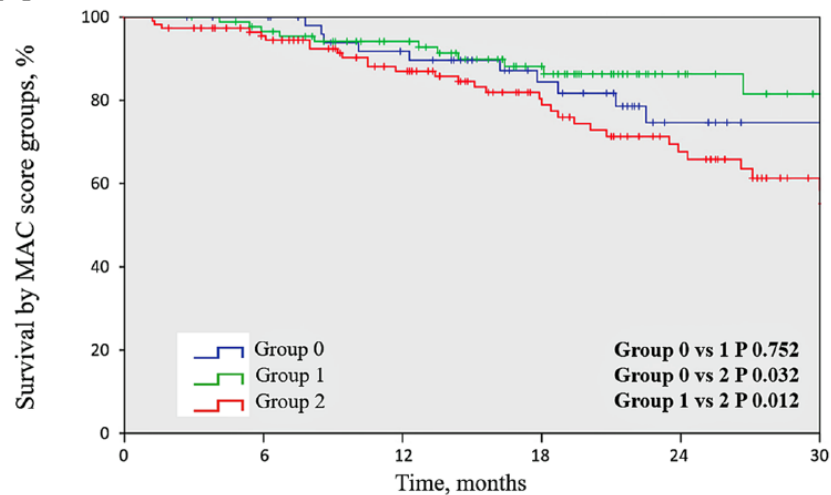
Sum all
points

0-1 = no MAC

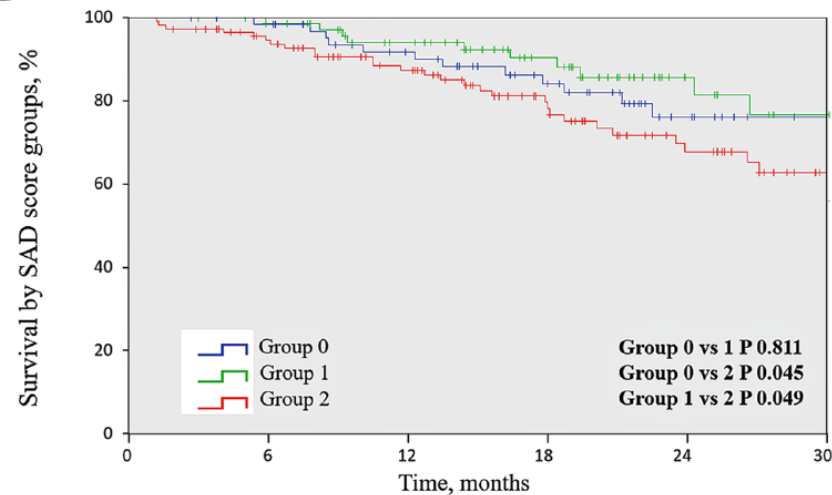
2-3 = moderate MAC

4-5 = severe MAC



A

Time, months	6	12	18	24
MAC group 0 at risk	52	42	30	16
Estimate, %	100	89.7	81.7	74.6
SE, %	0	4.4	5.9	7.3
MAC group 1 at risk	82	68	48	20
Estimate, %	96.6	94.2	88.2	86.3
SE, %	2	2.5	3.8	4.1
MAC group 2 at risk	98	77	53	36
Estimate, %	94.5	87	78.9	65.8
SE, %	2.2	3.4	4.4	5.6

B

Time, months	6	12	18	24
SAD group 0 at risk	63	51	39	20
Estimate, %	98.5	90.1	84.2	76.1
SE, %	1.5	3.9	4.9	6.3
SAD group 1 at risk	70	58	40	19
Estimate, %	98.6	94.2	88.2	81.4
SE, %	1.4	1.8	4.3	6.2
SAD group 2 at risk	99	78	52	33
Estimate, %	93.7	87.4	78.2	67.8
SE, %	2.3	3.3	4.4	5.5

Figure 8. Survival estimates for the (A) medial arterial calcification (MAC) groups and the (B) small artery disease (SAD) groups. SE, standard error.

ORIGINAL ARTICLE



Below-the-ankle arterial disease: a new marker of coronary artery disease in patients with diabetes and foot ulcers

Marco Meloni^{1,2} · Alfonso Bellia^{1,2} · Laura Giurato^{1,2} · Davide Lauro^{1,2} · Luigi Uccioli³

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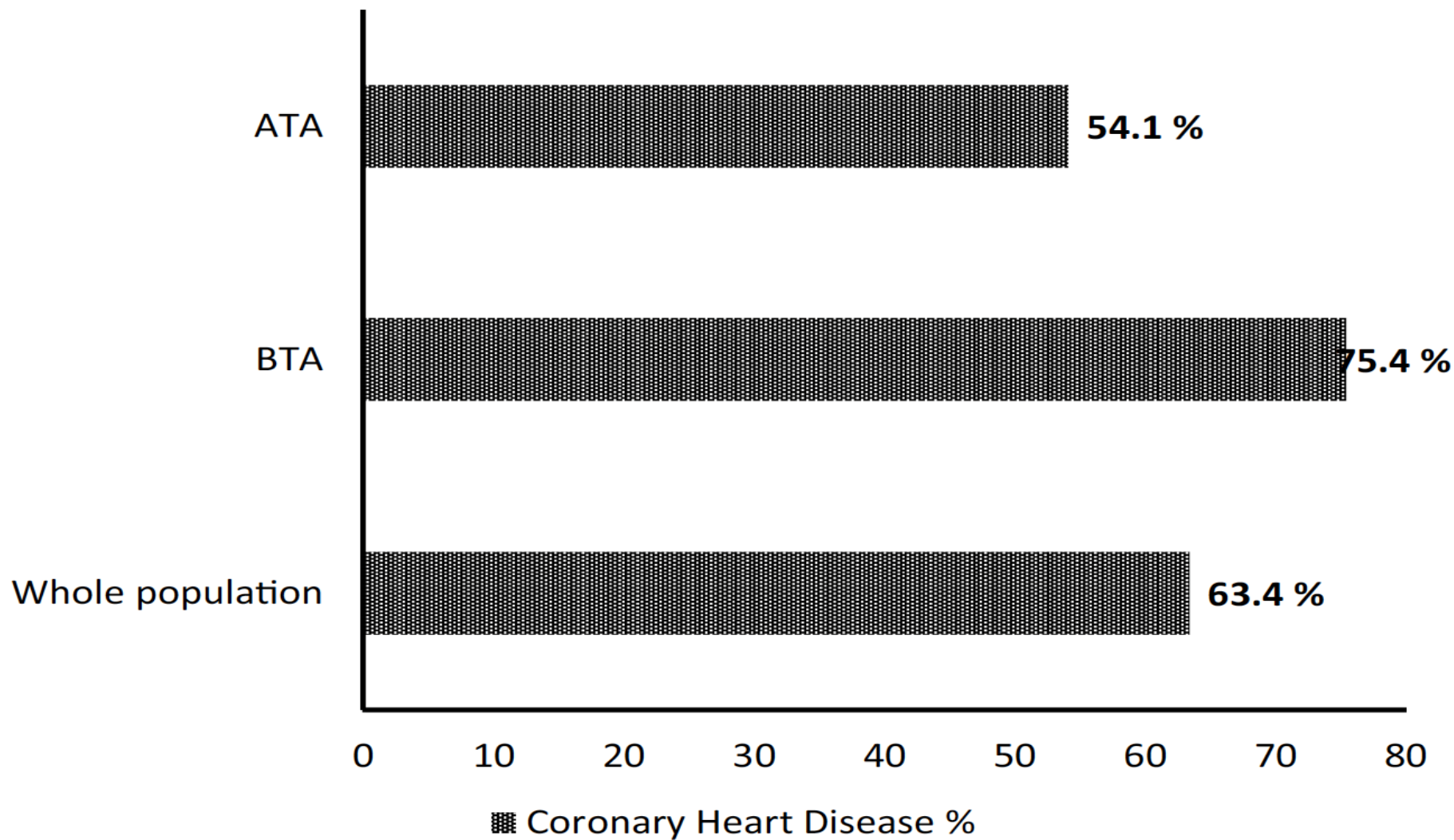
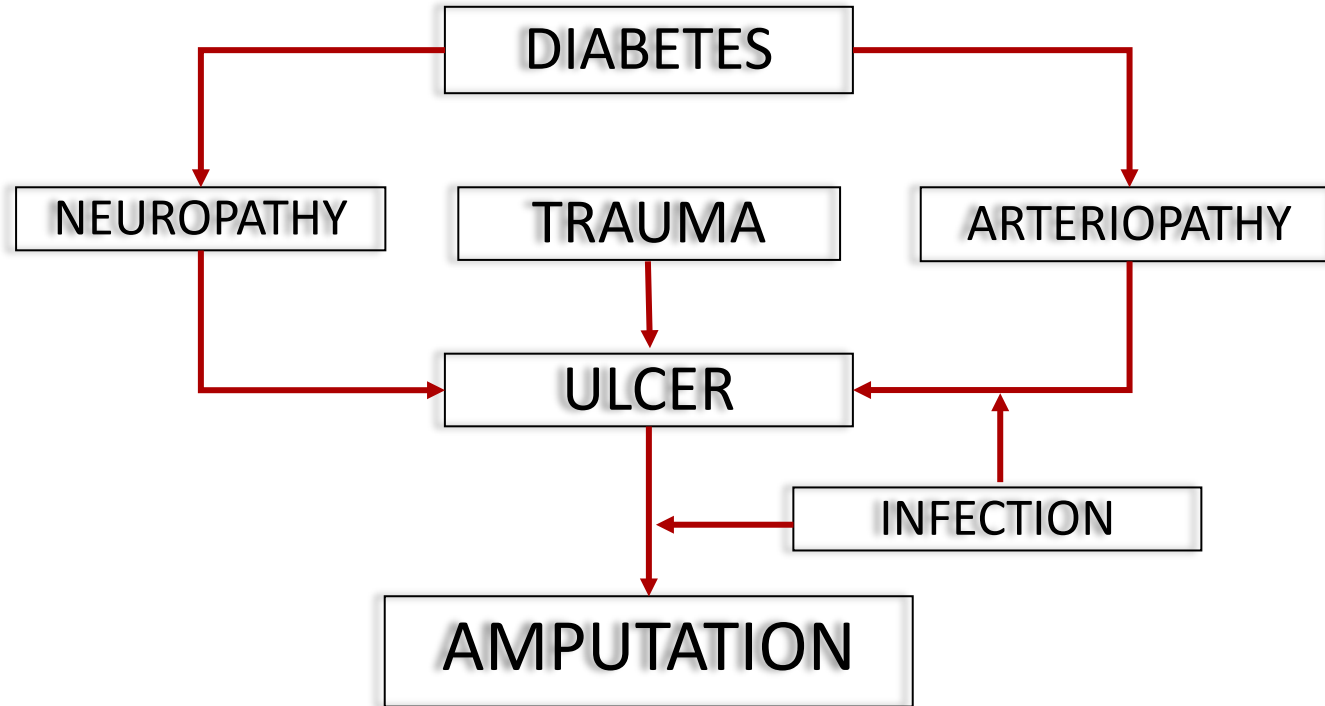
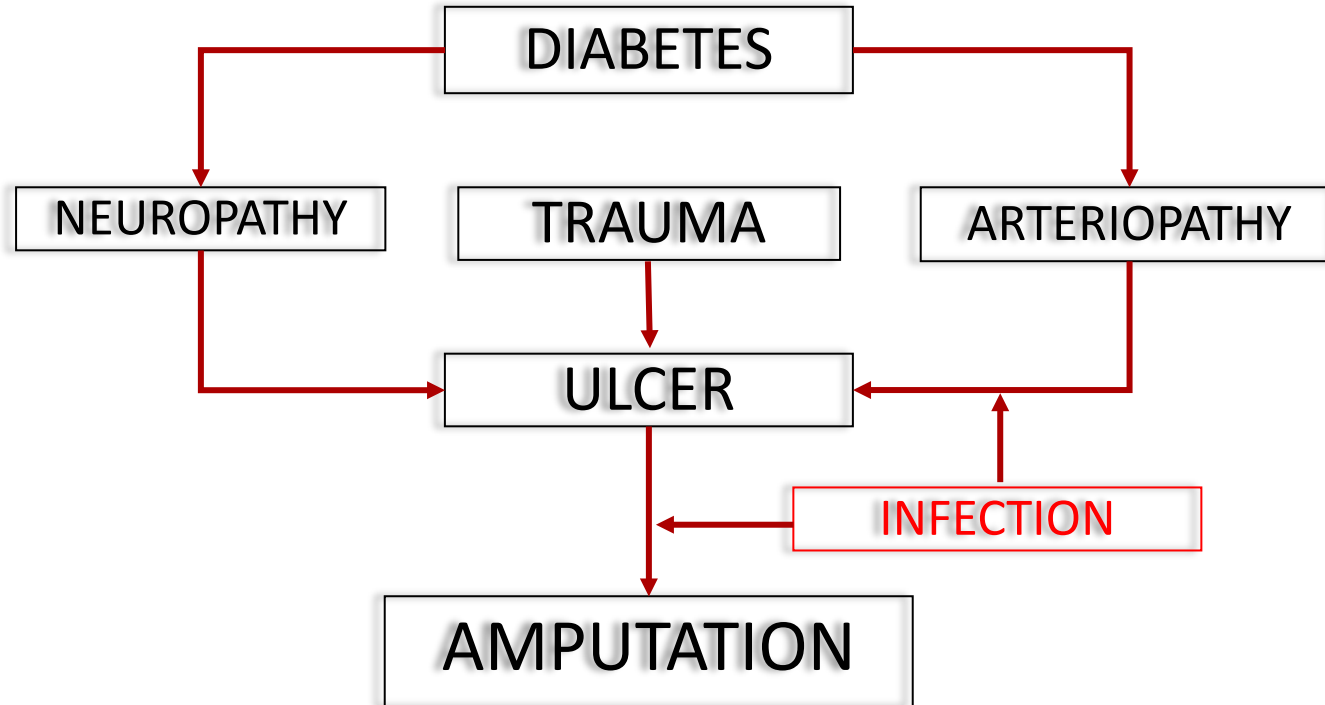


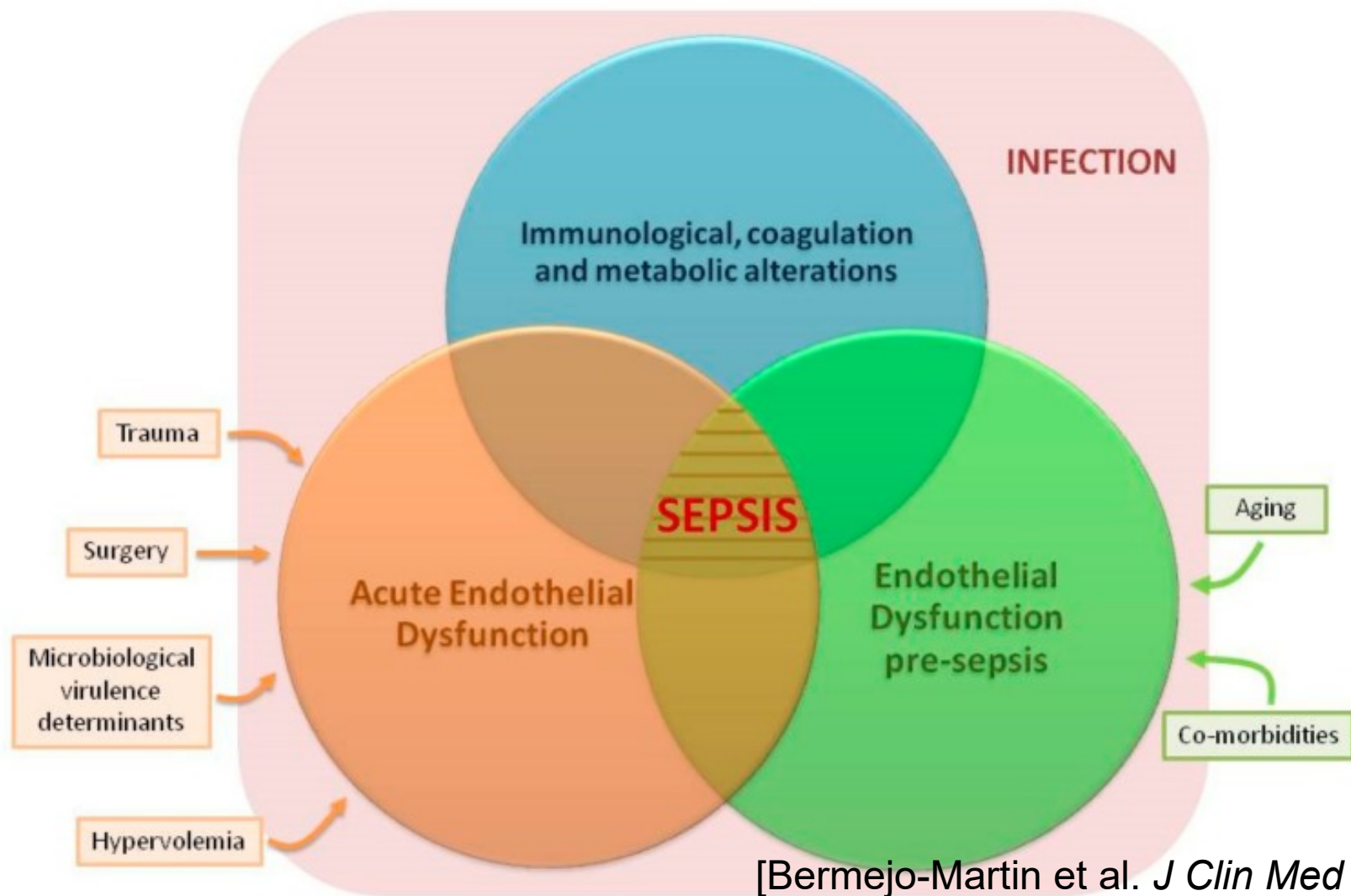
Table 4 Multivariate analysis of factors associated with coronary artery disease (CAD)

	OR	95%	<i>p</i> value*
Age, per 10 years	1.1	0.7–1.4	0.06
Diabetes duration > 10 vs < 10 years	0.9	0.8–1.7	0.4
ESRD	1.5	1.1–2.2	0.001
BTA vs ATA arterial disease	1.9	1.3–4.5	0.0001
TcPO ₂ (< 25 mmHg)	1.2	0.9–1.7	0.08

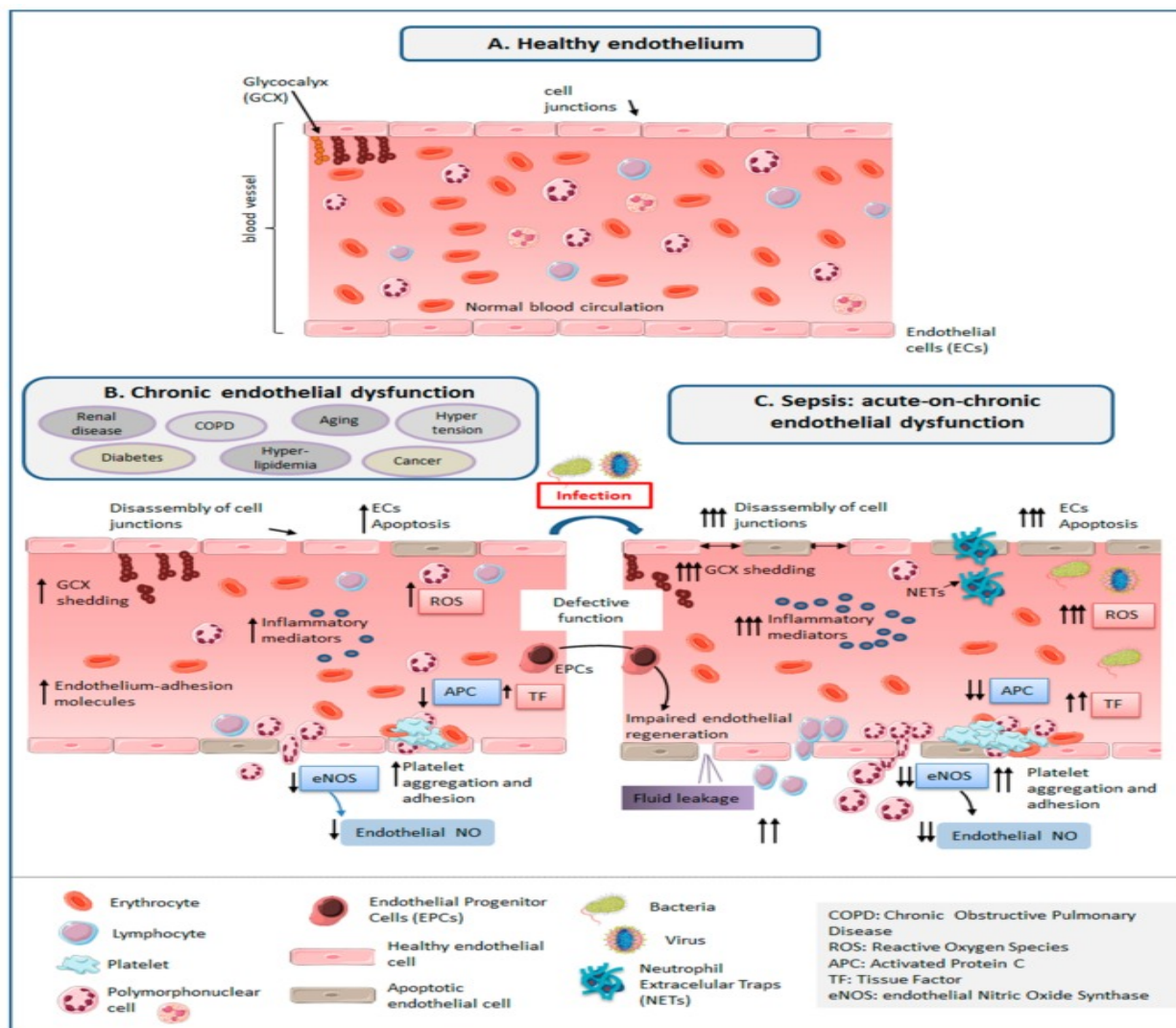




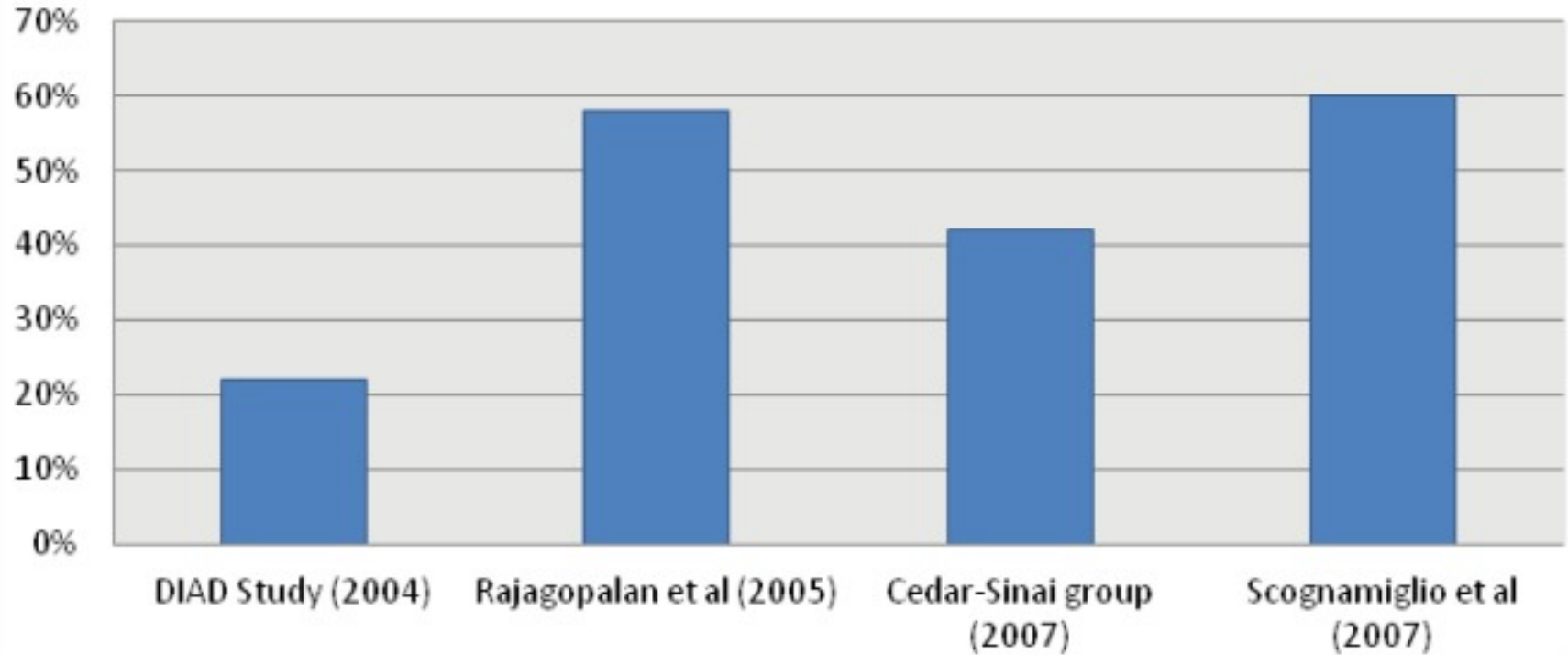




[Bermejo-Martin et al. *J Clin Med* 2018]



RATE OF ASYMPTOMATIC CORONARY ARTERY DISEASE IN TYPE 2 DIABETIC PATIENTS



[Pathak et al. *Assoc Physicians India*. 2021]

ORIGINAL INVESTIGATION

Open Access

Adiponectin, resistin and IL-6 plasma levels in subjects with diabetic foot and possible correlations with clinical variables and cardiovascular co-morbidity

Antonino Tuttolomondo^{1*}, Sergio La Placa¹, Domenico Di Raimondo¹, Chiara Bellia², Antonietta Caruso², Bruna Lo Sasso², Giovanni Guercio³, Giuseppe Diana³, Marcello Ciaccio², Giuseppe Licata¹, Antonio Pinto¹

Table 2 Laboratory variables in cases and controls

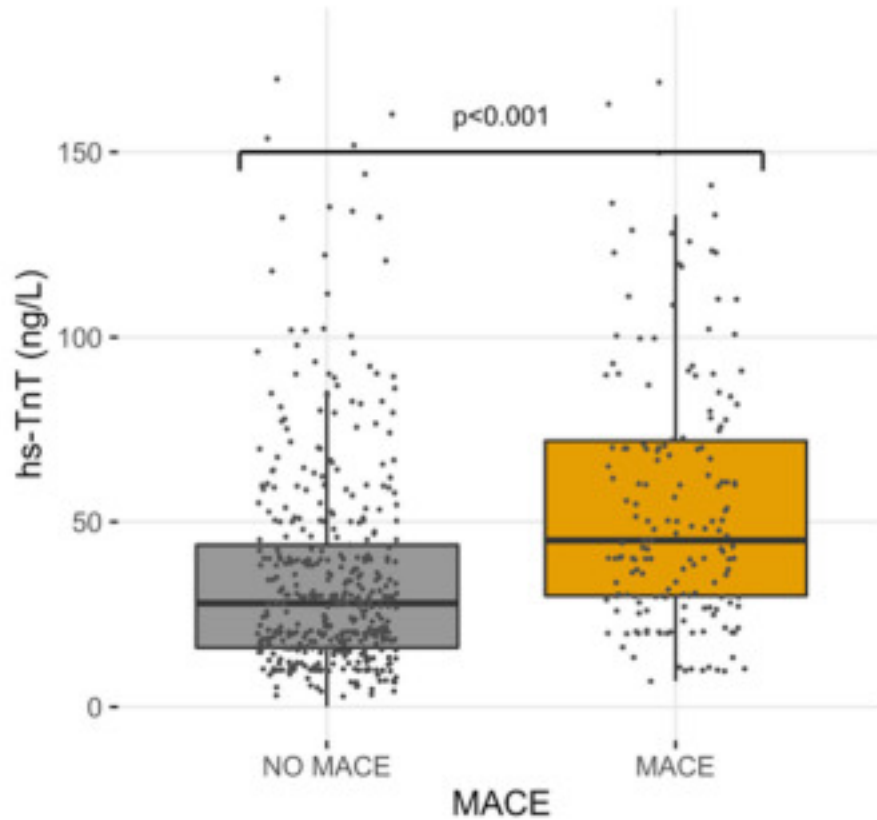
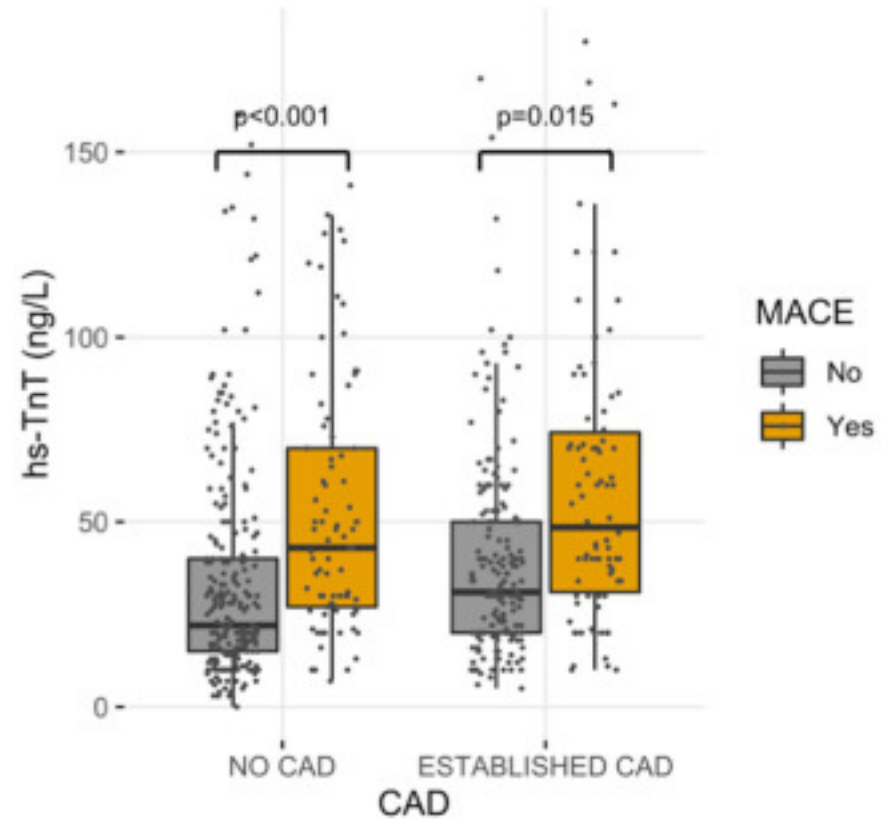
	Diabetic foot patients	Diabetics without foot complications	p
HbA1c	8 (7.28-9.40)	6.85 (6.10-8.00)	0.018
CRP	4 (2.25-5.15)	2.25 (1.90-3.08)	0.041
Total cholesterol (mg/dl)	215.50 (166,50-243,00)	204.00 (185,50-210,00)	0.054
LDL cholesterol (mg/dl)	121.70 (98,75-148,75)	104.50 (78,00-123,00)	0.032
Tryglicerids (mg/dl)	160.50 (119,50-209,25)	180.50 (144,50-199,00)	0.012
Globuli bianchi	12.675 (10775,00-14140,00)	10.700 (8850,00-12027,50)	0.032
Adiponectin (µg/ml)	7.1450 (4.47-12.17)	8.480 (5.15-12.87)	0.022
Resistin (ng/ml)	5.160 (2.96-6.29)	3.290 (2.37-6.5)	0.021
IL-6 (pg/ml)	3.21 (1.23-5.34)	2.13 (1.24-3.97)	0.033

Demographic and anamnestic data are expressed as n° (percentage); HbA1c: Hemoglobin A1c; CRP: C-reactive protein; IL-6: Interleukin-6

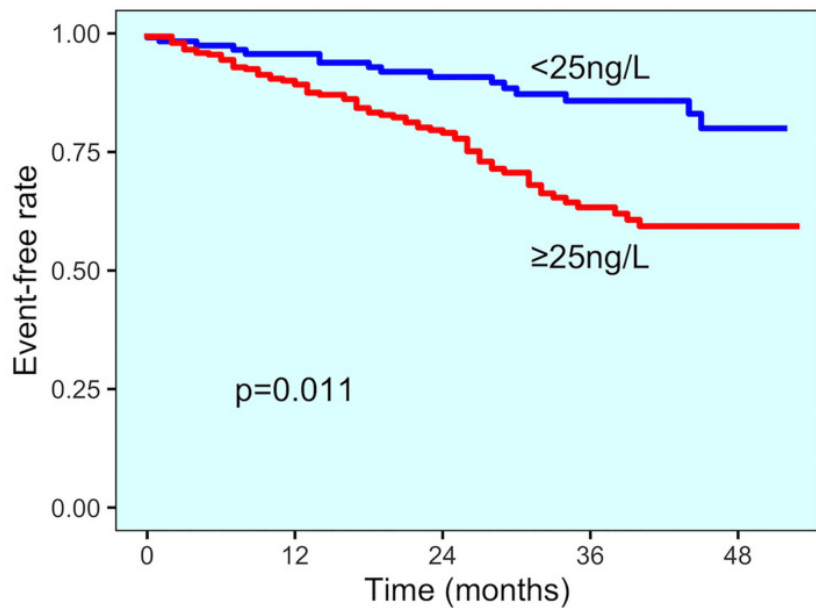
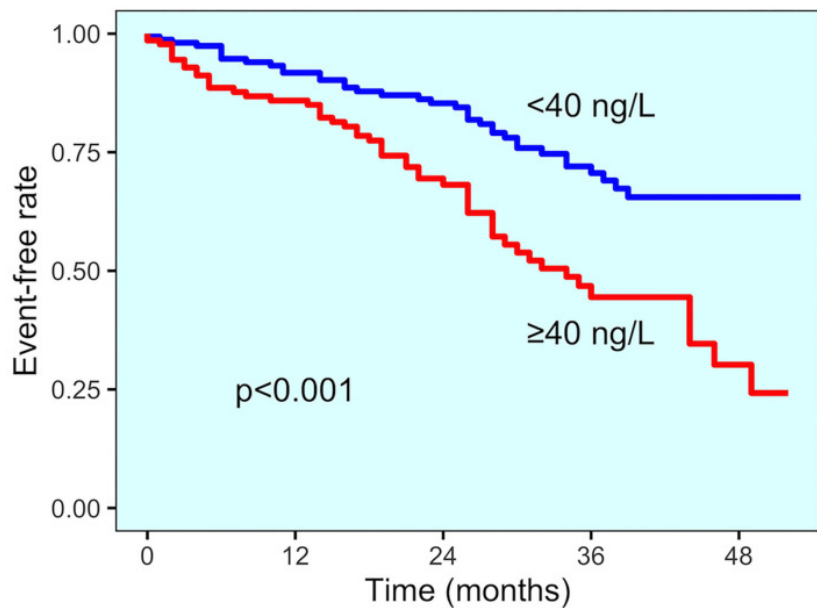
Table 4 Cox regression analysis of clinical and laboratory variables associated with diabetic foot presence

	Univariate analysis			Multivariate analysis		
	Regression coefficient	Hazard ratio (95% CI)	P value	Regression coefficient	Hazard ratio (95% CI)	P value
Age	0.69	2.32 (1.78-5.19)	0.021	0.49	2.12 (1.82-4.48)	0.031
Diabetes duration (y)	1.56	7.26 (3.80-13.87)	<0.001	1.21	5.67 (2.70-8.34)	<0.001
Hypercholesterolemia	0.59	1.55 (1.16-2.64)	0.21	0.44	0.87 (0.166-1.62)	0.42
Hypertension (n/%)	0.32	0.78 (1.70-4.34)	0.33	0.39	0.67 (0.30-1.12)	0.71
Obesity (n/%)	0.32	0.86 (0.31-1.23)	0.23	0.29	0.77 (0.42-0.98)	0.56
Chronic renal failure (n/%)	0.11	0.89 (0.53-1.31)	0.35	0.11	0.59 (0.21-0.89)	0.71
Mycroalbuminuria (n/%)	0.41	1.87 (1.32-3.51)	0.018	0.41	1.55 (1.11-2.99)	0.032
Retinopathty (n/%)	0.33	2.31 (1.78-4.78)	0.012	0.33	1.99 (1.45-3.24)	0.021
PAD (n/%)	0.61	3.5 (2.7-4.1)	<0.005	0.59	2.9 (2.1-3.8)	<0.005
CAD (n/%)	0.54	1.6 (1.4-2.7)	0.033	0.54	0.89 (0.5-1.1)	0.56
TIA/Stroke (n/%)	0.42	1.4 (1.21-2.09)	0.041	0.42	0.78 (0.33-0.91)	0.44
IL-6	1.12	4.8 (3.1-5.5)	<0.005	0.98	3.6 (2.8-4.1)	<0.005
Resistin	0.49	2.1 (1.4-3.9)	0.041	0.43	1.78 (1.4-2.9)	0.031
Adyponectin	-0.29	-3.4 (-1.9-3.6)	<0.001	-0.29	-2.9 (-1.5-3.4)	<0.001

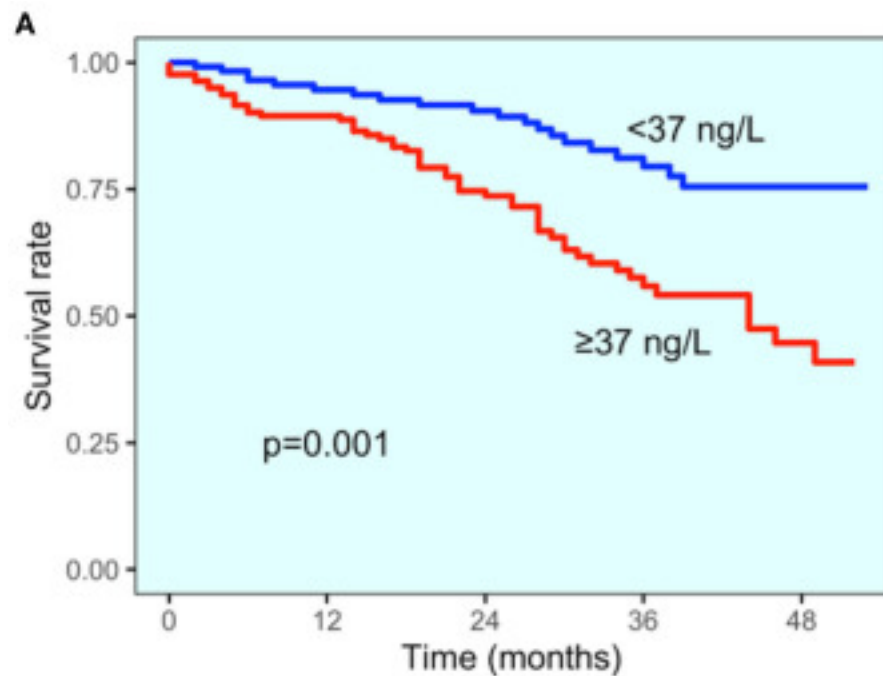
[Tuttolomondo et al. *Cardiovasc Diabetol*, 2010]

A**B**

[Cimaglia et al. *Front Cardiovasc Med* 2021]

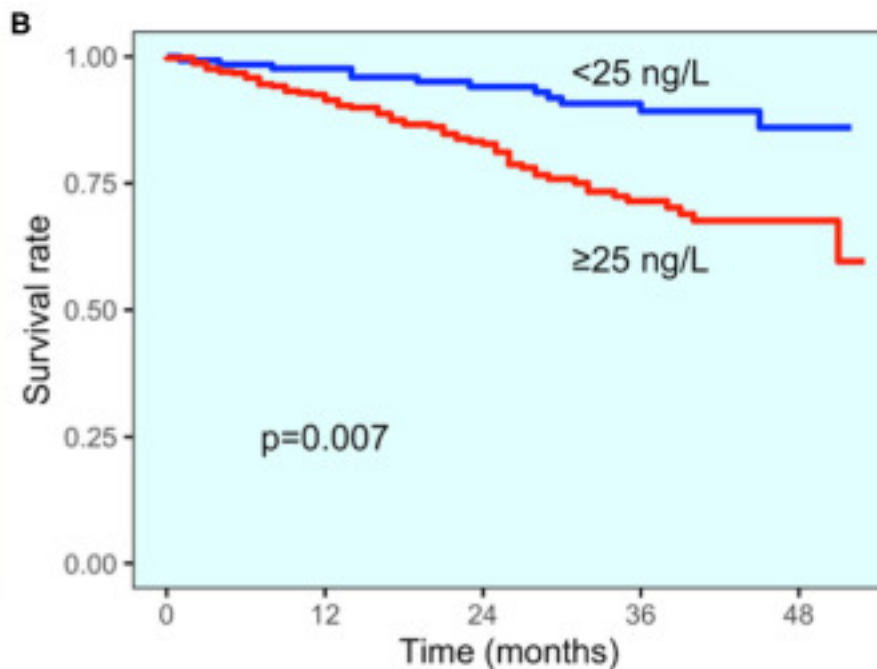


[Cimaglia et al. *Front Cardiovasc Med* 2021]



No. at risk

130	103	88	53	26
140	97	65	31	12



No. at risk

151	132	107	70	21
197	149	101	45	18

[Cimaglia et al. *Front Cardiovasc Med* 2021]

CONCLUSIONI

- La Sindrome del Piede Diabetico [SPD] è una complicanza multifattoriale nel cui determinismo concorrono la neuropatia, la vasculopatia e la immunopatia diabetica.
- Ciascuna di queste componenti a sua volta si associa ad un coinvolgimento cardiaco in grado di condizionare negativamente la prognosi.
- L'interessamento cardiaco nel piede diabetico è la causa principale della elevata mortalità che caratterizza questi pazienti.
- La scarsa sintomaticità della patologia miocardica a causa della neuropatia aumenta il rischio di MACE.
- Uno screening proattivo precoce ed il follow up sono essenziali per ridurre il rischio cardiovascolare nei pazienti con SPD.