CLINICAL DECISION RULES APPLIED TO DIABETIC FOOT ULCER PREDICTION

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Janeiro 2009
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À Podologia que merece que acreditem nela e a todos os que acreditam em mim.
Este Mestrado surgiu numa altura de grande incerteza no futuro. Fez-me seguir em frente e abriu (e de que modo) os meus horizontes. Assim queria começar por agradecer ao Professor Doutor Altamiro da Costa Pereira pela existência do Mestrado e por ter aceite “a menina dos quinze”. Penso que nunca esquecerei aquela entrevista...

Agradeço ao Professor Doutor Mário Dinis-Ribeiro por, como já lhe disse, ter sido um orientador no sentido lato da palavra. Espero que este trabalho honre tudo o que me ensinou...Obrigado por me ter guiado, ensinado, compreendido os meus momentos mais em baixo e por me fazer constantemente sentir que me falta ainda tanto por aprender.

Quero agradecer também a todo o pessoal do CHVNG/ Espinho EPE com quem eu trabalho: à Drª Manuela Ribeiro (obrigada por me ter dado a oportunidade de exercer a Podologia na área que mais gosto – o Pé Diabético - num local que adoro), à Drª Graça Vargas (por ter aceite e facilitado a execução desta tese), à minha colega Rosa (por tudo o que me tem vindo a ensinar), à Enfermeira Aldora (pela ternura e ajuda na organização da revisão sistemática), à Enfermeira Ema (pela frontialidade em todas as situações), à Enfermeira Isaura (por partilhar o meu gosto pela organização e pela sua simpatia), ao Enfermeiro Sobral (pelo seu carinho – que é recíproco), à “Paulinha” (por me fazer gostar ainda mais de ir trabalhar), à Drª Merlinde (pela sua verdadeira paixão pelo Pé Diabético e pela Medicina em si) e ao Dr Campos Lemos (por pôr logo mãos à obra quando preciso de ajuda e por respeitar a Podologia).

Agradeço também à Drª Isabel Ribeiro pelas imensas revisões ao texto e por ter sido a 3ª autora da revisão sistemática, à Drª Joana Ribeiro por ter aceite ser a 2ª autora da revisão sistemática e à Drª Nídia Rocha por mais revisões ao texto.

I would like also to thank to the authors that replied to my emails, answered to questions I had and specially to those that send me their articles free of charge: Armstrong DG, Boulton AJ, Boyko EJ, Chantelau E, Coppini D, Control Disease Center, Faglia E, Iversen M, Kästenbauer T, Lavery L, Ledoux W, Olmos P, Stocks A, Veves A. You were all very kind and gave me a new energy and dedication to perform my studies.

A nível pessoal gostaria de agradecer a todos os professores do MEDS por tudo que me ensinaram, mas especialmente ao Professor Luís Azevedo pelas conversas que fizeram surgir tantas ideias luminosas e me ajudaram a definir o que iria fazer, à Professora Cristina e Professor Armando por me tirarem o medo da Bioestatística e substituírem-no por gosto e aos meus colegas Joana, Tiago e Raúl por tornarem o primeiro ano do mestrado tão divertido.

Não poderia deixar de agradecer aos meus amigos por me apoiarem incondicionalmente e por todo o carinho e Amizade que nos une.

Por fim, mas não por último, aos meus pais por acreditarem sempre que sou capaz (fazendo-me acreditar também), por me estimularem a conseguir um pouco mais e por me ajudarem a consegui-lo.

Obrigada a todos por tornarem a minha vida tão rica!!
Foot complications are an agent of high morbidity among patients with diabetes. An effective and well planned prevention programme, based on a validated foot ulcer risk stratification system, is central. To improve the available evidence on this subject, this thesis was developed.

**Clinical decision rules**

**Aim:** To conduct a literature review in order to create a stepwise and checklist for the development and critical analysis of clinical decision rules (CDR).

**Material and methods:** We performed a sensible search in MEDLINE database for articles published until July 2009, in English, French, Italian, Spanish or Portuguese, that addressed CDR’s development, diagnostic accuracy and/or prognostic studies’ development process and possible bias or the creation of studies quality assessment checklists.

**Results:** This review resulted in 13 articles addressing directly CDR’s development, 15 describing diagnostic or prognostic studies development process and 4 pertinent quality assessment checklists. Accordingly, we have proposed a stepwise composed by 10 steps for a well-conducted CDR’s derivation, 8 for validation and 9 for impact analysis and a 29 items checklist for CDRs reporting and assessment.

**Conclusion:** Despite its importance, low attention has been given to the standardization of CDR’s methodology. We have proposed for the first time a structured stepwise for CDR’s derivation, validation and impact analysis and a checklist as guides for their creation and analysis.

**Predictive factors for diabetic foot ulceration: a systematic review**

**Aim:** To conduct a systematic review (SR) of predictive factors (including existing foot ulcer risk stratification systems) for diabetic foot ulcer occurrence.

**Material and methods:** We carried out a sensible search in MEDLINE database (PubMed) for studies published until December 2008, in English, French, Italian, Spanish or Portuguese; that analyzed possible predictive factors for diabetic foot ulceration.

**Results:** A total of 71 studies were included in this SR: 58 in the predictive variables section, 11 in the risk stratification systems section and 2 in both. The retrieved studies assessed the association between foot ulceration and more than 100 independent variables (namely nephropathy, diabetic neuropathy tests, visual acuity, foot deformities and previous foot complications) and described 5 distinct foot ulcer risk stratification systems.

**Conclusion:** Despite the amount of available evidence, a great lack of standardization essentially in outcome definition and selection and variable collection was observed. Moreover, the existing stratification systems development stands still in a low evidence level.

**External validation and optimization of a model for predicting foot ulcers in patients with diabetes**

**Aim:** To validate and optimize a CDR evaluating the risk of developing diabetic foot ulcers.

**Material and methods:** A retrospective cohort study was conducted on all patients with diabetes attending to the Podiatry section of a Diabetic Foot Clinic at a tertiary Hospital in Portugal (n=360). Assessment at baseline included variables evaluated in Boyko’s study and also other pertinent and available variables.
Results: Subjects had type 2 diabetes in 98% of cases, 45% were male and (at baseline) the median age was 65 years old. Median follow-up was 25 months and 94 patients (26%) developed a foot ulcer. Boyko’s model had an area under the receiver operating curve (AUC) of 0.83 (CI 95% 0.78-0.88) and the optimized model, including a footwear variable, of 0.88 (CI 95% 0.84-0.91). Both models presented high classification accuracy for predicting foot ulceration. However, the optimized model tended to produce higher specificity and positive likelihood ratio values at all levels.

Conclusion: This study confirmed, for the first time at an external setting, that Boyko’s proposed model has a high capacity to predict foot ulceration in patients with diabetes of both genders. Our results suggest that including a variable regarding footwear could improve it.

As complicações a nível podológico, particularmente as úlceras, são responsáveis por uma alta morbilidade em pessoas com diabetes. Um programa preventivo estruturado e eficaz, tendo por base um sistema de estratificação por risco de ulceração, é vital. De forma a contribuir para o desenvolvimento da evidência existente à volta deste tópico, a seguinte tese foi desenvolvida.

Regras de decisão clínica

Objective: Realizar uma revisão da literatura de modo a criar um stepwise e uma checklist para o desenvolvimento e análise crítica de estudos sobre regras de decisão clínica (RDC).

Material e métodos: Conduzimos uma pesquisa sensível na base de dados de MEDLINE para obter artigos publicados até Julho de 2009, em Inglês, Francês, Italiano, Espanhol ou Português; que abordassem o desenvolvimento de RDCs, o desenvolvimento de estudos de diagnóstico e/ou prognóstico ou a criação de checklists para a avaliação da qualidade metodológica dos mesmos.

Resultados: Esta revisão incluiu 13 artigos sobre o desenvolvimento de RDCs, 15 sobre estudos de diagnóstico e/ou prognóstico e 4 checklists; resultando na proposta de um stepwise composto de 10 passos para a derivação, 8 para a validação e 9 para a análise de impacto de uma RDC e numa checklist para a sua descrição e avaliação de 29 itens.

Conclusão: Apesar da sua importância, pouca atenção tem sido dada à standartização da metodologia das RDCs. Neste estudo, propusemos pela primeira vez um stepwise estruturado para a derivação, validação e análise de impacto das mesmas e uma checklist para auxiliar na sua criação e avaliação.

Factores preditivos de úlcera no pé do diabético: uma revisão sistemática

Objective: Desenvolver uma revisão sistemática sobre os factores preditivos de úlcera no pé do diabético (incluindo os sistemas de estratificação por grau de risco de ulceración existentes).

Material e métodos: Efectuamos uma pesquisa sensível na base de dados da MEDLINE para estudos publicados até Dezembro de 2008, em Inglês, Francês, Italiano, Espanhol ou Português; que analizassem os possíveis factores preditivos de úlcera a nível do pé do diabético.
**Resultados:** Foram incluídos 71 estudos nesta revisão: 58 na secção das variáveis preditivas, 11 na secção dos sistemas de estratificação por grau de risco e 2 em ambas as secções simultaneamente. Os estudos recolhidos avaliaram a associação entre ulceração e mais de 100 variáveis independentes (nomeadamente nefropatia, testes para a detecção de neuropatia diabética, acuidade visual, deformidades podológicas e complicações podológicas prévias) e descreverem e/ou avaliaram 5 sistemas distintos de estratificação por grau de risco.

**Conclusão:** Apesar da quantidade de evidência disponível, existe um vazio particularmente a nível da standartização da definição e selecção do outcome e da metodologia de recolha de diversas variáveis. Adicionalmente, o grau de desenvolvimento dos sistemas de estratificação encontra-se ainda num baixo nível de evidência.

**Validação externa e optimização de um modelo preditivo de úlcera a nível do pé do diabético**

**Objectivo:** Validar (retrospectivamente) e optimizar um RDC para o desenvolvimento de úlcera a nível do pé do diabético.

**Materiais e métodos:** Desenvolvemos um estudo de coorte retrospectivo, incluindo todos os utentes da consulta de Podologia, no Serviço de Pé diabético de um hospital terciário no Norte de Portugal (n=360). Na primeira consulta, foram recolhidas todas as variáveis presentes no estudo desenvolvido por Boyko e outras variáveis pertinentes e acessíveis.

**Resultados:** A amostra foi constituída 98% por utentes com diabetes tipo 2, 45% do sexo masculino e com uma idade média de base de 65 anos. O seguimento médio foi de 25 meses, durante os quais 94 utentes (26%) desenvolveram úlcera a nível podológico. O modelo proposto por Boyko resultou numa área sobe a curva ROC de 0,83 (IC 95% 0,78-0,88) e o optimizado, incluindo uma variável referente ao calçado, de 0,88 (IC 95% 0,84-0,91). Ambos os modelos apresentaram uma boa capacidade discriminatória. No entanto, o modelo optimizado tendeu a produzir especificidades e likelihood ratio positivos superiores a todos os níveis.

**Conclusão:** Este estudo confirmou, pela primeira vez num contexto externo, que o modelo proposto por Boyko apresenta uma grande capacidade de predição de desenvolvimento de úlcera a nível podológico em pessoas com diabetes de ambos os sexos. Os nossos resultados sugerem que a inclusão de uma variável referente ao calçado poderia melhorá-lo.
1st: First

ABI: Ankle-Brachial Index
ADA: American Diabetes Association
AUC: Area Under the ROC Curve

BMI: Body Mass Index

Cat: Categorical variable
CDC: Control Disease Center
CDR: Clinical Decision Rule
CI: Confidence Interval
Cm2: Square centimeters
CO: Cut-Off
CONSORT: Consolidated Standards for Reporting of Trials
Cont: Continuous variable
CPR: Clinical Prediction Rule

Der: Derivation
DM: Diabetes Mellitus
DN: Diabetic Neuropathy

EBM: Evidence Based Medicine
ESRD: End-Stage Renal Disease

F/R R: Forefoot/Rearfoot Ratio

g: Grams

HAV: Hallux Abductus Valgus
HBA1C: Glycated Hemoglobin
HDL: High Density Lipoprotein
HR: Hazard Ratio
Hz: Hertz

IWGDF: International Working Group on Diabetic Foot

Kg: Kilograms

LDL: Low Density Lipoprotein
LE: Lower Extremity
LR: Likelihood Ratios
LR -: Negative Likelihood Ratio
LR +: Positive Likelihood Ratio

MEDLINE: Medical Literature Analysis and Retrieval System Online
MNCV: Motor Nerve Conduction Velocity
MNSS: Michigan Neuropathy Screening Score
MTPJ: Metatarso-Phalangeal joint
MTT: Metatarsal
NA: Not Assessed
NAP: Not Applicable
NDS: Neuropathy Disability Score
NPV: Negative Predictive Value
NR: Not Reported
NSS: Neuropathy Symptoms Score
O: Variable present in the Original stratification system
OND: National Diabetes Observatory / Observatório Nacional de Diabetes
OR: Odds Ratio

PMSS: Peak Maximal Shear Stress
PPG: Peak Pressure Gradient
PPP: Peak Plantar Pressure
PPV: Positive Predictive Value
PVD: Peripheral Vascular Disease
PVS: Peripheral Vascular Surgery

QUADAS: Quality Assessment of Diagnostic Accuracy Studies

R: Variable present in the Revised stratification system
RCT: Randomized Controlled Trial
RDC: Regras de Decisão Clínica
READER: REporting and Assessing clinical DEcision Rules
ROC: Receiver Operating Characteristic
RR: Relative Risk

Se: Sensitivity
SIGN: Scottish Intercollegiate Guideline Network
Sp: Specificity
SR: Systematic Review
SSEPS: Short latency Somatosensory Evoked Potentials
STARD: Standards for Reporting of Diagnostic Accuracy
STJ: Sub-Tarsal Joint
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
SWM: Semmes Weinstein Monofilament

TcPO2: Transcutaneous Oxygen Pressure

UTFRS: University of Texas Foot Risk Stratification

V: Volt
Val: Validation
VPT: Vibratory Perception Threshold

WHO: World Health Organization
I. RATIONALE
Diabetes Mellitus (DM) is a relevant health problem for its high morbidity and mortality ([World Health Organization - WHO, 1994]), leading to a lifetime risk for foot ulcer occurrence of 12 to 25% (Al-Maskari et al, 2007; Brem et al, 2006; Boulton et al, 2004a, 2005, 2008a, 2008b; Fard et al, 2007; Frykberg et al, 2006) and a recurrence rate of 34% and 70% after 1 and 5 years, respectively. (Fard et al, 2007)

It was reported that in subjects with diabetes 7% to 20% of foot ulcers evolve to amputation (Frykberg et al, 2006) and that 85% of the amputations are preceded by an ulcer. (Brem et al, 2006; Boulton et al, 2004a; Frykberg et al, 2006). It is estimated that a person with diabetes has 15 (Brem et al, 2006; SIGN, 2001) to 40 (Fard et al, 2007) times more chance of suffering a non-traumatic amputation in comparison with a non-diabetic, with an incidence of amputation of the opposite member superior to 50% in the 3 following years. (Frykberg et al, 2006; Morbach et al, 2003) For all that, patients face foot amputation as one of the most feared diabetes’ related complication. (Bowering et al, 2001)

The chronic hyperglycemia (that characterizes the poorly controlled DM) progresses, through the years, in a more or less simultaneous fashion, to a peripheral neuropathy and to an accelerated and severe arteriosclerosis, which eventually results in diabetic foot complications. The diabetic foot has a great number of risk factors that contribute for its development and sustaining. Knowing each factor and how it affects each patient allows a more rational approach to the prevention and treatment of complications.

Prevention is the key element to avoid ulcers, ulcer recurrence and, in last instance, amputation of the lower extremity. In fact, clinical guidelines consider essential to include a direct and sustained follow-up, the education of the diabetic patient and an early discrimination of the foot at risk. (Apelqvist et al, 2000, 2008) The last should be performed using risk stratification systems founded on a structured clinical evaluation of the patient in a way to incorporate data from diagnostic tests, as from clinical history or examination (physical signs), integrating in practice the best evidence available originated from prognostic and diagnostic studies that assess the importance of this variables. (Crawford et al, 2007) The most effective way to do so is through the creation of a Clinical Decision Rule (CDR). (Beattie et al, 2006)

CDR’s should be developed, as with all sorts of studies, according to strict and clearly defined methodological standards. For that reason and due to its importance, Wasson and colleagues (Wasson et al, 1985) and posteriorly Laupacis and colleagues (Laupacis et al, 1997) published methodological standards for CDR’s creation and development. These and other papers have been dedicated to describing the essential steps to develop and validate a CDR, but none of them tries to synthesize this knowledge into a systematic and practical stepwise for this complex process (Beattie et al, 2006; Childs et al, 2006; Laupacis et al, 1997; McGinn et al, 2000; Stiell et al, 1999, 2000; Wasson et al, 1985)

Additionally, as a particular form of a diagnostic/prognostic cohort study, CDRs should require an exclusive checklist for reporting and assessing it, fusing the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and Standards for Reporting of Diagnostic Accuracy (STARD) checklists in a way to reflect the ensemble of characteristics needed for its construction. On the other hand, some of the fundamental steps essential for a CDR derivation or validation of good quality are not contemplated by any of the checklists available. Thus, is vital that some of the items be based on literature review. Therefore, we found it indispensable to carry out a literature review for developing a stepwise and a checklist (READER – REporting and Assessing clinical DEcision Rules) as a supporting tool for the creation of CDR’s and/or critical reading of papers using this kind of study.
Although diabetic foot is in the order of the day, we have realized that the available evidence is very deficient and that only scarce research has been dedicated to the crucial tool that a foot ulcer risk stratification system represents. Furthermore, we verified that each working research group developed its own results independently without aggregating the other groups’ conclusions, which leaded to a lack of methodology, report and results homogeneity and in low level available evidence.

Therefore, we felt the necessity of validating externally in our population a robust foot ulcer risk stratification system. In 2006, Boyko et al. (Boyko et al, 2006) developed a CDR for the prediction of foot ulcer occurrence, using seven commonly available clinical variables, with good results. They included around 1300 diabetic veterans with a mean age of 62 years, mainly male and with diabetes type 2 and followed prospectively up to 5 years (mean of 40 months).

This foot ulcer risk stratification system, is the only one (that we are aware of) that includes the glycated hemoglobin (HbA1C) value for the calculation of the risk degree, the variable selection was performed through univariate and multivariate analysis using Cox proportional hazard regression (in spite of literature reviews and consensus) and that its predictive ability was assessed using the area under the receiver operating characteristic (ROC) curve (AUC) at 1 and 5 years of follow-up.

To our knowledge, this risk stratification system was never externally validated. For that reason, and applying into practice the proposed stepwise and checklist, we validated and tried to optimize this CDR in our population through a retrospective cohort study.
II. AIMS AND OUTLINE
A. To conduct a literature review in order to create a stepwise and checklist (READER) for the development and critical analysis of clinical decision rules.

CDRs are an extremely important tool in clinical decision making which may incorporate variables from the medical history, physical examination and other patient characteristics. However, as a somewhat recent form of evidence its development and validation process still needs to undergo some refinements. Therefore, in chapter III (section A) we reviewed the evidence available and suggested a stepwise for the derivation, validation and impact analysis of CDRs and a checklist for its reporting and assessment, given that there is no such statement in a unique proposal.

Due to its uniqueness this study was sent for publication with the title: “READER – Reporting and Assessing clinical DEcision Rules”.

B. To conduct a literature review of the importance, pathophysiology and prevention of diabetic foot ulcer development.

Diabetic foot ulcers occur due to a multiplicity of factors combined. And so, we believed it was fundamental to carry out a literature review of its importance, pathophysiology and prevention (chapter III, section B) to better understand this event and so optimize the development of the following section.

C. To conduct a systematic review of predictive factors for developing diabetic foot ulcers.

An important step in the optimization of a CDR is the creation of a list of all possible and reasonable predictive variables. The most standardized way of doing it is through a systematic review of all the studies that address the association between variables and ulcer development.

In chapter III (section B), its methods and results will be described in a comprehensive fashion. For its pertinence, this study was sent for publication with the title: “Predicting diabetic foot ulceration using independent variables: a systematic review”.

D. To conduct a systematic review of the existing stratifications of risk degree for developing diabetic foot ulcers.

Before developing or validating a CDR, researchers should consider its actual usefulness. CDR’s should be developed only when there is some degree of clinical uncertainty, possibility of under-diagnosis or the need to classify patients for some interventions and only those with methodological quality and promising results should be validated in our population of interest.

Consequently, we reviewed (in chapter III, section B) the existing diabetic foot ulcer development risk degree stratifications and their diagnostic accuracy, justifying the Boyko’s et al stratification system selection for external validation in our population.

For its importance, this study was sent for publication with the title: “The state of the art of diabetic foot ulcer risk stratification systems: a systematic review”.
E. To validate (retrospectively) and optimize a Clinical Decision Rule evaluating the risk of developing diabetic foot ulcers.

Boyko et al, in the article “Prediction of Diabetic Foot Ulcer Occurrence Using Commonly Available Clinical Information - The Seattle Diabetic Foot Study”, developed a risk stratification system for diabetic foot ulceration using only available clinical information having good results. In chapter IV, we validated this model and described an optimization proposal.

Subsequently this study was sent and accepted for publication in the Diabetologia journal with the title: “External validation and optimization of a model for predicting foot ulcers in patients with diabetes”. 
III. BACKGROUND
A. CLINICAL DECISION RULES
1. INTRODUCTION

Making accurate clinical decisions is vital in our daily practice. Traditionally, health practitioners rely on their judgment, knowledge and intuition to decide which evaluative procedures to perform, how to interpret the results of these procedures, and what interventions to choose. (Beattie et al, 2006)

With the constant multiplication of the scientific publications, clinicians need increasingly to integrate it with their professional perception and the patient individual characteristics, so that they can make the best clinical decision possible; this is, practice Evidence Based Medicine (EBM).

Although CDRs are one of the most efficient ways to transport research results to clinical decision-making (Beattie et al, 2006), little has been reported on how to develop and assess them. (Cook et al, 2008) Consequently, this paper aims to propose a stepwise and a checklist to help authors to create, develop and report CDRs in an optimized way and readers to evaluate their methodological quality, based on a literature review of the current evidence available.

a. CLINICAL DECISION RULE DEFINITION


- are a clinical decision support tool that try to formally test, simplify, and increase the accuracy of clinicians’ diagnostic and prognostic assessments,
- should be developed according to clearly defined methodological standards (yet to standardize),
- are derived from results of, adequately conducted, original research (including synthesis studies),
- standardize the collection and interpretation of clinical data in an effort to diminish the uncertainty in decision-making,
- incorporate 3 or more specific and relevant patient characteristics (clinical history, physical examination, diagnostic procedures and/or patient beliefs),
- summarizes and quantifies in a numeric index the probability of an outcome of interest or suggests an intervention (diagnostic or therapeutic).

Although some differences may exist in the concept and in the role of clinical decision and prediction rules (CPR) in decision making (Beattie et al, 2006; Reilly et al, 2006; Sackett et al, 1996), their methodology is similar. (Laupacis et al, 1997; Lijmer et al, 1999). Hence, every time we refer to CDR we regard to CDR and CPR as synonyms.

One must not confuse the CDR concept with practice guidelines. While CDRs concentrate on 1 isolated decision at 1 distinct stage of patient care and are utterly evidence based with its performance validated in several studies, guidelines address a number of topics for the optimal care of patients with a particular syndrome and usually translate the results of an expert consensus not always evidence based. (Reilly et al, 2006)
2. MATERIAL AND METHODS

We performed a sensible search in MEDLINE (Medical Literature Analysis and Retrieval System online) database (PubMed) for articles published until July 2009 (including) that described a CDRs development methodology, using key terms such as “prediction”, “clinical rules”, “study methodology”, “prognosis” and related terms, in several combinations.

In a first stage, all the retrieved article’s titles and abstracts were assessed. Studies were included if they fulfilled the following selection criteria:

1. Publication date: until July 2009 (including)
2. Published in the following languages: English, French, Italian, Spanish or Portuguese
3. Theme: CDRs development and evaluation. When pertinent, articles addressing the creation of study quality assessment checklists and illustrating diagnostic accuracy and/or prognostic studies’ development process and possible bias were also included.
4. Availability of full text version.

The full text version (when available) from the retrieved studies was analyzed and they were selected according to their pertinence. The reference list of the included articles was evaluated and new articles were retrieved. This process was repeated until no new study emerged.

3. STEPWISE APPROACH FOR DEVELOPING CLINICAL DECISION RULES

One of the fundamental pillars of EBM is the use of the best evidence available. This condition necessarily restricts the focus to optimally designed studies. (Beattie et al, 2006) To improve the rigor in methodology a well defined and structured stepwise is central. In fact, all CDRs, as an extremely important tool in patient care decision making, should be developed according to strict and homogeneous methodological standards. (Beattie et al, 2006; Childs et al, 2006; Cook et al, 2008; McGinn et al, 2000; Reilly et al, 2006; Stiell, 2007; Wason et al, 1985)

The development and test of a CDR is built upon 3 major stages: the rule’s derivation, validation and impact assessment on clinical practice. (Beattie et al, 2006; Childs et al, 2006; McGinn et al, 2000; Reilly et al, 2006; Stiell, 2007; Wason et al, 1985) However, before developing a CDR, researchers should consider its real need or utility (degree of clinical uncertainty, possibility of under-diagnosis, etc.) and the prevalence of the disease. (Beattie et al, 2006; Blackmore, 2005; Bhandari et al, 2005; Greenhalgh, 1997; Jaeschke et al, 2002; Reilly et al, 2006; Sackett et al, 1999; Stiell et al, 1999)

3. DERIVATION

1. Clearly define an outcome of interest that is clinically important and can be reliably measured. (Beattie et al, 2006; Cook, 2008; Jaeschke et al, 2002; Laupacis et al, 1997; McGinn et al, 2000; Reilly et al, 2006; Stiell et al, 1999, 2000; Wason et al, 1985)

2. Develop a complete and reasonable list of all possible and logical predictive factors for the diagnostic or prognostic of the outcome of interest (Beattie et al, 2006; Childs et al, 2006; Jaeschke et al, 2002; Laupacis et al, 1997; McGinn et al, 2000; Reilly et al, 2006; Stiell et al, 1999, 2000; Wason et al, 1985) and report method for variable selection (Laupacis et al, 1997; Wason et al, 1985).
   a. There must be a balance between including all likely predictors, so that no important factor is missing, and the increase in the sample size that is required for each additional variable included. Is recommended 10 to 15 subjects to identify one predictor variable. (Beattie et al, 2006; Childs et al, 2006; Cook, 2008; Jaeschke et al, 2002; Stiell et al, 1999)

   b. A prospective cohort study with a consecutive group of subjects from the clinical population is the best way to guarantee the previous criterions. (Bossuyt et al, 2003; Cook, 2008; Fritz et al, 2001; Lijmer et al, 1999; McGinn et al, 2000; Sox, 1996; Stiell et al, 1999)

4. Sample size should be justified and ideally addressed by power analysis, but maximizing the follow-up. (Altman et al, 2001; Beattie et al, 2006; Stiell et al, 1999; Vandenbroucke et al, 2007)
   a. Determine sample size taking in account:
      i. The context of the risks and benefits of decision making based on the rule
      ii. The prevalence of the outcome
      iii. The degree of precision in the confidence interval (CI) around the measure of accuracy (Beattie et al, 2006; Childs et al, 2006; McGinn et al, 2000; Reilly et al, 2006; Stiell et al, 1999).

This is, to observe larger benefits or smaller risks between the CDR and the standard test, when the outcome has low prevalence and/or the desired precisions’ degree is smaller the sample must be larger.

b. Patient attrition due to loss to follow-up must be the minimal possible. (Beattie et al, 2006; Laupacis et al, 1997; Mak et al, 2005)
5. Examine all the subjects to determine the presence or absence of each predictor variable at baseline. (Beattie et al., 2006; Bossuyt et al., 2003; Childs et al., 2006; Fritz et al., 2001; Gilbert et al., 2001; Greenhalgh, 1997; Jaeschke et al., 2002; Laupacis et al., 1997; Mak et al., 2005; McGinn et al., 2000; Reilly et al., 2006; Stiell, 2000; Wasson et al., 1985) Reporting data collection methods. (Bossuyt et al., 2003; Sox, 1996)

a. The examiner should be blind to the presence or absence of the outcome. (Beattie et al., 2006; Bossuyt et al., 2003; Childs et al., 2006; Fritz et al., 2001; Goodacre, 2009; Greenhalgh, 1997; Jaeschke, 1994, 2002; Laupacis et al., 1994, 1997; McGinn et al., 2000; Reilly et al., 2006; Scales et al., 2008; Schranz et al., 2007; Sox, 1996; Wasson et al., 1985; Whiting et al., 2003)

b. The examinators should be adequately trained to assess the subjects and collect the data standardizedly. (Jaeschke et al., 2002; Laupacis et al., 1997; Stiell et al., 1999; Wasson et al., 1985)

6. Establish the presence or absence of the condition of interest, according to the gold standard, by a second examiner blinded to the previous clinical examination and its results. (Archibald et al., 2001; Beattie et al., 2006; Bhandari et al., 2005; Bossuyt et al., 2003; Cardarelli et al., 2007; Childs et al., 2006; Cook, 2008; Fritz et al., 2001; Gilbert et al., 2001; Goodacre, 2009; Greenhalgh, 1997; Jaeschke, 1994, 2002; Laupacis et al., 1994, 1997; Lijmer et al., 1999; Reilly et al., 2006; Scales et al., 2008; Schranz et al., 2007; Sox, 1996; Stiell et al., 1999, 2003; Scales et al., 2008; Stiell et al., 1999)

a. Reference or gold-standard designates the criterion in which is based the diagnostic (if the patient has or has not the condition) (Beattie et al., 2006; Bhandari et al., 2005; Bossuyt et al., 2003; Childs et al., 2006; Gilbert et al., 2001; Goodacre, 2009; Jaeschke, 1994; Schranz et al., 2007; Sox, 1996; Whiting et al., 2003) and should be safe and easy to apply. (Goodacre, 2009)

b. Preferably the gold standard should be applied at all subjects to avoid verification or workup bias. (Archibald et al., 2001; Bhandari et al., 2005; Fritz et al., 2001; Greenhalgh, 1997; Goodacre, 2009; Jaeschke, 1994, 2002; Laupacis et al., 1997; Lijmer et al., 1999; Sox, 1996; Whiting et al., 2003) This bias tends to occur when the gold standard is invasive and/or complex (Bhandari et al., 2005; Lijmer et al., 1999; Scales et al., 2008) and to overrate sensitivity (Goodacre, 2009; Sox 1996) and likelihood ratios (LR) (Archibald et al., 2001; Sox, 1996) estimation.

c. To avoid incorporation bias the gold standard should be independent of all the diagnostic tests that are being evaluated as predictive factor (Bhandari et al., 2005; Goodacre, 2009). This bias tends to overrate specificity estimation. (Bhandari et al., 2005; Goodacre, 2009)

d. A correct blinding is especially important when the test interpretation requires a certain subjectivity degree. (Goodacre, 2009; Laupacis et al., 1994; Lijmer et al., 1999; Scales et al., 2008; Stiell et al., 1999; Wasson et al., 1985)

e. It is necessary to take in consideration the necessary follow-up period to allow the outcome to occur. (Cardarelli et al., 2007; Laupacis et al., 1994; Mak et al., 2005)

7. Describe in detail the used methods for data and outcome collection in a way permitting replication (Archibald et al., 2001; Fritz et al., 2001; Jaeschke, 1994; Laupacis et al., 1997; Lijmer et al., 1999; Scales et al., 2008; Wasson et al., 1985; Whiting et al., 2003), preferably using the available checklists (STARD or READER).

8. Assess the intra-observer and inter-observer reliability of the predictor variables and of the condition of interest through agreement proportion and/or kappa value (weighted or not) for nominal data and intraclass correlation coefficient and/or limits of agreement for interval data. (Archibald et al., 2001; Bossuyt et al., 2003; Cook, 2008; Fritz et al., 2001; Gilbert et al., 2001; Goodacre, 2009; Greenhalgh, 1997; Jaeschke, 1994, 2002; Laupacis et al., 1997; Scales et al., 2008; Stiell et al., 1999, 2000)

a. Only those with good agreement beyond that expected by chance alone should be considered. (Stiell et al., 1999)

9. Perform statistical analysis to determine the grouping of variables that gives the best degree of accuracy and which predictors can be omitted. (Cardarelli et al., 2007; Childs et al., 2006; Jaeschke et al., 2002; Laupacis et al., 1997; Mak et al., 2005; McGinn et al., 2000; Stiell et al., 1999, 2000; Wasson et al., 1985)

a. Describe and justify the mathematical method used to derive the CDR – usually multivariable logistic regression (Childs et al., 2006; Cook, 2008; Jaeschke et al., 2002; Laupacis et al., 1997; McGinn et al., 2000; Stiell et al., 1999; Wasson et al., 1985) or survival analysis methods (Cox regression) (Mak et al., 2005).

b. Analysis should be intention-to-treat; this is, including subjects that dropped out due to adverse events or death. (Beattie et al., 2006; Cardarelli et al., 2007)
10. **Provide the accuracy and/or the classification performance** (Beattie et al, 2006; Bossuyt et al, 2003; Childs et al, 2006; Fritz et al, 2001; Goodacre, 2009; Greenhalgh, 1997; Jaeschke et al, 2002; Laupacis et al, 1997; Ljmere et al, 1999; McGinn et al, 2000; Reilly et al, 2006; Scales et al, 2008; Stiell et al, 1999, 2000; Wasson et al, 1985)


   b. **Sensitivity and specificity are very useful at a population level, however at patient level are difficult to apply. Predictive values have as disadvantage its dependence with the condition prevalence. LR are the most intuitive and useful diagnostic accuracy measure (Bhandari et al, 2005; Fritz et al, 2001; Goodacre, 2009; Scales et al, 2008)** Interconnecting pretest probability with posttest probability (increasing it when superior to 1 or decreasing it when inferior to 1). (Archibald et al, 2001; Beattie et al, 2006; Bhandari et al, 2005; Childs et al, 2006; Fritz et al, 2001; Gilbert et al, 2001; Jaeschke et al, 2002; McGinn et al, 2000; Scales et al, 2008; Schrzan et al, 2007; Stiell et al, 1999)

   c. A test’ accuracy relies on how well it can separate the subjects with from those without a condition and can also be measured by the AUC. A ROC graph illustrates the tradeoff relation between true positives and false positives. In a different context from the diagnostic tests, Ling and coworkers even proved empirical and formally that AUC is more discriminating and consistent than accuracy. (Ling et al, 2003)

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**b. VALIDATION**

The validation process consists on a series of studies with broader populations of clinicians and patients (Beattie et al, 2006; McGinn et al, 2000), with different prevalence and spectrum of disease (McGinn et al, 2000), to reassure the reliability of the results obtained in the “derivation set”, in different settings. (Childs et al, 2006; McGinn et al, 2000)

1. **Describe the study subjects, the selection process and study setting in detail.** (Altman et al, 2001; Bossuyt et al, 2003; Childs et al, 2006; Jaeschke et al, 1994, 1997; Ljmere et al, 1999; McGinn et al, 2000; Sox, 1996; Stiell et al, 1999; Wasson et al, 1985; Whiting et al, 2003)

   b. A prospective cohort study with a consecutive group of subjects from the clinical population is the best way to guarantee the previous criterions. (Bossuyt et al, 2003; Cook, 2008; Fritz et al, 2001, Ljmere et al, 1999; McGinn et al, 2000; Sox, 1996; Stiell et al, 1999)

2. **Sample size should be justified and ideally addressed by power analysis but maximizing the follow-up.** (Altman et al, 2001; Stiell et al, 1999; Wasson et al, 2007)

3. **Ensure that all investigators conducting the validation process know how to correctly apply the CDR, training them, if necessary.** (Childs et al, 2006; Jaeschke et al, 2002; Laupacis et al, 1997; Stiell et al, 1999; Wasson et al, 1985)

4. **Apply, if possible, prospectively** (Cook, 2008; Fritz et al, 2001; Jaeschke et al, 2002; Laupacis et al, 1997; McGinn et al, 2000; Sox, 1996; Stiell et al, 1999; Wasson et al, 1985) the CDR to a new population, preferably in a new clinical setting by other clinicians that those used in the derivation process. (Beattie et al, 2006; Cook, 2008; Laupacis et al, 1997; Mak et al, 2005)

   a. It is necessary to take in consideration the necessary follow-up period to allow the outcome to occur. (Cardarelli et al, 2007; Laupacis et al, 1994)

7. Assess the accuracy of interpretation, the intra-observer and/or the inter-observer reliability (Archibald et al, 2001; Blackmore, 2005; Bossuyt et al, 2003; Childs et al, 2006; Fritz et al, 2001; Goodacre, 2009; Greenhalgh, 1997; Jaeschke et al, 1994, 2002; Laupacis et al, 1997; Scales et al, 2008; Stiell et al, 1999, 2000) of the CDR itself, as well as the comfort and compliance with its use and clinical sensibility (Blackmore, 2005; Cook, 2008; Laupacis et al, 1997; Reilly et al, 2006; Stiell, 2000, 2007) (the latter may be determined by a simple survey question) (Stiell et al, 1999).

   b. Analysis should be intention-to-treat; this is, including subjects that dropped out due to adverse events or death. (Candarelli et al, 2007; McGinn et al, 2000)

A validation study provides a unique opportunity for the investigator to review the value of each component variables in the CDR, and possibly to simplify it, or consider re-evaluating some variables that were demonstrated to be important but not essential in the derivation process. After this refinement the rule must pass again by validation, in a new sample. (Stiell et al, 1999)

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### c. IMPACT ANALYSIS

The last stage in a CDR development – the impact analysis - is fundamental: to determine if it can change or have changed the behavior of clinicians and if it is cost-effective. (Stiell, 2000)

1. Choose a CDR to use and evaluate. (Reilly et al, 2006; Sackett et al, 1996)

2. Choose, justifying, a study design. It can be performed essentially by 1 of 3 ways: (Childs et al, 2006; McGinn et al, 2000; Sackett et al, 1996; Stiell et al, 1999; Wasson et al, 1985)
   a. Each patient is randomly assigned to decisions based on the CDR or in traditional practice. This is the ideal approach. As disadvantage this study obligates clinicians to constantly swap the decision process.
   b. Randomly assign clinical sites or periods of time when the CDR is or is not used.
   c. Non-randomized study - in which similar outcomes are evaluated before and after CDR’s implementation.  
      i. The last two designs are weaker, subject to temporal and “wash over” confounding. (Reilly et al, 2006)

3. Describe the study subjects, the selection process and study setting in detail. (Jaeschke et al, 2002; Reilly et al, 2006)
   a. Subjects’ choice must be unbiased and represent a wide spectrum (Fritz et al, 2001; Greenhalgh, 1997; Laupacis et al, 1997; McGinn et al, 2000; Reilly et al, 2006), similar to the clinical practice.

4. Sample size should be calculated for major measures of the impact analysis (is often required a very large sample size). (Reilly et al, 2006)
5. Ensure that all clinicians involved in the study know how to correctly apply the CDR, training them, if necessary. (Jaeschke et al, 2002)

6. Apply the CDR or use the standard clinical practice, accordingly to the randomization.

7. Describe in detail the used methods for data and outcome collection in a way permitting replication. (Scales et al, 2008)

8. The assessment of outcomes should be blind to risk stratification and to group of decision method. (Reilly et al, 2006; Sackett et al, 1996) There are 4 essential items in an impact analysis: (Reilly et al, 2006; Sackett et al, 1996; Stiell et al, 1999)
   a. Accomplishment of the intentioned impact on patient care: reduction of use of the resource in question, cost-effectiveness or benefit, improvement of quality and/or satisfaction.
   b. Comparison of the actual impact with potential impact - measured by analyzing the rule’s recommended decisions, regardless of implementation.
   c. Accuracy’s conservation of the original CDR or improvement of accuracy by some modifications of the CDR. It is vital to perform a careful follow-up to detect possible missed diagnosis and then recalculate accuracy measures of the CDR.
   d. Safety (proportion of subjects with the predicted outcome that received a proper diagnostic and/or therapeutic action) and efficiency (proportion of subjects without the predicted outcome that received a negative diagnostic and/or no therapeutic action).

9. Apply a survey to all clinicians that used the CDR evaluating comfort and simplicity of use and to patients assessing their satisfaction with clinical care. (Sackett et al, 1996)
Several studies have concluded that published original research (diagnostic accuracy, prognostic or even randomized controlled trial [RCT] studies) frequently present poor methodological design, which greatly compromises the reported results and its applicability. (Bossuyt et al, 2003; Lijmer et al, 1999; Moons et al, 2003; von Elm et al, 2007)

EBM must be based on the best evidence available (Fritz et al, 2001). But how should we appraise it? Checklists are a simple tool that allows readers to ensure that all the essential and adequate methodological criteria are fulfilled and authors to report their studies in an optimized way. Each type of study needs a specific worksheet with a different approach.

A CDR, as a specific form of diagnostic/prognostic cohort study, requires an exclusive checklist to report and assess it. It should be a fusion of the STROBE (von Elm et al, 2007) and STARD (Bossuyt et al, 2003 BMJ) checklists in order to reflect the various characteristics necessary for its construction (see table 1).

Some of the items included on the checklist proposal are based also on the CONSORT checklist (Altman et al, 2001) due to the importance of analyzing a CDR as an intervention. Nevertheless some of the fundamental steps essential for a good quality CDR’s derivation or validation are not contemplated by any of the checklists available. So it was vital that some of the items were based on the described above literature review.

As a particular type of diagnostic study it is important to assess essentially if the results are valid (gold-standard selection and application, blinding and sample spectrum), what the results are (particularly LR) and if they will help in the caring of patients (reproducibility, generalizability and impact in care). (Archibald et al, 2003; Goodacre, 2009; Jaeschke et al, 1994, 2002; Laupacis et al, 1994) The proposed stepwise and checklist reflect these 3 main items’ importance. Consequently, this research resulted in a 29 items checklist, present in the following page, emphasizing the methods and results reporting but also explicating all the remaining essential requirements for a good quality study.

Each present item should be accounted with 1 point and those absent with 0 points. We have tried to avoid items with multiple requisites (as it happens with the STROBE checklist). However in some points it was not possible (particularly in the participants and setting and in outcomes and estimation sections), therefore an incomplete reporting may be accounted as half a point. (See table 1)
<table>
<thead>
<tr>
<th>Section and Topic</th>
<th>Description</th>
<th>Item present</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TITLE</strong></td>
<td>Identify the article as derivation and/or validation of a CDR</td>
<td></td>
</tr>
<tr>
<td><strong>ABSTRACT</strong></td>
<td>Build an informative and structured summary of the article, addressing key items in this checklist.</td>
<td></td>
</tr>
<tr>
<td><strong>INTRODUCTION</strong></td>
<td><strong>Background</strong> Elaborate a scientific background and explanation of rationale</td>
<td></td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
<td>Specify research questions or objectives.</td>
<td></td>
</tr>
<tr>
<td><strong>METHODS</strong></td>
<td><strong>Participants and setting</strong> Describe the study population: inclusion and exclusion criteria, sources and methods of participants’ selection, setting and locations where the data were collected and possible selection bias.</td>
<td></td>
</tr>
<tr>
<td><strong>Recruitment</strong></td>
<td>Describe participant recruitment, sampling and when the study was done, including beginning and ending dates of recruitment.</td>
<td></td>
</tr>
<tr>
<td><strong>Sample Size</strong></td>
<td>Report how simple size was determined (power analysis is recommended) and if it was adequate (including adequate number of outcome events).</td>
<td></td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Clearly define the outcome of interest, how it is measured and, when applicable, any methods used to enhance the quality of measurements.</td>
<td></td>
</tr>
<tr>
<td><strong>Predictive variables</strong></td>
<td>Clearly describe the list of all predictive factors evaluated, even those that were not included in the rule (all important predictors should be included) (Der)</td>
<td></td>
</tr>
<tr>
<td><strong>Data collection</strong></td>
<td>Describe the process of data collection (recommended prospectively).</td>
<td></td>
</tr>
<tr>
<td><strong>Test methods</strong></td>
<td>(Gold-standard, predictive variables &amp; CDR) Describe technical specifications of the material and methods involved.</td>
<td></td>
</tr>
<tr>
<td><strong>Blinding</strong></td>
<td>Describe whether the readers of the predictor variables (Der) or CDR (Val) and reference standard were blinded to the results in the other test(s).</td>
<td></td>
</tr>
<tr>
<td><strong>Statistical Methods</strong></td>
<td>Describe and justify the mathematical method used to derive or validate the CDR (usually logistic regression)</td>
<td></td>
</tr>
<tr>
<td><strong>RESULTS</strong></td>
<td><strong>Participants</strong> Describe baseline demographic, clinical and other important characteristics inclusively of eligible but not included subjects.</td>
<td></td>
</tr>
<tr>
<td><strong>Numbers analyses</strong></td>
<td>Report the number of participants included in the study and whether the analysis was by “intention-to-treat”. State the results in absolute numbers when feasible.</td>
<td></td>
</tr>
<tr>
<td><strong>Test results</strong></td>
<td>Report time interval from the predictor variables (Der) or CDR (Val) to the gold-standard, and any treatment administered between.</td>
<td></td>
</tr>
<tr>
<td><strong>Outcomes and estimation</strong></td>
<td>Report distribution of the disease’s severity.</td>
<td></td>
</tr>
<tr>
<td><strong>Discrete outcomes and continuous outcomes</strong></td>
<td>Report any adverse events from performing any of the tests. Report estimates of diagnostic accuracy and/or classification performance (mainly likelihood ratios and AUC), measurements of statistical uncertainty and potential savings (if applicable). Report follow-up, indeterminate results, missing responses and outliers and how they were handled.</td>
<td></td>
</tr>
<tr>
<td><strong>DISCUSSION</strong></td>
<td><strong>Interpretation</strong> Elaborate a cautious overall interpretation of the results in light of current evidence and study limitations, paying attention to alternative interpretations.</td>
<td></td>
</tr>
<tr>
<td><strong>Applicability and generalizability</strong></td>
<td>Discuss clinical applicability and generalizability of the study findings.</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical sense</strong></td>
<td>Analyze if the CDR is clinically sensible and if predictors are both comprehensive (no potential predictors omitted from consideration) and appropriate for the rule’s purpose.</td>
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</table>

Der: Derivation; Val – Validation
5. HIERARCHY OF EVIDENCE FOR CLINICAL DECISION RULES

The CDR’s initial step resides in identifying all important predictors and relevant outcome measures based on clinical experience and preferably on systematic review of the literature...

A hierarchy of 4 levels for validating CDR’s has been proposed by McGinn and colleagues. (McGinn et al, 2000) The first levels (3 and 4) of validation are essential to assure that the derivation process’s results are not due only to chance.

The derivation is the process that determines the most powerful predictor variables in the selected population. McGinn and coworkers reported that there are 3 major motives for even CDRs with a well-conducted derivation process are not yet prepared for clinical application: significant predictive variables as a result of chance alone, idiosyncratic predictive variables and CDR’s application feasibility. (McGinn et al, 2000) Thus CDR’s that have been just derived are not ready for clinical application. (McGinn et al, 2000) In order to pass to next level it must be determined if the derivation process was rigorous and methodologically correct. (McGinn et al, 2000)

A level 4 consists in CDRs “derived but not validated or validated in split samples, large retrospective databases or statistical techniques” (McGinn et al, 2000) They are developed in a well-defined population and provide important preliminary information about the CDR’s potential to classify subjects accurately under very restricted conditions (Beattie et al, 2006). However, additional assessment is necessary before clinical application. (McGinn et al, 2000; Stiell et al, 1999)

External validation is the only way to assess the models’ generalizability. (Altman et al, 2009) In a level 3, the CDR has been validated in an analogous patient population in a different center of the level before, with similar examiners and preferably in a prospective way or in a retrospective fashion including all variables included in the model; which allows it to be applied, with caution, on similar patients to the derivation process. (Altman et al, 2009; McGinn et al, 2000)

If, until this point, results are positive the CDR can be validated in other populations and settings. (Altman et al, 2009) A level 2 validation may consist in one large prospective study, with a large range of patients and examiners, or several small studies with heterogeneous samples indicating reliable accuracy. This level allows the CDR to be used in greater range of settings but consistent with the patients and clinicians used. (McGinn et al, 2000)

The level 1 is the final, most difficult and rarely achieved step for a complete validation of a CDR, allowing it to be used in a broad range of settings. This level consists in making an impact analysis of at least a level 2 CDR, that demonstrates a modification of clinical behaviour and a cost-effectiveness improvement. (McGinn et al, 2000) Reilly and colleagues, proposed one more level - a broad evaluation of the CDR’s clinical impact in several settings. (Reilly et al, 2006)

After encouraging and consistent results in the above stages, a dissemination and implementation plan is crucial for the CDRs’ use and acceptance. (Stiell et al, 1999, 2007)
6. DISCUSSION

With the constant production of sound studies and the continuous evolution and use of EBM; CDRs (as a process that merges clinical experience, literature review and clinical findings in an attempt to minimize bias) naturally appeared as a form of integrating research into practice. (Beattie et al, 2006) However, it was stated that CDRs are not yet integrated in the regular patient care. (Reynolds, 2001)

CDRs can modify the clinical behavior; reduce needless costs while keeping quality of care and patients’ satisfaction. A robust CDR allows a reliable stratification of patients by groups with different diagnosis, prognosis or recommended therapeutics. Nevertheless, a good performance in the initial sample is insufficient to show its real accuracy (Altman et al, 2009) and impact. Deficiencies in the study design, statistical methods or patient spectrum in the derivation phase may affect the models’ reproducibility. (Altman et al, 2009)

As a relatively recent form of study category there are still many items to work on to improve CDR’s value, use and homogeneity. A standardized methodology, into a form of a stepwise and a checklist, is a keystone in that effort. Therefore, this paper aimed to present for the first time a structured and easy-to-use stepwise for derivation, validation and impact analysis of CDR and a checklist to facilitate the critical appraisal of these studies; resulting from a structured literature review.

Only 12 studies directly addressed CDR’s development, which translates a lack of evidence available. This deficit was increased by not including non free available full text articles (n=3). In an attempt to reduce that void, articles addressing broader topics were included in this review.

A well-conducted CDR derivation can be performed through 10 steps and validation through 8, having at the end the possibility to refine it. Although an impact analysis can be accomplished through 9 steps it requires a large amount of resources, effort and patients. We also proposed a 29 items checklist for CDRs reporting and assessment, maintaining it the more complete possible as it should represent a starting point for a future work – the selection of the items present in the checklist through an expert consensus. We highlight, that these recommendations should be looked at as a process in constant improvement, subject to posterior changes and refinements.

This section was developed in order to perform in the most accurate and standardized manner the Boyko’s stratification system external validation, therefore we have applied into practice the proposed stepwise and checklist for the execution of chapter IV.
B. PREDICTIVE FACTORS FOR DIABETIC FOOT ULCERATION:

A SYSTEMATIC REVIEW
1. INTRODUCTION

As mentioned earlier, several studies report that amputations in patients with diabetes can be drastically diminished (Apelqvist et al, 2000). To achieve that goal, the most fundamental step is foot ulcer prevention through an ample comprehension of all the predictive factors of its occurrence in a way to optimize patient’s risk degree stratification according to which a preventive plan should be elaborated. (Frykberg et al, 2006; Lavery LA, 1998)

Presently there is a multiplicity of proposed guidelines with that purpose, inconsistent with each other, which turns difficult their homogeneous implementation in a worldwide scale. (Apelqvist et al, 2000, 2008) On the other hand, none of them is based on a formalized systematic review (SR) and there is none around the stratification systems topic that helps evaluating their similarities and value.

That we are aware of, only Singh and colleagues (Singh et al, 2005) performed a SR where almost all stratifications systems were described. Nevertheless, their effectiveness is not analyzed.

Many studies evaluated the role of specific variables for the prediction of foot ulcer development. (Lavery et al, 2008) However, to our knowledge, only one SR has synthesized them. (Crawford et al, 2007) Nonetheless, we believe that the referred article was very restrictive in the inclusion criteria, which resulted in a small fraction of all the available evidence. This may also reflect that guidelines are created without directly integrating the results of original research. (Crawford et al, 2007)

For all this, we were compelled to perform a review regarding foot ulceration importance, pathophysiology and prevention. Additionally, to its significance we believed that a systematic review was essential to understand which variables are associated with foot ulcer development and to characterize the risk stratification systems state of the art.

a. IMPORTANCE

Diabetes mellitus is one of the most frequent metabolic disorders (Fard et al, 2007; Khanolkar et al, 2008), achieving an epidemic magnitude (Khanolkar et al, 2008), with a near 3% worldwide prevalence. Moreover specialists expect an increase to more than 4% in 2030, which represents 366 million people. (Brem H, 2006; Frykberg et al, 2006)

In 2008, the Portuguese National Diabetes Observatory (OND) reported a diabetes’ prevalence around 11.7% and that from those 5% were unaware of their condition. (OND, 2010)

Foot disease is one of the most serious, costly (Apelqvist et al, 2000; Boulton et al, 1999; Fard et al, 2007; Frykberg et al, 2006) and frightening (Khanolkar et al, 2008) diabetes’ complication. Conversely, with the constant rising of diabetes prevalence and the insufficiency of health care resources, foot problems treatment and prevention are frequently inadequate. (Leese et al, 2007)

In the diabetic population amputations are 15 (Brem et al, 2006; SIGN, 2001) to 40 (Fard et al, 2007) times more frequent than in the non-diabetic population. Foot ulcer is the major predisposing factor for non-traumatic foot amputations (Brem et al, 2006; Frykberg et al, 2006), preceding about 85% of them. (Brem et al, 2006; Boulton et al, 2004 a; Frykberg et al, 2006) The amputation impact is so immense that is was estimated that every 30 seconds a lower limb amputation occurs due to diabetes (Brem et al, 2006; Boulton et al, 2005; Khanolkar et al, 2008), with an estimated incidence of 50–500 per 100,000 patient years. (Leese et al, 2006, 2007)
The lifetime risk for foot ulcer occurrence, in individuals with diabetes, is 12-25% (Al-Maskari et al, 2007; Brem et al, 2006; Boulton et al, 2004 a, 2005, 2008 a, 2008 b; Fard et al, 2007; Frykberg et al, 2006), the annual incidence in European countries is around 2% (Boulton et al, 2004 a, 2008) and almost 5% of the diabetic community has a foot ulcer history. (Boulton, 2004 a; Boulton, 2006; SIGN, 2001) Nonetheless, it is essential to be aware that diabetic foot ulceration is highly more frequent in patients with some predisposing factors (for example, in individuals with neuropathy the annual incidence raises to 5 to 7% (Boulton et al, 2004 a)) and that 50% of older diabetics’ type 2 patients present one or more of those factors. (Boulton et al 2008 a, 2008; EP)

The high prevalence of foot ulcers and subsequent amputation maintain the elevated morbidity and mortality of people with diabetes (Brem et al, 2006; Khanolkar et al, 2008), and also the enormous social, psychological and financial costs. (Khanolkar et al, 2008) Studies report that 20% of hospitalizations among people with diabetes are due to foot complications (Al-Maskari et al, 2007; Fard, et al, 2007) and that their treatment represents around 25% of the hospital total costs in diabetes care. (Al-Maskari et al, 2007)

In a study from Great Britain, it was reported that diabetic foot complications resulting in hospitalization represent a 375 million Euros cost annually. A superficial diabetic foot ulcer treatment costs around 4,500 Euros, if a deep infection occurs it raises to 23,500 Euros and if gangrene occurs it may achieve a 50,000 Euros cost. (Morbach et al, 2003) However, once an ulcer is completely healed, and according to the quality of the following care, the relapse risk annually raises to between 30 and 100%. (Morbach et al, 2003) Furthermore, after a lower limb amputation the risk of additional amputations is 50% in 3 years (Morbach et al, 2003) and the mortality rate is about 40 to 75% in 5 years. (Brem et al, 2006; Morbach et al, 2003)

According to Morbach and coworkers, with the prevention of 9 limb amputations the treatment of 400 diabetic patients per year, 820 hours of group education plus 1100 hours of individual sessions and 1500 foot appointments could be financed. (Morbach et al, 2003) In addition, another study reported that a programme including preventive attitudes, patient and their care-giver education, foot ulcer treatment by a multidisciplinary team and periodically surveillance can diminish amputation rate by 49 to 85%. (Apelqvist et al, 2000) Hence, various studies concluded that an amputation is always more expensive than its prevention. (Boulton et al, 1999)

For all of this, it is crucial to elaborate an effective approach for the prevention of foot ulceration and consequently amputation. (Khanolkar et al, 2008) The first step must be the correct identification of all the patients at risk of foot ulceration. (Boulton et al, 2008 a, 2008 b) At least the patients with previous history of ulcer and/or amputation should be faced as being in extremely high-risk for relapse and should be given a rigorous and well-thought care programme. (Morbach et al, 2003) Ideally, such care programme should be given to all diabetic patients with one or more foot ulcer risk factors.
b. PATHOPHYSIOLOGY

Diabetic foot ulceration scarcely occurs due to a unique factor/variable; (Boulton et al, 2004; Apelqvist et al, 2000) which turns its’ clinical pathway somewhat complex, but with various similarities among cases. (Apelqvist et al, 2000, 2008) The foot ulcer pathophysiology is multi-factorial with a particular protagonism of trauma, neuropathy and/or peripheral vascular disease (PVD). (Boulton et al, 2004, 2006, 2008 a, b; Bowering et al, 2001; Frykberg et al, 2006; Khanolkar et al, 2008; Morbach et al, 2003; SIGN, 2001)

The majority of diabetic foot ulcers (more than 60%) have as primary cause the presence of neuropathy (Armstrong et al, 1998 a; Boulton et al, 2004 b; Bowering et al, 2001; Frykberg, et al., 2006; Olmos et al, 1995; Papanas et al, 2006), which is why it is considered as the main factor for their occurrence. (Boulton et al, 2004 a; Morbach et al, 2003) Diabetic neuropathy (DN) correlates with poor metabolic control (Laughlin et al, 1995) that can be translated by the mean level of HbA1C over time. (Bowering et al, 2001). When chronic hyperglycemia occurs, it causes alterations in cell membranes’ function, mainly through ischemia of the endoneurial microvascular circulation (Bowering et al, 2001), Deteriorating the nerves (especially those with smaller diameter and less myelinated) (Fard et al, 2007) and thus affecting somatic (motor and sensory) and autonomic fibers. (Breem et al, 2006; Bowering et al, 2001; Fard et al, 2007; Laughlin et al, 1995; Sumpio et al, 2000)

Motor neuropathy produces, by collagen glycoxidation (Fard et al, 2007; Frykberg et al, 2006), muscle intrinsic weakness and atrophy, paresis, ataxic gait and foot deformities which alter the foot biomechanics, creating areas with hyper-pressure peaks. (Breem et al, 2006; Fard et al, 2007; Sumpio et al, 2000) This neuropathy type is commonly distal and affects the foot small intrinsic muscles promoting unbalanced forces between the long flexor and extensor muscles. The increased strength of the flexor group causes a cavus foot and/or the very frequent claw-toe deformity. Such deformity induces alterations in the metatarsal-phalangeal joints that result in a metatarsal verticalization, increasing their prominence. At the same time, the metatarsal fat pad is dislocated reducing its natural function (Bowering et al, 2001; Frykberg et al, 2006; Laughlin et al, 1995; Sumpio et al, 2000) to dissipate the weight-bearing forces in all directions. (Sumpio et al, 2000) These alterations increase the risk of dorsal and plantar foot ulceration. (Laughlin et al, 1995)

Although less commonly, motor neuropathy can also affect a single major peripheral nerve, and therefore cause anterior crural muscle atrophy, producing ankle equines, which is characterized by a diminished dorsiflexory range of the subtalar joint, or a varus hind foot. This biomechanical alteration causes an increase in the foot pressure and shearing forces (Fard et al, 2007; Frykberg et al, 2006; Laughlin et al, 1995; Sumpio et al, 2000) and has been identified as a precipitant factor for development, recurrence and recalcitrance foot ulceration. (Frykberg et al, 2006)

These changes are responsible for a rigid foot, with plantar hyper-pressure and consequently hypertrophy of the stratum corneum (callus).This leads to a triangular foot, wither and thicker making it difficult to adapt to regular shoes (Bowering et al, 2001), increasing the risk of foot ulceration. (Boulton et al, 2004 a, 2004 b)

The autonomic nervous system regulates perspiration, skin temperature and arteriovenous shunting. Therefore autonomic neuropathy leads to decreased sweating, dry skin and callus formation in areas of more pressure. Additionally, it also leads to a warm foot with vasodilatation of the dorsal foot veins, when PVD is absent. (Boulton et al, 1999, 2004 a, 2004 b, 2006; Breem et al, 2006; Bowering et al, 2001; Fard et al, 2007; Frykberg et al, 2006; Laughlin et al, 1995; Sumpio et al, 2000)
Arteriovenous shunts increase pressure and arterial flow. This causes peripheric edema and impaired microvascular response to damage (Frykberg et al, 2006), therefore adding to the risk of foot ulceration when shoes are incorrectly sized. (Bowering et al, 2001) With denervation of dermal structures skin loses integrity, mainly through cracks and fissures. This process facilitates microbial invasion and consequently foot infection. (Brem et al, 2006; Fryberg et al, 2006; Laughlin et al, 1995; Morbach et al, 2003; Sumpio et al, 2000)

Motor and autonomic neuropathy would have a smaller impact if it was not for the simultaneous presence of sensory neuropathy, which is responsible for loss of protective sensation in the foot. (Bowering et al, 2001)

Motor neuropathy causes biomechanical alterations, autonomic neuropathy alters the tissue perfusion and both create hiperqueratosic areas, which intensify plantar pressures. These areas during gait suffer from higher pressure and for longer time, creating further pressures into the subcutaneous tissue (Medina, 2006). In a normal sensitive foot it would compensate these alterations and relieve it, allowing tissues to heal. However, an insensitive foot, with sensory neuropathy, will continue to suffer with repetitive intrinsic or minor extrinsic trauma (for example caused by ill-fitting footwear or nail thickness) which frequently leads to bruising, subcutaneous hemorrhage and posterior ulcer. (Apelqvist et al, 2000, 2008; Fryberg et al, 2006; Laughlin et al, 1995; Sumpio et al, 2000)

Sensory neuropathy, that progresses from distal to proximal in a stocking pattern (Laughlin et al, 1995), diminishes the foot’s pain and temperature perception (Brem et al, 2006; Laughlin et al, 1995) affecting the protective response to lesions or biomechanical alterations. The patient may feel himself comfortable even with a very deep ulcer (Bowering et al, 2001), often delaying search for treatment. (Brem et al, 2006) Consequently, the main factor for foot ulcer development is the presence of peripheral sensory neuropathy along with unperceived trauma. (Boulton et al, 2006; Fryberg et al, 2006; Morbach et al, 2003; Sumpio et al, 2000)

Especially due to this neuropathy type, there is a high prevalence of asymptomatic patients and so health professionals cannot rely on patients’ symptoms alone to identify those at high-risk. (Boulton et al, 2006) Therefore, a regular screening and risk stratification of all patients with diabetes is vital. (SIGN, 2001)

The other protagonist of the foot ulcer pathway is PVD. (Bowering et al, 2001) While about 55-60% of diabetic ulcers are purely neuropathic, 35 to 45% are caused simultaneously by neuropathic and ischemic factors. (Boulton et al, 2004a; Fryberg et al, 2006) However, this proportion is inverting. In most United Kingdom diabetic foot clinics neuro-ischemic ulcers are now more frequent. (Boulton et al, 2006)

PVD diminishes the oxygen levels in the tissues, decreasing tissue resilience (Sumpio et al, 2000), which together with trauma and/or sensory and motor nerve alterations will lead to tissue anoxia and cell death (Boulton et al, 1999) and consequent ulceration. (Apelqvist et al, 2000; Fard et al, 2007) Therefore, oxygen deficiency is considered of major relevance. (Fard et al, 2007) However, it is important to mention once more that patients with concomitant neuropathic and ischemic alterations are commonly asymptomatic, even if with severe peripheral ischemia. (Apelqvist et al, 2000)

For a better understanding of the foot ulceration process, a schematic illustration of the complete clinical pathway is down presented. (See figure 1)
Various complications (such as cardiovascular, nephropathy, retinopathy and diabetic foot) are related with the microvascular, macrovascular and metabolic alterations caused by the Diabetes' characteristic chronic hyperglucemia. The diabetic foot is characterized by peripheral vascular disease and/or diabetic neuropathy (sensory, motor and autonomic) and may lead to foot ulcer development through several interconnected pathways.

For an effective prevention of diabetic foot ulceration a profound knowledge of its pathogenesis and associated clinical risk factors is required. (Al-Maskari et al, 2007) This would help care providers to classify patients through risk degree stratification (Lavery et al, 1998) and consequently direct resources allocation (Leese et al, 2007). However, all of these topics are still not well understood and further research is vital. (Al-Maskari et al, 2007)

There is a great need for cost-effective measures to prevent ulcers. (Boulton et al, 2004 a) The current guidelines advocate that education should be provided to all diabetic patients on foot care and footwear purchase and evaluated their risk status at least once every year. (Boulton et al, 2006) Those patients with one or more risk factors for ulceration should be reevaluated more frequently (Boulton et al, 2006) although consensus has not been achieved regarding periodicity and which risk factors to consider. In high risk patients, adequate podiatric care, patient education, foot examination, risk screening, and therapeutic footwear can prevent the development of foot ulcers. (Apelqvist et al, 2000, 2008; Boulton et al, 1999; Lavery et al, 1998; Leese et al, 2007; Peters DJ, 2001; SIGN, 2001)

Regrettably, feet are frequently neglected. (Boulton et al, 1999; Lavery et al, 1998; Morbach, 2003) Only less than 20% of the diabetic patients have their feet examined by a health care professional and the rate of annual foot exams ranges from 30 to 50% in the physician’s office. (Boulton et al, 1999) In addition to the low frequency of foot examinations, their quality is also inadequate. A complete assessment is only performed in about 10% of the diabetic population in outpatient clinics and 14% in those admitted to hospital due to foot ulceration. (Morbach et al, 2003) This may be partly explained by the little knowledge of the most important items to search during screening evaluation. (Lavery et al, 1998)

Although structured podiatric care should be available to all diabetic patients (Leese et al, 2007; SIGN, 2003), in reality with the existing resource limitation such is impossible. Therefore, those in most need should be given priority. (Iversen et al, 2008; Lavery et al, 1998; Leese et al, 2007) But how can we best decide? Through a risk stratification system (Peters et al, 2001), that incorporates associated risk factors for foot ulcer development, often quick, easy and inexpensive to collect through foot examination or simple anamnesis. (Lavery et al, 1998)

An efficient risk stratification system is a vital tool for an appropriate resource distribution. Depending on risk degree, a preventive programme will be planned varying in the regularity of visits and treatment of non-ulcerative pathology, in the content and frequency of educational interventions and in the therapeutic footwear and insoles provision. (Frykberg et al, 2006)
2. MATERIAL AND METHODS

a. LITERATURE SEARCH STRATEGY

To conduct this SR, we carried out a sensible search in MEDLINE database (PubMed) for studies published until December 2008 (including) that analyzed possible predictive factors for foot ulcer occurrence, using the following query:


We believe that the evaluation of isolated predictive variables and stratifications systems in separate would maximize the result analysis. Thus, although the methods are described together, results are reported independently.

b. STUDY SELECTION

This search retrieved 2094 articles. They were included in the SR if they fulfilled the following selection criteria:

1. Publication date: until December 2008 (including)
2. Published in the following languages: English, French, Italian, Spanish or Portuguese
3. Type of study: randomized controlled trials or cohort, case-control, cross-sectional or epidemiological studies. For the risk degree stratifications review descriptive articles were also accepted.
4. Theme: studies that evaluated variables (clinical data or diagnostic tests results) or stratifications systems for diabetic foot ulcer occurrence prediction
5. Results:
   a. Variables: studies must permit to conclude that there is or is not a statistically significant relationship between the variables and the development of diabetic foot ulcer (calculating measures of association or regression analysis)
   b. Risk degree stratifications: must describe the creation or modification and/or evaluate the effectiveness of one or several diabetic foot ulcer risk degree stratifications
6. Availability of the full text version

Exclusion factors were registered and analyzed.
Initially, articles were selected by assessing their pertinence through their titles and abstracts (when available) by 2 investigators (Matilde Soares and Joana Ribeiro), independent and blind to each other. In this phase the most common cause for exclusion was the articles’ theme (n=1225). Osteomyelitis, diabetic foot infection, diabetic foot ulcers treatment, diabetic neuropathy diagnosis and Charcot foot were the most frequent topics.

In a second phase, the previously chosen articles (n=141) were examined in their integral version (with the respective reference list) and selected, by the 2 investigators in separate. In this phase the majority of the exclusions were due to type of study (n=47) and the impossibility to conclude if there was or not a statistically significant relationship between variables and foot ulcer occurrence through the reported results (n=35). At this stage 52 articles were included.

With a disagreement in the inclusion of 146 studies by title and/or abstract (in a total of 2094), a 93% interobserver agreement proportion and a 0,86 kappa value were achieved, reflecting a good agreement. The same occurred in the selection of papers in their integral version, with a disagreement in the inclusion of 6 studies creating a 96% interobserver agreement proportion and a 0,91 kappa value.

Finally, after analyzing the reference list of all the selected articles and relevant reviews that were excluded, new articles were found. These were subjected to the first and second phases and were included or excluded from the study. This procedure was repeated until there was no new article found through the reference list analysis, which resulted in the inclusion of 19 more articles. In every stage, divergence was solved by the decision of a third investigator (Isabel Ribeiro).

For the foot ulcer risk stratification systems review 2 experts in the topic (Dr. Armstrong and Dr. Lavery) were contacted by email with the intention of identifying any gap in the search process. However, no new information was given.

Some studies were not available online. In these cases, authors were contacted through the email provided in the respective article requesting it. Those not send were excluded from the study (n=8). (Birke et al, 1995; Edmonds et al, 1986; Kumar et al, 1991; Litzelman et al, 1993; Sosenko et al, 1990; Malone et al, 1989; Wooldridge et al, 1994; Young et al, 1994) In conclusion, a total of 71 studies were included in the review: 58 in the SR of predictive variables, 11 in the risk stratification systems SR and 2 in both (Boyko et al, 2006; Lavery et al, 1998) (see figure 2).

| c. DATA EXTRACTION |

Until this stage, the articles’ identification data was omitted (authors, nationality, journal...) to avoid selection bias. Once the article selection was completed, the following data were collected from each article to a checklist created for this review:

1. Article identification: title, author(s), publication date, journal
2. Outcome definition
3. Methods: study design, setting, period(s) of data collection, inclusion and exclusion criteria, sources and methods of participants’ selection, sample size, clinical factors analyzed, diagnostic tests analyzed, potential bias.
4. Results: study participants’ characteristics, outcome’s prevalence, method of statistical analysis, list of variables and degree of statistically significance in predicting the outcome’s development or risk degree stratification diagnostic accuracy measures.
The articles’ quality was assessed (by Matilde Monteiro-Soares) through the number of items fulfilled in the correspondent checklist according to the type of study (STROBE for observational studies, STARD for diagnostic accuracy studies, CONSORT for randomized control trial or READER for derivation or validation of CDR). The STROBE checklist is the only one that has several paragraphs in each item, which caused difficulties in scoring. Therefore, we stipulated that the total completion of an item scored 1 point, the partial completion scored \( \frac{1}{2} \) point and the null completion 0 points.

**FIGURE 2: SYSTEMATIC REVIEW FLOW DIAGRAM OF ARTICLES SELECTION PROCESS**
3. RESULTS

a. PREDICTIVE VARIABLES: STUDIES’ DESCRIPTION

In this review 60 studies were included (58 only included in predictive variables section and 2 in both this and stratification systems section).

From the included studies:
- 21 studies evaluated the association of specific variables with ulcer development (see table 2A),
- 12 studies with ulcer recurrence or re-ulceration (see table 2B),
- 9 studies with active or recently healed ulcer (see table 2C),
- 7 studies with active or past foot ulcer history (see table 2D) and
- 11 studies with foot ulcer history (see table 2E).

Although these outcomes are somewhat different, we aimed at the most wide-ranging review and so included all these studies characterizing and analyzing them in separate.

When not all the patients had an active, recently healed or past foot ulcer history we considered the outcome to be foot ulcer development.

According with study category and reporting quality:
- 44 were observational, with a score in the STROBE checklist (von Elm et al, 2007) varying from 7 to 21,
- 8 were diagnostic accuracy studies, with a score in the STARD checklist (Bossuyt et al, 2003) varying from 12 to 18 and
- 8 were randomized trials, with a score in the CONSORT (Altman et al, 2001) checklist varying from 13 to 17.

From the retrieved studies:
- 8 were RCTs,
- 21 were prospective cohort studies,
- 2 were retrospective cohort studies,
- 3 were prospective case control studies,
- 2 were retrospective case control studies,
- 14 were cross-sectional case control studies and
- 10 were cross-sectional studies.

In some studies the comparison was made between more than two groups. Therefore we have decided to exclude the non-diabetic group from analysis and characterization (sample size and prevalence). In those cases and when only crude data was reported association was evaluated using the Review Manager 5 software.

Only with a p inferior to 0,05 the association between variables and foot ulcer was considered as statistically significant. In studies in which the association was reported only through risk measures [Relative Risk (RR), Odds Ratio (OR) or Hazard Ratio (HR)] the analysis was performed accordingly.
### TABLE 2A: STUDIES’ CHARACTERIZATION AND CLASSIFICATION FOR THE PREDICTION OF FOOT ULCER DEVELOPMENT ACCORDING TO TYPE AND QUALITY OF STUDY

<table>
<thead>
<tr>
<th>Study (1st author, year)</th>
<th>Participants characterization</th>
<th>Mean follow up (months)</th>
<th>Setting</th>
<th>Outcome</th>
<th>Other outcomes analyzed</th>
<th>Items present</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized Controlled Trials</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Armstrong, 2007</td>
<td>225</td>
<td>&gt; 95</td>
<td>&gt; 68</td>
<td>NR</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Lavery, 2004</td>
<td>85</td>
<td>51</td>
<td>&gt; 55</td>
<td>NR</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Armstrong, 2005</td>
<td>70</td>
<td>97</td>
<td>70</td>
<td>NR</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td><strong>Prospective Cohort Studies</strong></td>
<td></td>
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</tr>
<tr>
<td>Boyko, 1999</td>
<td>749 ‡</td>
<td>98</td>
<td>63</td>
<td>94</td>
<td>11</td>
<td>44</td>
</tr>
<tr>
<td>Abbott, 2002</td>
<td>6663</td>
<td>54</td>
<td>61</td>
<td>NR</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>Boyko, 2006</td>
<td>1285</td>
<td>98</td>
<td>62</td>
<td>95</td>
<td>&gt; 10</td>
<td>41</td>
</tr>
<tr>
<td>Kästenbauer, 2001</td>
<td>187</td>
<td>55</td>
<td>&gt; 57</td>
<td>NR</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Ledoux, 2005</td>
<td>398 ‡</td>
<td>77</td>
<td>62</td>
<td>NR</td>
<td>¥</td>
<td>24</td>
</tr>
<tr>
<td>Suico, 1998</td>
<td>253</td>
<td>19</td>
<td>60</td>
<td>NR</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Pham, 2000</td>
<td>248</td>
<td>51</td>
<td>58</td>
<td>80</td>
<td>14</td>
<td>30</td>
</tr>
<tr>
<td>Armstrong, 2004</td>
<td>100</td>
<td>95</td>
<td>69</td>
<td>NR</td>
<td>14</td>
<td>8</td>
</tr>
</tbody>
</table>
Abbott, 1998 1035 75 60 75 NR 12 Multicenter 7,2 No other 14,5 

Lavery, 2003 1666 50 69 NR 11 24 Outpatient clinic 15,8* NR

Caselli, 2002 248 46 >50 77 >8 30 Multicenter (foot center, foot care clinic, university, college) 29,4* NR

Armstrong, 2003 1588 50 69 NR 11 24 NR NR Full thickness wounds Charcot foot, infections

Murray, 1996 63 68 >52 60 17 16 Multicenter (Diabetes centre and diabetic foot clinic) 9,5* plantar surface of the foot and not associated with external trauma

Chantelau, 1990 41 62 59 74 17 25 Diabetic foot clinic 59,0* NR

Margolis, 2008 125933 47 65 NR NR 26 Multicenter (general medical practices) 2,1* NR Amputation 21 b

Carrington, 2002 169 65 >53 51 >18 72 Diabetes center 37,3* Full thickness skin break Amputation, death

Pascual, 2001 318 45 68 NR 9 55 Outpatient clinic 10,0 NR No other 13 b

McGill, 2005 472 73 59 94 >9 24 Diabetes center 6,0* No other 12 b

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a: RCTs’ quality were assessed using the CONSORT checklist; b: Observational studies were assessed using the STROBE checklist; NR: Not reported; * not all patients were free of active, recently healed or past foot ulcer history; †: only high risk population; ‡: foot analysis; ‡: foot intrinsic ulcers; ¥: 44% of the subjects have more than 10 years of diabetes duration
<table>
<thead>
<tr>
<th>Study (1st author, year)</th>
<th>Sample size</th>
<th>Male (%)</th>
<th>Mean age (years)</th>
<th>Type II diabetes (%)</th>
<th>Diabetes duration (years)</th>
<th>Mean follow up (months)</th>
<th>Setting</th>
<th>Prevalence (%)</th>
<th>Definition</th>
<th>Other outcomes analyzed</th>
<th>Items present</th>
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<tr>
<td><strong>RANDOMIZED CONTROLLED TRIALS</strong></td>
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<tr>
<td>Lincoln, 2008</td>
<td>172</td>
<td>67</td>
<td>NR</td>
<td>77</td>
<td>NR</td>
<td>12</td>
<td>Multicenter (diabetic foot clinics)</td>
<td>41,0</td>
<td>NR</td>
<td>Amputation</td>
<td>19⁴</td>
</tr>
<tr>
<td>Lavery, 2007</td>
<td>173</td>
<td>54</td>
<td>&gt;64</td>
<td>95</td>
<td>&gt;13</td>
<td>15</td>
<td>Multicenter (Veterans Health Care System and Group Health Cooperative)</td>
<td>22,5</td>
<td>NR</td>
<td>No other</td>
<td>17¹</td>
</tr>
<tr>
<td>Reiber, 2002</td>
<td>400</td>
<td>77</td>
<td>62</td>
<td>93</td>
<td>NR</td>
<td>24</td>
<td>Multicenter (Veterans Health Care System and Group Health Cooperative)</td>
<td>16,0</td>
<td>Cutaneous erosion extending into or through the dermis to deeper tissue or other cuts that did not heal within 30 days</td>
<td>Non ulcerative lesions</td>
<td>16¹</td>
</tr>
<tr>
<td>Plank, 2003</td>
<td>91</td>
<td>75</td>
<td>&gt;64</td>
<td>97</td>
<td>&gt;13</td>
<td>13</td>
<td>Diabetic foot clinic</td>
<td>47,5</td>
<td>NR</td>
<td>No other</td>
<td>14¹</td>
</tr>
<tr>
<td>Uccioli, 1995</td>
<td>69</td>
<td>62</td>
<td>&gt;60</td>
<td>75</td>
<td>&gt;17</td>
<td>12</td>
<td>Multicenter (2 teaching hospitals)</td>
<td>43,0</td>
<td>Any ulceration at the same or different site of a previous ulcer or an ulcer in the contralateral foot</td>
<td>No other</td>
<td>13¹</td>
</tr>
<tr>
<td><strong>PROSPECTIVE COHORT STUDIES</strong></td>
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<tr>
<td>Lemaster, 2003</td>
<td>400</td>
<td>77</td>
<td>62,5</td>
<td>NR</td>
<td>¤</td>
<td>24</td>
<td>Multicenter (Veterans Health Care System and Group Health Cooperative)</td>
<td>15,5</td>
<td>Break in the cutaneous barrier extending into or through the dermis to deeper tissue that did not heal within 30 days</td>
<td>No other</td>
<td>17,5⁵</td>
</tr>
<tr>
<td>Dargis, 1999</td>
<td>145</td>
<td>48</td>
<td>&gt;59</td>
<td>79</td>
<td>&gt;14</td>
<td>13</td>
<td>Multicenter (outpatient clinics)</td>
<td>47,6</td>
<td>New ulcers and ulcers appearing at a previous ulcer site</td>
<td>Amputation</td>
<td>16³</td>
</tr>
<tr>
<td>Busch, 2003</td>
<td>92</td>
<td>53</td>
<td>&gt;62</td>
<td>91</td>
<td>&gt;12</td>
<td>Up to 42</td>
<td>General practice-based diabetes clinic</td>
<td>40,0</td>
<td>Any partial or complete disruption of the skin (Wagner 1-2)</td>
<td>No other</td>
<td>11,5⁶</td>
</tr>
<tr>
<td>Faglia, 2001</td>
<td>88</td>
<td>73</td>
<td>63</td>
<td>NR</td>
<td>17</td>
<td>78</td>
<td>Diabetic foot clinic</td>
<td>26,0</td>
<td>Any ulceration at the same or different site of a previous ulcer or an ulcer in the contralateral foot</td>
<td>Amputation, death</td>
<td>10³</td>
</tr>
<tr>
<td>Peters, 2007</td>
<td>81</td>
<td>77</td>
<td>&gt;53</td>
<td>95</td>
<td>¥</td>
<td>32</td>
<td>Diabetic foot clinic</td>
<td>60,5</td>
<td>NR</td>
<td>Amputation, arterial bypass</td>
<td>7³</td>
</tr>
<tr>
<td><strong>RETROSPECTIVE COHORT STUDIES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diouri, 2002</td>
<td>90</td>
<td>60</td>
<td>56</td>
<td>76</td>
<td>5</td>
<td>NR</td>
<td>Hospital</td>
<td>46,6</td>
<td>Ulcer development 30 days after complete cicatrization on the same foot on the same site or in a different site in the contralateral limb</td>
<td>No other</td>
<td>14³</td>
</tr>
<tr>
<td><strong>CROSS-SECTIONAL CASE-CONTROL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chantelau, 1994</td>
<td>51</td>
<td>59</td>
<td>63</td>
<td>71</td>
<td>20</td>
<td>48</td>
<td>Diabetic foot clinic</td>
<td>67,0</td>
<td>NR</td>
<td>No other</td>
<td>13³</td>
</tr>
</tbody>
</table>

---

a: RCTs' quality were assessed using the CONSORT checklist; b: Observational studies were assessed using the STROBE checklist; NR: Not reported; ¤: 12% of the subjects have more than 25 years of diabetes duration; ¥: 67% of the subjects have more than 10 years of diabetes duration
TABLE 2C: STUDIES’ CHARACTERIZATION AND CLASSIFICATION FOR THE PREDICTION OF ACTIVE OR RECENTLY HEALED FOOT ULCER ACCORDING TO TYPE AND QUALITY OF STUDY

<table>
<thead>
<tr>
<th>Study (1st author, year)</th>
<th>Participants characterization</th>
<th>Mean follow up (months)</th>
<th>Setting</th>
<th>Prevalence (%)</th>
<th>Outcome</th>
<th>Other outcomes analyzed</th>
<th>Items present</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROSPECTIVE COHORT STUDIES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Litzelman, 1997 a</td>
<td>352 61 NR 10 12</td>
<td>General medicine practice</td>
<td>18.0</td>
<td>Wounds &gt; or equal to 1.2 in the Seattle Wound Classification</td>
<td></td>
<td></td>
<td>17²</td>
</tr>
<tr>
<td><strong>RETROSPECTIVE CASE-CONTROL STUDIES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olmos, 1995</td>
<td>199 100 12</td>
<td>Teaching hospital (diabetes clinic)</td>
<td>7.0</td>
<td>Wounds &gt; or equal to 1.2 in the Seattle Wound Classification</td>
<td>No other</td>
<td></td>
<td>15£</td>
</tr>
<tr>
<td><strong>CROSS-SECTIONAL CASE-CONTROL STUDIES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Armstrong, 1998 b</td>
<td>219 100 12</td>
<td>Multicenter (Diabetes institute and university)</td>
<td>32.0</td>
<td>NR</td>
<td></td>
<td></td>
<td>15£</td>
</tr>
<tr>
<td>Sriussadaporn, 1997</td>
<td>165 100 12</td>
<td>Hospital (diabetic clinic)</td>
<td>33.3</td>
<td>No other</td>
<td></td>
<td></td>
<td>16£</td>
</tr>
<tr>
<td><strong>CROSS-SECTIONAL STUDIES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lavery, 1998</td>
<td>225 100 12</td>
<td>Multicenter (Diabetes institute and university)</td>
<td>34.0</td>
<td>NR</td>
<td></td>
<td></td>
<td>13£</td>
</tr>
<tr>
<td>Sauseng, 1999</td>
<td>43 93 12</td>
<td>Multicenter (Diabetes institute and university)</td>
<td>46.5</td>
<td>NR</td>
<td></td>
<td></td>
<td>12£</td>
</tr>
<tr>
<td>Porciúncula, 2007</td>
<td>32 64 17</td>
<td>Diabetes center</td>
<td>56.3</td>
<td>No other</td>
<td></td>
<td></td>
<td>15£</td>
</tr>
<tr>
<td>Armstrong, 1997</td>
<td>143 67 16</td>
<td>Diabetic foot center</td>
<td>31.0</td>
<td>Charcot foot</td>
<td></td>
<td></td>
<td>14£</td>
</tr>
</tbody>
</table>

b: Observational studies were assessed using the STROBE checklist; c: Diagnostic accuracy studies were assessed using the STARD checklist; NR: Not reported; ¤: neuropathic ulcers
<table>
<thead>
<tr>
<th>Study (1st author, year)</th>
<th>Participants characterization</th>
<th>Mean follow up (months)</th>
<th>Setting</th>
<th>Outcome</th>
<th>Other outcomes analyzed</th>
<th>Items present</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sample size</td>
<td>Male (%)</td>
<td>Mean age (years)</td>
<td>Type II diabetes (%)</td>
<td>Diabetes duration (years)</td>
<td>Prevalence (%)</td>
</tr>
<tr>
<td>Jirkovská, 2001</td>
<td>322</td>
<td>NR</td>
<td>&gt;66</td>
<td>93</td>
<td>13</td>
<td>13.7</td>
</tr>
<tr>
<td>Frykberg, 1998</td>
<td>251</td>
<td>50</td>
<td>59</td>
<td>80</td>
<td>14</td>
<td>39.4</td>
</tr>
<tr>
<td>Bresätter, 1996</td>
<td>82</td>
<td>100</td>
<td>&gt;69</td>
<td>NR</td>
<td>&gt;8</td>
<td>34.0</td>
</tr>
<tr>
<td>de Sonaville, 1997</td>
<td>609</td>
<td>43</td>
<td>65</td>
<td>NR</td>
<td>4</td>
<td>14.0</td>
</tr>
<tr>
<td>Guerrero-Romero, 1998</td>
<td>670</td>
<td>33</td>
<td>&gt;55</td>
<td>100</td>
<td>&gt;8</td>
<td>16.4</td>
</tr>
<tr>
<td>Saltzman, 2004</td>
<td>92</td>
<td>NR</td>
<td>&gt;49</td>
<td>74</td>
<td>&gt;11</td>
<td>51.0</td>
</tr>
<tr>
<td>Miranda-Palma, 2005</td>
<td>93</td>
<td>56</td>
<td>NR</td>
<td>93</td>
<td>NR</td>
<td>57.0</td>
</tr>
</tbody>
</table>

<sup>b</sup>: Observational studies were assessed using the STROBE checklist; <sup>c</sup>: Diagnostic accuracy studies were assessed using the STARD checklist; NR: not reported, LE: lower extremity
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants characterization</th>
<th>Setting</th>
<th>Other outcomes analyzed</th>
<th>Items present</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RETROSPECTIVE CASE-CONTROL STUDIES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bennett, 1996</td>
<td>77</td>
<td>&gt;58</td>
<td>Multicenter (Hospitals)</td>
<td>13</td>
</tr>
<tr>
<td>Armstrong, 1998a</td>
<td>115</td>
<td>&gt;51</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>McNeely, 1995</td>
<td>368</td>
<td>&gt;60</td>
<td>Veterans Medical Center</td>
<td>17</td>
</tr>
<tr>
<td>Gulliford, 2002</td>
<td>2106</td>
<td>&gt;60*</td>
<td>Multicenter (Health Centers)</td>
<td>14</td>
</tr>
<tr>
<td>Boulton, 1986</td>
<td>135</td>
<td>&gt;52</td>
<td>Hospital</td>
<td>12</td>
</tr>
<tr>
<td><strong>CROSS-SECTIONAL CASE-CONTROL STUDIES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Armstrong, 1998a</td>
<td>115</td>
<td>&gt;51</td>
<td>Multicenter (Health Centers)</td>
<td>14</td>
</tr>
<tr>
<td>McNeely, 1995</td>
<td>368</td>
<td>&gt;60</td>
<td>Multicenter (Health Centers)</td>
<td>14</td>
</tr>
<tr>
<td>Gulliford, 2002</td>
<td>2106</td>
<td>&gt;60*</td>
<td>Multicenter (Health Centers)</td>
<td>14</td>
</tr>
<tr>
<td>Boulton, 1986</td>
<td>135</td>
<td>&gt;52</td>
<td>Multicenter (Health Centers)</td>
<td>14</td>
</tr>
<tr>
<td><strong>CROSS-SECTIONAL STUDIES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iversen, 2008</td>
<td>1494</td>
<td>66*</td>
<td>Population based</td>
<td>18</td>
</tr>
<tr>
<td>Control Disease Center, 2003</td>
<td>NR</td>
<td>NR</td>
<td>Population based</td>
<td>18</td>
</tr>
<tr>
<td>Lott, 2008</td>
<td>38R</td>
<td>&gt;63</td>
<td>Multicenter (Diabetes center and health system)</td>
<td>16</td>
</tr>
<tr>
<td>Jayasinghe, 2007</td>
<td>94</td>
<td>&gt;54</td>
<td>Multicenter (2 teaching hospitals)</td>
<td>14</td>
</tr>
<tr>
<td>Maluf, 2003</td>
<td>22</td>
<td>&gt;55</td>
<td>Multicenter (Outpatient clinics and community health fairs)</td>
<td>13</td>
</tr>
<tr>
<td>Papanas, 2006</td>
<td>109</td>
<td>&gt;52</td>
<td>Multicenter (Diabetes center and outpatient department of hospital)</td>
<td>12</td>
</tr>
</tbody>
</table>

b: Observational studies were assessed using the STROBE checklist; c: Diagnostic accuracy studies were assessed using the STARD checklist; NR: Not reported; *: median; R: only patients with diabetic peripheral neuropathy; MTT: metatarsal
b. PREDICTIVE VARIABLES: DATA SYNTHESIS

DEMOGRAPHIC FACTORS

AGE

As a very easy to collect variable, the association between age and foot ulcers has been widely evaluated (35 studies retrieved). However, their results are very contradictory. (See table 3)

For the prediction of foot ulcer development, from the 10 retrieved studies only 4 showed a statistically significant association: Armstrong [Armstrong et al, 2007] in a RCT verified that younger the patient bigger was the risk; while Abbott in 1998 and 2002 [Abbott et al, 1998; Abbott et al, 2002], in 2 prospective cohorts, and Margolius [Margolius et al, 2008], in a retrospective cohort, concluded the opposite in their uni and multivariate analysis. While for the prediction of foot ulcer recurrence or re-ulceration no study (n= 4) demonstrated an association with the age variable.

Only 2 cross-sectional studies [Armstrong et al, 1997; Sauseng et al, 1999], found an association between age and active or recently healed ulcer observing that minor age represented higher risk. In opposition the 2 cross-sectional case control studies [Frykberg et al, 1998; Guerrero-Romero et al, 1998] observing a statistically significant association with active or past foot ulcer history concluded the contrary (a higher age represented a higher risk).

Of the 3 cross-sectional [Center of Disease Control, 2003; Iversen et al, 2008; Lott et al, 2008] and 1 cross-sectional case-control [McNeely et al, 1995] studies that reported a statistical significant association between age and foot ulcer history, Iversen et al [Iversen et al, 2008] was the only one concluding that those with higher age had greater risk.

GENDER

Were retrieved 27 studies assessing the association between gender and foot ulcer. Only 8 found statistically significance (2 prospective cohort studies [Abbott et al, 2002; Pham et al, 2000] for ulcer development, 1 retrospective cohort study for ulcer recurrence or re-ulceration [Dauiri et al, 2002], 2 cross-sectional case-control [Armstrong et al, 1998 b; Lavery LA, 1998] and 1 case-control [Armstrong et al, 1997] studies for active or recently healed ulcer, 1 study for active or past foot ulcer history [Frykberg et al, 1998] and 1 cross-sectional study for foot ulcer history [Papanas et al, 2006]), all verifying an increased risk for the male gender. (See table 3)

These results are in agreement with the current literature where the male gender was frequently associated with a higher risk for lower extremity diabetes related complications, such as peripheral diabetic neuropathy and peripheral vascular disease. [Lavery et al, 1998]

MARITAL STATUS OR COHABITING

Frequently, individuals with diabetes show visual and physical disabilities. And so, the presence of a caregiver is crucial for foot ulcer prevention helping in the glyceamic control, foot care habits and examination.
Only 6 studies evaluated the association between cohabiting or marital status and foot ulcer. Abbott et al (Abbott et al, 2002) in a prospective cohort study found a statistically significant association of living alone with higher foot ulcer development risk, but only in the univariate analysis. On the other hand, for the prediction of an active or recently healed or foot ulcer history, 2 cross-sectional case-control studies found no association with being married (McNeely et al, 1995; Sriussadaporn et al, 1997). The same occurred in a cross-sectional case-control study (Bresåter et al, 1996) with being divorced.

Iversen and coworkers (Iversen et al, 2008) in a cross-sectional study observed no association in the univariate analysis between foot ulcer history and being single or alone; in opposition with the Control Disease Center (CDC) study (CDC, 2003) that verified that those married or cohabiting presented significantly less foot ulcer history prevalence.

ETHNICITY

Only 5 studies assessed the association between different ethnicities. In a prospective cohort, Boyko (Boyko et al, 2006) found no statistically significant difference in the risk of foot ulcer development for Caucasian subjects in comparison with other ethnicities. The same conclusion was made by McNeely (McNeely et al, 1995), in a cross-sectional case-control, for foot ulcer history.

On the other hand, Frykberg and associates (Frykberg et al, 1998) verified that Caucasians presented a significant higher prevalence of active or past foot ulcer history, lower sub-tarsal joint and first (1st) metatarso-phalangeal joint (MTPJ) mobility and associated higher foot pressures when compared with both Black and Hispanic subjects.

Olmos (Olmos et al, 1995), in a retrospective cohort, for the prediction of active or recently healed ulcer verified no difference between Caucasian and Black subjects. However, the CDC (CDC, 2003) in a cross-sectional study, observed statistically significant higher foot ulcer history prevalence in Caucasian subjects in comparison with Black. The same did not occur comparing Caucasian with Hispanic subjects.

EDUCATION DEGREE

No study, from the 7 retrieved, found an association between education degree and foot ulcer recurrence or re-ulceration (Peters et al, 2007), active or recently healed foot ulcer (Lavery et al, 1998; Olmos et al, 1995; Sriussadaporn et al, 1997) or foot ulcer history (CDC, 2003; Iversen et al, 2008; McNeely et al, 1995).

OTHERS DEMOGRAPHIC FACTORS

Only Sriussadaporn (Sriussadaporn et al, 1997), in a cross-sectional case-control study, evaluated the association between religion, living area, occupations and economic status with active or recently healed foot ulcer. No variable was considered as having a statistically significant association.

LIFESTYLE

SMOKING HABITS

Smoking is a well known risk factor for PVD, causing vasoconstriction and reducing blood’s oxygen transport. (Frykberg et al, 2006) Therefore it was hypothesized an association between smoking habits and foot ulceration.
We retrieved 13 studies evaluating the association between smoking habits and foot ulcer. Only 2 cross-sectional case control studies presented statistically significant results, showing a higher prevalence of active or past foot ulcer history in current smokers (de Sonnville et al, 1997; Guerrero-Romero et al, 1998). (See table 3)

ALCOHOL HABITS

Alcohol abuse is related with neuropathy (Edmonds et al, 2004) and consequently with foot ulcer development. In a prospective cohort study (Kästenbauer et al, 2001), daily alcohol intake was significantly associated with foot ulcer development in uni and multivariate analysis (RR 5.1).

Peters (Peters et al, 2007), in a prospective cohort study, and Lavery (Lavery et al, 1998), in a cross-sectional case control study, found no association between alcohol abuse and foot ulcer recurrence or re-ulceration and active or recently healed foot ulcer respectively. Also Sriussadaporn (Sriussadaporn et al, 1997), de Sonnville (de Sonnville et al, 1997) and McNeely (McNeely et al, 1995), in cross-sectional case control studies, did not verified an association between alcohol use and active or recently healed foot ulcer, active or past foot ulcer history and foot ulcer history respectively.

Only, Bresäter (Bresäter et al, 1996), in a cross-sectional case control study, observed that alcohol users showed a higher prevalence of active or past foot ulcer history.

PHYSICAL INACTIVITY

Just Iversen (Iversen et al, 2008), in a cross-sectional study, assessed the impact of this variable in the risk of foot ulcer history, finding a statistically significant association in the univariate analysis.

METABOLIC SYNDROME

HEIGHT

The association between height and foot ulcer was assessed in 4 studies, in which it was considered as statistically significant (Boyko et al, 1999; Bresäter et al, 1996; Iversen et al, 2008; Porciúncula et al, 2007). This link can be explained by the relation with axon length (longer axons are more predisposed to metabolic damages and therefore to DN). (Iversen et al, 2008)

WEIGHT

A person’s weight is directly related with foot pressure and therefore foot deformity and callus formation. On the other hand, obesity and/or poor vision impair foot self-care. (Singh et al, 2005)

Only 4 studies evaluated the association between weight and foot ulcer, with contradictory results. In 2 prospective cohort studies (Boyko et al, 1999; Kästenbauer et al, 2001), it was reported that those with higher weight were at greater risk of foot ulcer development, in univariate and both uni and multivariate analysis, respectively. In Boyko’s et al study (Boyko et al, 2006) such association was not observed as in a cross-sectional case-control study (Bresäter et al, 1996) for active or past foot ulcer history.
BODY MASS INDEX (BMI)

Weight and BMI are related to the amount of foot pressure and macro-vascular complications which may help explain an association tendency between this variables and foot ulceration. However, from the 22 studies that analyzed the association between BMI and foot ulcer, only 3 reported it to be statistically significant. (See table 3)

In a prospective case control study, Carrington et al, in 2002, observed that those with higher BMI values were at superior risk of foot ulcer development. Also McNeely and colleagues (McNeely et al, 1995), in a cross-sectional case control study, and CDC (CDC, 2003), in a cross sectional study, verified higher prevalence of foot ulcer history in those subjects with bigger BMI values.

WAIST

None of the 2 studies (Iversen et al, 2008; Porciúncula et al, 2007) that evaluated the association between waist and active or recently healed ulcer or foot ulcer history found it statistically significant.

DISLIPIDEMY

Only 2 studies, Faglia (Faglia et al, 2001) and Porciúncula (Porciúncula et al, 2007), assessed the association between the presence of dislipidemy and foot ulcer recurrence or re-ulceration and active or recently healed ulcer, respectively, considering it not statistically significant.

We must highlight that in Faglia et al study (Faglia et al, 2001) no variable was statistically significant with foot ulcer recurrence. It is important to highlight that they only included 115 subjects for analyzing more than 25 different variables – which is insufficient.

TRIGLYCERIDES

None of the 4 studies that evaluated the association between triglycerides value and active or recently healed ulcer (Litzelman et al, 1997 b; Porciúncula et al, 2007; Sriussadaporn et al, 1997) and foot ulcer history (Iversen et al, 2008) considered it statistically significant.

TOTAL CHOLESTEROL

Only one prospective cohort study (Peters et al, 2007) evaluated the association between the total cholesterol value and foot ulcer recurrence or re-ulceration and concluded it was not statistically significant. On the other hand, the association between total cholesterol and active or recently healed ulcer was assessed by 3 studies. In a prospective cohort study (Litzelman et al, 1997 b) and in a cross-sectional case control study (Sriussadaporn et al, 1997) it was also not statistically significant. Porciúncula et al (Porciúncula et al, 2007), in a cross sectional study, were the only observing statistical significance.

HIGH DENSITY LIPOPROTEIN (HDL)

The association between the HDL value and foot ulcer was evaluated in 4 studies. A prospective cohort study (Suico et al, 1998) found no statistically significance with the HDL value and foot ulcer development, as also a cross-sectional case control study (Sriussadaporn et al, 1997) and a cross-sectional with active or recently healed ulcer and a cross-sectional case control study (de Sonnaville et al, 1993) with active or past foot ulcer history.
On the other 2 cohort studies (Litzałman et al, 1997 a, 1997 b) reported that subjects with superior levels of HDL showed higher risk of having an active or recently healed foot ulcer, in their univariate and multivariate analysis.

LOW DENSITY LIPOPROTEIN (LDL)

The LDL value was found to be not statistically significant associated with active or recently healed ulcer in a cross-sectional study (Porciúncula et al, 2007).

HYPERTENSION HISTORY

Margolis and colleagues (Margolis et al, 2008) were the only one observing a statistically significant association between hypertension history and foot ulcer development and Guerrero-Romero with active or past foot ulcer history (but only in the univariate analysis) (Guerrero-Romero et al, 1998). Conversely, the other 5 retrieved studies found no association between this variable and foot ulcer recurrence or re-ulceration (Faglia et al, 2001), active or recently healed foot ulcer (Porciúncula et al, 2007; Sriussadaporn et al, 1997) or with foot ulcer history (Iversen et al, 2008).

MEAN BLOOD PRESSURE

Only one study assessed the association between the mean blood pressure and active or recently healed ulcer (Litzałman et al, 1997 b), reporting it to be not statistically significant.

SYSTOLIC BLOOD PRESSURE

Hypertension was reported in some studies has being associated with DN. (Barbosa et al, 2001) From the 5 retrieved studies analyzing the association between the systolic blood pressure and foot ulcer development (Carrington et al, 2002), active or recently healed foot ulcer (Olmos et al, 1995; Porciúncula et al, 2007; Sriussadaporn et al, 1997) and active or past foot ulcer history (de Sonnville et al, 1997; Guerrero-Romero et al, 1998) only Carrington (Carrington et al, 2002) reported a statistical significance.

DIASTOLIC BLOOD PRESSURE

Of the 5 retrieved studies none reported a statistically significant association between diastolic blood pressure and active or recently healed ulcer (Olmos et al, 1995; Porciúncula et al, 2007; Sriussadaporn et al, 1997) or with active or past foot ulcer history (de Sonnville et al, 1997; Guerrero-Romero et al, 1998).

DIABETES CHARACTERIZATION AND CONTROL

DIABETES TYPE

From the 15 retrieved studies, only one cross-sectional case control study reported that subjects with diabetes type 1 presented higher prevalence of active or past foot ulcer history (Frykberg et al, 1998) as in a cross-sectional study having foot ulcer history as outcome (Iversen et al, 2008). (See table 3)
**DIABETES TREATMENT**

The evidence available about the association between diabetes’ treatment and foot ulcer is somewhat ambiguous. (See table 3) Nonetheless, in all the studies where an association is reported the treatment with insulin represented an increased risk for foot ulceration.

No association was observed between this variable with ulcer recurrence or re-ulceration nor with active or recently healed ulcer (Diouri et al, 2002; Faglia et al, 2001).

From the 3 retrieved studies, 2 prospective cohort studies (Boyko et al, 1999, 2006) Concluded that subjects using insulin had higher risk of foot ulcer development. The same conclusion was made by 2 cross-sectional case control studies analyzing the association between this variable and active or past foot ulcer history (Bresäter et al, 1996; de Sonnaville et al, 1997). Additionally, from the 4 studies retrieved, a cross-sectional case control study (Gulliford et al, 2002) and 2 cross-sectional studies also verified that subjects using insulin showed a higher prevalence of foot ulcer history.

**DIABETES DURATION**

One may assume that longer the disease duration higher are the chance of having diabetic retinopathy, DN (Barbosa et al, 2001) and/or PVD; which may increase the risk of foot ulceration. Several studies evaluated the association between diabetes duration and foot ulceration, although it resulted in a very dissimilar information. (See table 3)

The majority of the studies for the prediction of foot ulcer development (Abbott et al, 2002; Boyko et al, 1999, 2006; Margolis et al, 2008; McGill et al, 2005; Pham et al, 2009) and active or past foot ulcer history (Bresäter et al, 1996; de Sonnaville et al, 1997; Frykberg et al, 1998) concluded that there was a statistically significant association between this variable and the outcome, in contraposition with all the studies for the prediction of foot ulcer recurrence or re-ulceration (Diouri et al, 2002; Faglia et al, 2001; Peters et al, 2007; Uccioli et al, 1995) where statistical significance was not achieved.

From the 7 studies retrieved, only 2 cross-sectional case control studies (Armstrong et al, 1998 b; Sauseng et al, 1999) conclude that longer the diabetes’ duration higher was the risk for active or recently healed ulcer. Lavery (Lavery et al, 1998) evaluated this association in uni and multivariate analysis achieving statistical significance in both for diabetes’ duration equal or superior to 10 years.

From the 9 retrieved studies, 5 (Boulton et al, 1986; CDC, 2003; Gulliford et al, 2002; Iversen et al, 2008; Maluf et al, 2003) Concluded that those subjects with diabetes for a longer period of time had a higher prevalence of foot ulcer history. Iversen and coworkers, in 2008, also attained a statistical significant association in the multivariate analysis for diabetes’ duration equal or superior to 10 years.

**BLOOD SUGAR MONITORING**

Blood sugar monitoring, in the 2 retrieved studies, was not found to be associated with foot ulcer recurrence (Diouri et al, 2002) nor with foot ulcer history (CDC, 2003).

**FASTING BLOOD GLUCOSE**

A good glyceamic control reduces the development of some complications such as DN, respective intrinsic muscles atrophy and consequent foot deformities (Bennett et al, 1996; Lavery et al, 1998) and PVD. The fasting blood glucose value was significantly associated with foot ulcer development in a prospective cohort study (Boyko et al, 1999). However, such association was not reported with active or recently healed foot ulcer nor with foot ulcer history. (See table 3)
The association between this variable and active or recently healed ulcers is also scarce. One cross-sectional case control (Breslauer et al, 1996) found a statistical significant association in opposition with other 2 similar studies that did not (de Sonnevile et al, 1997; Guerrero-Romero et al, 1998).

GLYCATED HEMOGLOBIN

Due to its characteristics this is the long term diabetes’ control measure more frequently used. One study reported that a 1% mean reduction in the HbA1C value represented a 25% decrease of microvascular complications, including DN. (Singh et al, 2005)

The majority of the studies that evaluated the association between the HbA1C value and foot ulcer development showed statistical significance (Royko et al, 1999; Royko et al, 2006; Carrington et al, 2002; Margolis et al, 2008). That association was reported by a minority of studies; having as outcome active or recently healed ulcers (Porrini et al, 2007; Sritussadaphorn et al, 1997), active or past foot ulcer history (Breslauer et al, 1996) and foot ulcer history (Iversen et al, 2008). Conversely, it had no impact in the prediction of foot ulcer recurrence or re-ulceration (Gilouri et al, 2002; Peters et al, 2007). (See table 3)

MACRO-VASCULAR COMPLICATIONS

ANY MACRO-VASCULAR COMPLICATIONS

The presence of macro-vascular complications may be a sign of disease severity. (Iversen et al, 2008) In a 2008 cross-sectional study, Iversen and colleagues observed a significant association between the presence of any macro-vascular complications and foot ulcer history, in the univariate and multivariate analysis. (Iversen et al, 2008)

CARDIOVASCULAR COMPLICATIONS

In a Portuguese study, myocardial infarction or ischemia was found to be an independent predictive factor for DN. (Barbosa et al, 2001) Moreover, the majority of premature death among persons with diabetes is caused by these complications, representing around 65% of deaths in this population. (Fryberg et al, 2006)

STROKE

The association between the stroke variable and foot ulcer recurrence or re-ulceration was evaluated only in one prospective cohort study (Faiella et al, 2001), with no statistical significant results. The reported results for the association between this variable and foot ulcer history are conflicting. While a cross-sectional study (Iversen et al, 2008) found statistically significance, the same did not occur in a cross-sectional case control study (McNely et al, 1995).

MYOCARDIAL INFARCTION

In a retrospective cohort study, Margolis (Margolis et al, 2008) reported a statistically significant association between myocardial infarction and foot ulcer development. However, in 2 other studies (Iversen et al, 2008; McNely et al, 1995) this variable was not associated with foot ulcer history.

ANGINA PECTORIS

Only one study (Iversen et al, 2008) assessed the association between angina pectoris and foot ulcer history, not achieving statistical significance.
ANY MICRO-VASCULAR COMPLICATIONS

Only Iversen (Iversen et al, 2008) evaluated the association between the presence of any micro-vascular association and foot ulcer history, reporting a statistical significance in the uni and multivariate analysis.

NEPHROPATHY

Several studies verified that this variable is associated with peripheral arterial disease and may be considered as an indicator of micro and macro vascular complications, and therefore of a higher risk of foot ulceration. (Margolis et al, 2008) The 2 studies analyzing the association between this variable with foot ulcer development (Abbott et al, 2002; Margolis et al, 2008) and the only study with active or recently healed foot ulcer (Lavery et al, 1998) achieved statistical significance. On the other hand, the 3 studies having as outcome foot ulcer recurrence or re-ulceration (Deen et al, 2002; Faglia et al, 2001; Peters et al, 2007) and one foot ulcer history (McNeeley et al, 1995) did not attained statistical significance.

END-STAGE RENAL DISEASE (ESRD)

Only 2 studies evaluated the association between ESRD and foot ulcer, verifying that those with this condition presented higher risk for foot ulcer development (Margolis et al, 2008) and active or recently healed ulcer (Lavery et al, 1998).

MICROALBUMINURIA

Microalbuminuria must be faced not only as a renal disease predictor but at the same time as an indicator of endothelial damage, atherosclerotic disease, cardiovascular disease and retinopathy. (Guerrero-Romero et al, 1998)

Only 4 studies appraised the value of this variable in foot ulceration risk, but each one for a different outcome. Guerrero-Romero (Guerrero-Romero et al, 1998) and Iversen (Iversen et al, 2008) conclude that this variable was significantly associated with active or past foot ulcer history and foot ulcer history, respectively. However, such association was not verified for the prediction of foot ulcer recurrence or re-ulceration (Faglia et al, 2001) and active or recently healed foot ulcer (Lavery et al, 1998).

MACROALBUMINURIA

Only Lavery (Lavery et al, 1998) assessed the impact of this variable in the risk for active or recently healed foot ulcer, reporting a statistical significant association.

SERUM CREATININE

One prospective cohort study (Boyko et al, 1999) and one cross-sectional case control study (Sriussadaporn et al, 1997) described a statistical significant association between the serum creatinine value and foot ulcer development and active or recently healed foot ulcer, respectively. In contrast, such association was not reported in a retrospective case control and a cross-sectional study with active or recently healed foot ulcer (Omos et al, 1995; Porciúncula et al, 2007) and in one cross-sectional case control study with foot ulcer history (McNeeley et al, 1995).
Only one study evaluated the association between the urea levels and active or recently healed foot ulcer, achieving statistical significance (Sriussadaporn et al, 1997).

RETINOPATHY

The 2 studies assessing the association between retinopathy presence and active or recently healed foot ulcer (Lavery et al, 1998; Sriussadaporn et al, 1997) reported statistical significance, while in the 2 studies for the prediction of foot ulcer recurrence or re-ulceration (Faglia et al, 2001; Peters et al, 2007) such association was not observed.

One cross-sectional study (Mchowi et al, 1995) concluded that those subjects with retinopathy showed higher prevalence of foot ulcer history, while in a cross-sectional case-control study (Iversen et al, 2008) such association did not achieved statistical significance.

VISUAL ACUITY

A good visual acuity is essential for a correct self foot care. (Crawford et al, 2007) Lavery and colleagues observed that 15% of the subjects with foot ulceration were legally blind and 54% did not have sufficient visual acuity and physical ability to perform the self foot care. (Lavery et al, 1998)

From the 5 retrieved studies, 3 studies (Abbott et al, 2002; Boyko et al, 1999, 2006) observed that those with poor vision had significantly higher risk for foot ulcer development (2 maintaining statistical significance in the multivariate analysis (Boyko et al, 1999, 2006)). On the other hand, Sriussadaporn (Sriussadaporn et al, 1997) and Lavery (Lavery et al, 1998), in cross-sectional case control studies, had opposites results for the risk of active or recently healed foot ulcer. The first study showed statistical significance in both uni and multivariate analysis.

LASER PHOTOCOAGULATION

Boyko in 1999 and 2006 (Boyko et al, 1999; Boyko et al, 2006) concluded that the subjects with laser photocoagulation had a superior risk for foot ulcer development (but only in the univariate analysis).

As said earlier, DN plays a central role in the foot ulcer pathophysiology (Armstrong et al, 1998 a; Bowering, 2001; Frykberg et al, 2006; Papanas et al, 2006) and is directly related to age, diabetes duration and glucose control (most frequently translated by the HbA1C value). (Boulton et al, 1999; Kästenbauer et al, 2001) Although the reported prevalence in patients with diabetes ranges from 15 up to almost 50% (Boulton et al, 1999) (30% in Portugal (Barbosa et al, 2003)), DN is asymptomatic and undetected by almost half of the patients. (Boulton et al, 1999) This lack of symptoms frequently leads to a minimization of this complication by the patient and an unawareness of the risk it represents. The application of tests for the detection of DN is vital not only for the diagnostic itself but also the patients’ alert and education.

Clinician diagnosed neuropathy was significantly associated with foot ulcer development in one prospective cohort study (Boyko et al, 1999). Conversely, in 2 studies for the prediction of foot ulcer recurrence an association with DN was not observed (Diouri et al, 2002; Peters et al, 2007).
NEUROPATHY SYMPTOMS

In all the 4 studies retrieved, the presence of neuropathic symptoms (numbness, burning or tingling) was significantly associated with foot ulcer development (Boyko et al, 1999), active or recently healed ulcer (in the uni and multivariate analysis (Lavery et al, 1998)) and foot ulcer history (Armstrong et al, 1998; Gulliford et al, 2002). In addition, Armstrong (Armstrong et al, 1998 a) reported that the presence of one or more neuropathic symptoms had a sensitivity of approximately 100% to detect foot ulcer history.

VIBRATION PERCEPTION THRESHOLD (VPT) AT HALLUX

The VPT is measured using a biothesiometer or a neurothesiometer and can be applied in the distal portion of the hallux or malleolli. (Crawford et al, 2007; Singh et al, 2005) Vibrations, Semmes-Weinstein monofilament, light touch and motor nerve conduction test large-fiber neuropathy. Porciúncula (Porciúncula et al, 2007) demonstrated no association between VPT at hallux with active or recently healed ulcer.

VPT AT MALLEOLLI

All the studies that evaluated the association between VPT at the malleolli and ulcer development (Abbott et al, 1998; Caselli et al, 2002; Carrington et al, 2002; Kästenbauer et al, 2001; McGill et al, 2005; Pham et al, 2000) active or past foot ulcer history (Frykberg et al, 1998; Jirkovská et al, 2001; Miranda-Palma et al, 2005) and foot ulcer history (Armstrong et al, 1998 a; Bennett et al, 1996; Boulton et al, 1986; Lott et al, 2008; Maluf et al, 2003; Papapanas et al, 2006) achieved statistical significance. In contrast, in all the studies for the prediction of foot ulcer recurrence or re-ulceration such association was not observed (Faglia et al, 2001; Peters et al, 2007). (See table 3)

In every study assessing this variable dichotomously, it was concluded that the subjects with a VPT equal or superior to 25 Volts (V) presented higher risk for foot ulceration (Armstrong et al, 1998 a; Frykberg et al, 1998; Lavery et al, 1998; Pham et al, 2000). With this cut-off, Armstrong et al (Armstrong et al, 1998 a) reported approximately a sensitivity of 90% and specificity of 85% for foot ulcer history, Miranda-Palma et al (Miranda-Palma et al, 2005) 92% and 39% respectively for the detection of active or previous foot ulcer and Pham et al (Pham et al, 2000) of 86% and 56% respectively for the prediction of foot ulcer development.

McGill et al, in a 2005 study were the only one using a 30 V cut-off presenting a statistically significant association with foot ulcer development.

Although this test represents an objective and quantitative DPN measurement it is rarely used in general clinics due to its high cost, calibration and power source necessity. (Feng et al, 2009)

ACHILLES REFLEX

This variable tests the S1 and S2 spinal reflex pathway. Its evaluation is made by tapping the Achilles tendon, using a tendon hammer, with the patient preferably sited with his foot slightly dorsi-flexed, (Crawford et al, 2007)

From the 6 retrieved studies, a statistical significant association was observed between an altered Achilles reflex and foot ulcer development (Abbott et al, 2002; Boyko et al, 1999; McGill et al, 2005) and foot ulcer history (McNeely et al, 1995). Conversely, such association was not verified with active or recently healed ulcer (Porciúncula et al, 2007) neither with active or past foot ulcer history (de Sonnaville et al, 1997).
ROTULIAN REFLEX

An altered rotulian reflex was considered to be associated, with statistical significance, with active or recently healed ulcer (Porciúncula et al, 2007) and active or past foot ulcer history (de Sonnaville et al, 1997) in the 2 retrieved studies.

SEMME'S WEINSTEIN MONOFILAMENT

The SWM is a noninvasive, quick to apply and inexpensive test (Feng et al, 2009), which is why it is one of the most used instruments for DN screening (Singh et al, 2005). However, it is important to stress that the SWM performance varies according to brand, frequency of use (Dros et al, 2009; Singh et al, 2005) and the examiner skill and interpretation (Dros et al, 2009; Jirkovská et al, 2001).

SWM are single-fiber nylon threads, calibrated in order to create a reproducible buckling stress in a way to assess the Merkel touch domes and Meissner’s corpuscles integrity. (Feng et al, 2009) To perform this test correctly one must apply the monofilament perpendicularly to the foot, in pre-specified non-queratosic points, until it bends (for about 1 second) and ask the patient, while he is with eyes closed, if he/she can feel it. One filament must not be used in more than 10 patients without a 24 hours recovery period. (Singh et al, 2005)

All the 19 studies appraising the association between SWM insensitivity and foot ulceration demonstrated statistical significance, except for a cross-sectional study (Porciúncula et al, 2007). However, the definition varies greatly among each study and there is no selected standard method (number and locations of application and diagnostic cut-off) (Dros et al, 2009; Feng et al, 2009; Jirkovská et al, 2001; Miranda-Palma et al, 2005) which has a great impact in this test reproducibility. (Feng et al, 2009) (See table 3)

Olmos and colleagues, in 195, developed a study with the purpose of selecting the better SWM size to predict active or past foot ulcers, applying monofilaments ranging from 0,0045 to 447 grams (g), and concluded that the 10g (5,07 size) was the best threshold (the most frequently used size).

Saltzman and colleagues, in 2004, concluded that the simple application of the SWM of 4,5 (=1 g) in both 1st metatarsal heads has a sensitivity of 100% and a specificity of 67% for detecting active or past foot ulcer history. It was considered as altered sensation when the patient could not feel the SWM under either 1st metatarsal head. For the same outcome and procedure (but with a 5,07 SWM), the 2005 Miranda-Palma et al study sensitivity was of 73% and specificity of 68%. On the other hand, the inability to detect the SWM in 1 or more sites from a total of 8 resulted in a 86% sensitivity and a 58% specificity.

Armstrong et al (Armstrong et al, 1998 a) reported a sensitivity of 100% for the detection of foot ulcer history if the patient was unable to feel the SWM in one or more of the 20 tested sites.

In the Pham and colleagues study (Pham et al, 2000), the patient inability to feel a 5,07 SWM (10 g) or superior pressure, in one or both plantar surfaces of the hallux, resulted in a 91% sensitivity and a 34% specificity for the prediction of foot ulcer development.

TUNING FORK

A tuning fork is an easy and inexpensive instrument used to detect vibratory sensation abnormalities (an early sign of DN) (Singh et al, 2005), applying it vibrating at the dorsum of the interphalangeal joint of both halluc. (Apelqvist et al, 2000)
An alteration in the vibratory sensation, using a 128 Hertz (Hz) tuning fork, was associated in all the retrieved studies with foot ulcer development (Abbott et al, 2002; Boyko et al, 1999), active or past foot ulcer history (de Sonnaville et al, 1997; Miranda-Palma et al, 2005) and foot ulcer history (McNeely et al, 1995).

NEUROTIP

Only Abbott (Abbott et al, 2002) assessed the association between pain sensation abnormalities, using a Neurotip ™, with foot ulcer development reporting a statistical significance only in the univariate analysis.

BALL-BEARING SCORE

This test is conducted placing a steel ball, with different diameters (1,5 to 3,5 millimeters) and corresponding numbers (1 to 6 from the smallest to higher diameter), in the second metatarsal head plantar surface. The score was defined as the number of the smallest ball-bearing felt by the patient. A higher score was significantly associated with a history of neuropathic ulceration (p<0,001).

In Papanas and colleagues study (Papanas et al, 2006) this test showed a k value of 0,811 (95% CI 0,710-0,972), which can be considered as a very good inter-observer reproducibility and although this test is somewhat time consuming (15-20 minutes), the authors refer that those with higher scores became concerned and demonstrated a desire to know more about DN and self preventive measures, which is of great importance. (Papanas et al, 2006)

NEUROPATHY DISABILITY SCORE (NDS)

The NDS score was associated with foot ulceration in 3 studies. Pham and coworkers, in 2000, and Abbott and coworkers, in 2002, observed that those subjects with higher score values had an increased risk for foot ulcer development (for a score superior to 5, in the Pham study, this association maintained statistical significance in the multivariate analysis).

Miranda-Palma et al (Miranda-Palma et al, 2005) concluded that those subjects with a score superior to 5 had more risk for active or past foot ulcer history, with a 92% sensitivity and a 53% specificity. Pham and colleagues (Pham et al, 2000), for the same cut-off, observed similar results for foot ulcer development (92% sensitivity and 43% specificity).

NEUROPATHY SYMPTOMS SCORE (NSS)

The 2 prospective cohort studies appraising the impact of this variable in the risk of foot ulcer development had different results. In one study (Pham et al, 2000) such association did not achieved statistical significance, while it was observed in the Abbott et al study (Abbott et al, 2002) (but only in the univariate analysis). As well, Gulliford (Gulliford et al, 2002) concluded that those subjects with superior NSS values showed higher foot ulcer history prevalence.

MICHIGAN NEUROPATHY SCREENING SCORE (MNSS)

Only Abbott (Abbott et al, 1998) evaluated the MNSS association with foot ulcer development, verifying a statistical significance in the univariate analysis.
THERMAL SENSITIVITY

Thermal sensitivity tests small-fiber neuropathy and was significantly associated with foot ulceration in all the 4 retrieved studies: Abbott (Abbott et al, 2002) and Carrington (Carrington et al, 2002) having as outcome foot ulcer development, Litzelman (Litzelman et al, 1997 b), using the Sensortek thermal ™, with active or recently healed foot ulcer as outcome and Papanas (Papanas et al, 2006) with foot ulcer history.

DRY, NON SWEATING FEET

Dry, non-sweating feet and absent hair are considered a marker of autonomic neuropathy. (Boulton et al, 1999; de Sonnaville et al, 1997) A sudoresis diminution leads to dry skin and ultimately to callus and fissures formation (Boulton et al, 1999), which are considered as foot ulcer risk factors (see Pressure, shear stress and activity and fissures sections).

The only study evaluating the association between this variable and active or recently healed ulcer did not observe statistical significance (Litzelman et al, 1997 b). On the other hand, the presence of dry non-sweating feet was significantly associated with a higher risk for active or past foot ulcer history (Bresäter et al, 1996; de Sonnaville et al, 1997). In the de Sonnaville study (de Sonnaville et al, 1997) Such significance was maintained in its multivariate analysis.

ABSENT HAIR

Only Bresäter and colleagues (Bresäter et al, 1996) assessed the association between this variable and active or past foot ulcer history observing a statistical significance.

SHORT-LATENCY SOMATOSENSORY EVOKED POTENTIALS (SSEPS)

Sriussadaporn et al (1997) concluded that those subjects with abnormal SSEPS presented a statistically significant higher risk for active or recently healed ulcers, in the univariate and multivariate analysis. An abnormal SSEPS was present in 95% and 12% of the subjects with and without foot ulcer, respectively. (Sriussadaporn et al, 1997)

MOTOR NERVE CONDUCTION VELOCITY (MNCV)

Commonly nerve conduction studies are considered as the gold standard for the DN diagnostic (Feng et al, 2009; Singh, et al., 2005) due to its objectiveness and sensitivity. (Feng et al, 2009) However, they are expensive and generally unavailable which greatly diminishes their value as a screening tool for this condition. (Feng et al, 2009; Singh, et al., 2005)

From the 4 retrieved studies all concluded that there was a statistical significant association between MNCV and foot ulcer development (Carrington et al, 2002; Kästenbauer et al, 2001) and active or recently healed foot ulcer (Olmos et al, 1995; Sauseng et al, 1999).

TRAUMA AND FOOT CARE HABITS

Trauma in the foot can be due to intrinsic (foot deformities, daily activity, etc.) or extrinsic factors (self-injury lesions, footwear, blunt injury, etc). Intrinsic trauma is an important cause for ulceration, particularly when in the presence of DN. (Frykberg et al, 2006)
EDEMA

A lower limb edema may be due to a fluid exchange mechanism disorder (Crawford et al, 2007) and may cause a higher predisposition to trauma. The presence of edema was associated with foot ulcer development in the 2 retrieved studies with this outcome (Boyko et al, 1999, 2006), but only in the univariate analysis. However, such association was not observed in the studies with active or recently healed (Litzelman et al, 1997 b) nor active or past foot ulcer history (de Sonnaville et al, 1997) as outcome.

REDNESS

Only Bresäter (Bresäter et al, 1996) assessed the association between this variable and active or past foot ulcer history, reporting statistical significance.

ONYCHOMYCOSIS

Patients with diabetes are more prone to fungal infections, particularly toe-web tinea and onychomycosis. (Singh et al, 2005) The last, frequently increases the toenail thickness which creates hyperpression points and leads to microlesions in the area beneath the toenails and may evolve to ulceration. Therefore, the presence of onychomycosis was significantly associated with ulcer development (Boyko et al, 2006), in the uni and multivariate. However, such association did not occur with active or recently healed ulcer (Litzelman et al, 1997 b) or with active or past foot ulcer history (Bresäter et al, 1996).

THERAPEUTIC NAIL LACQUER

This variable was analyzed presupposing that topical anti-fungal therapy could increase foot self-examination. (Armstrong et al, 2005) However, Armstrong (Armstrong et al, 2005), in a randomized controlled trial, concluded that the use of topical onychomycosis’ treatment was not associated with a decrease in the risk of foot ulcer development.

SELF FOOT CARE HABITS

There are several recommendations which are traditionally given to patients with diabetes with no evidence supporting them.

In a prospective cohort study, the irregular application of lubricant in dry skin of feet was associated with a higher risk of foot ulcer development, both in uni and multivariate analysis (3.1 times). Several other self foot care behaviors demonstrated no association with this outcome (washing, foot problem reporting, socks use, soaking feet, footwear inspection, toe drying, straight nail cut, foot inspection and water testing). (Suico et al, 1998) As a major limitation this study presents the fact that the outcome was only collected at the beginning and end of the study. (Suico et al, 1998)

Sriussadaporn and coworkers (Sriussadaporn et al, 1997) concluded that subjects with higher foot care score had an inferior risk for active or recently healed ulcer. Nevertheless, such association was not verified in the multivariate analysis.
NAIL CARE

The presence of ingrown nails was not associated with a higher risk for active or past foot ulcer history (Bresåter et al, 1996) and active or recently healed foot ulcers (Litzelman et al, 1997 b), as well as the presence of improperly trimmed nails (Litzelman et al, 1997 b). On the other hand, Gulliford and associates (Gulliford et al, 2002) concluded that those subjects that recur to friends or relatives for the nail care showed a higher prevalence of foot ulcer history.

FOOTWEAR

In several studies footwear is the most frequent precipitating factor for foot ulceration (Busch et al, 2003; Litzelman et al, 1997 a; Soares et al, 2007), preceding half of the amputations in patients with diabetes. (Boulton et al, 2000) Footwear (frequently mismatched in older subjects) can be particularly deleterious when DPN and/or foot deformity are present. Correct footwear and shoe inserts are intended to reduce hyper-pressure and shear stress, preventing callus formation and so protecting vulnerable areas.

Abbott and colleagues (Abbott et al, 2002), in a prospective cohort study, proposed a footwear risk categorization in which open-toe sandals, high-heeled shoes and flip-flops corresponded to the higher risk and were significantly associated with foot ulcer development (but only in the univariate analysis).

USE TIME

Jayasinghe (Jayasinghe et al, 2007) observed that in the group of subjects that wore footwear for less than 10 hours the foot ulcer history prevalence was significantly higher.

BAREFOOT

Walking barefoot inside house was not associated with an increase in neither foot ulcer development (Suico et al, 1998) risk nor foot ulcer history (Gulliford et al, 2002). Not using footwear outside the house was not associated with foot ulcer development (Suico et al, 1998), but was with foot ulcer history (Gulliford et al, 2002).

In one study (Jayasinghe et al, 2007) the subjects that walked regularly barefoot presented significantly higher foot ulcer history prevalence, while in other such association was not observed (Maluf et al, 2003). This variable is especially important in poorer countries in development, where walking barefoot is more common. (Jayasinghe et al, 2007)

QUALITY

Despite the footwear importance, in a prospective cohort study (Litzelman et al, 1997 a), it was observed that more than 25% of the subjects wore improperly sized shoes (too narrow or too short). In the univariate analysis of the same study, among several shoe related characteristics, only appropriate size (length and width), new shoe acquisition in the last semester and special shoe recommendation were significant associated with active or recently healed ulcer (at a 0,2 level). Only special shoe recommendation maintained significance in the multivariate analysis. (Litzelman et al, 1997 a)

In another study, the use of very poor quality footwear was not associated with active or past foot ulcer history (de Sonnaville et al, 1997).
THERAPEUTIC

A foot ulceration treatment costs £ 6200 to 10 000 per patient. This amount, according to Busch and Chantelau, can afford the distribution of 42 to 68 free pairs of therapeutic shoes. (Busch et al, 2003)

From the 6 retrieved studies, the use of therapeutic footwear was associated with a lesser risk of foot ulcer development (Boyko et al, 1999; Chantelau et al, 1990), recurrence or re-ulceration (Busch et al, 2003) and foot ulcer history (Maluf et al, 2003) in 4 of them. Conversely, significance was not achieved in 2 randomized controlled trials (Reiber et al, 2002; Uccioli et al, 1995) assessing the impact of therapeutic shoes in foot ulcer recurrence prevention. However, it is important to stress that in both studies patients with severe foot deformity were excluded; which may interfere with the results and its generalizability.

In the Uccioli and colleagues study, although the reported OR and respective CI did not presented statistical significance (OR 0,26; CI 95% 0,2-1,5) there were significantly (p=0,009) less ulcer relapses, at 1 year, in the Podiabetes therapeutic shoes group (27,7%) than in the control group (58,3%). In this study, foot care patient education and regular surveillance (every 6 months) was provided to both groups.

COMPLIANCE AND REGULARITY

In the 1990’s study from Chantelau (Chantelau et al, 1990) subjects with history of diabetic foot syndrome (DN, limb ischemia, previous foot ulcer [72%] and/or amputation [30%]) that wore the provided therapeutic shoes (custom shoes with cork, plastazote and leather insoles) regularly presented a smaller risk for foot ulcer development (RR 0,48; 95% CI 0,29-0,79) at the end of the study with a 25 months follow-up.

In another Chantelau’s study (Chantelau et al, 1994), the compliance with the provided therapeutic shoes (custom shoes with plastazote, neoprene and poron inserts) diminished significantly the risk for foot ulcer recurrence. Subjects were considered as compliant if they wore them at least 60% of the time. At 40 months 54% of the compliant group ulcerated in comparison with 100% of the non compliant group.

FOOT DEFORMITY

Besides DN and PVD, foot ulceration has mechanical or structural factors in its pathophysiology (Ledoux, et al, 2005). Foot deformities are often present in the diabetic foot due to collagen glycosylation that affects ligaments and capsular structures. (Frykberg et al, 2006)

In addition to the risk it represents per se, foot deformities are often due to weakness and wasting of the foot small muscles caused by somatic neuropathy, which is the responsible also for the so called insensitive foot. (Bouton, et al, 1999) An abnormal foot shape and posture concomitantly with insensitivity is a major risk for foot ulceration (Bouton, et al, 1999) due to intrinsic or extrinsic (footwear) factors that lead to excessive pressure during gait. (Frykberg et al, 2006; Singh et al; 2005)
RIGID TOE DEFORMITY

The presence of rigid toe deformity was associated with an increased risk for foot ulcer development (Abbott et al, 2002; Boyko et al, 1999; Ledoux et al, 2005), active or recently healed foot ulcer (Lavery et al, 1998) and active or past foot ulcer history (de Sonnaville et al, 1997) in all the retrieved studies. In the 2002 Abbott et al study such association maintained its significance in the multivariate analysis.

In one cross-sectional case control study (Bresåter et al, 1996), the subjects with hammer toes did not showed increased active or past foot ulcer history prevalence (Peters et al, 2007).

HALLUX LIMITUS/ RIGIDUS

The presence of hallux rigidus was associated with foot ulcer development (Boyko et al, 1999; Ledoux et al, 2005), but not with foot ulcer recurrence or re-ulceration (Peters et al, 2007). The only study assessing the association between ulcer development and the presence of hallux limitus (Boyko et al, 2006) did not observed statistical significance.

HALLUX ABDUCTUS VALGUS (HAV)

Ledoux and colleagues (Ledoux et al, 2005), in a prospective cohort study, verified that the presence of HAV was associated with foot ulcer development. However, such association was not observed for active or past foot ulcer history, in a cross-sectional case control study (Bresåter et al, 1996).

PES CAVUS AND PLANUS

Only one study evaluating the association between pes cavus or pes planus with foot ulcer development (Ledoux et al, 2005) reported no statistical significance.

CHARCOT FOOT

From the 2 retrieved studies, the independent presence of Charcot foot was significantly associated with foot ulcer development (Boyko et al, 1999) and active or past foot ulcer history (Bresåter et al, 1996). However, Peters and colleagues (Peters et al, 2007) did not verify an association between Charcot foot and/or rigid toe deformity with foot ulcer recurrence or re-ulceration.

ABNORMAL FOOT SHAPE

The both studies appraising the association between abnormal foot shape and foot ulcer development (Boyko et al, 2006; Ledoux et al, 2005) concluded that it was statistical significant.

SUB-TARSAL JOINT (STJ) MOBILITY

A limited STJ mobility was associated with foot ulcer development (Ledoux et al, 2005; Pham et al, 2000), active or recently healed ulcer (Lavery et al, 1998), active or past foot ulcer history (Frykberg et al, 1998) and foot ulcer history (Bennett et al, 1996; Boulton et al, 1986). The only study assessing the association between this variable and foot ulcer recurrence (Peters et al, 2007) or re-ulceration did not achieve statistical significance.

FIRST MTPJ MOBILITY

From the 3 retrieved studies, all of them concluded that a limited $1^{st}$ MTPJ mobility (< 70º (Crawford et al, 2007) increased the risk for foot ulcer development (Boyko et al, 1999; Pham et al, 2000) and active or past foot ulcer history (Frykberg et al, 1998).
These variables have a greater impact when in the presence of DN. [Frykberg et al, 1998]

CALLUS

Hyperkeratotic areas (callus) are a natural reaction to pressure or friction. However, they create even more pressure to the subcutaneous tissues and hemorrhaging into the callosity plaque is a common clinical finding (Boulton et al, 1999; Murray et al, 1996) especially in subjects with DN (Boulton et al, 1999), due to their inability to feel pain.

Callus debridement should be regularly performed by specialized health professionals (Boulton et al, 1999; Murray et al, 1996; Singh et al, 2005) and its cause analyzed and prevented (compensating bone deformities, modifying footwear habits, etc).

The presence of callus at baseline was significantly associated with active or past foot ulcer history (Broxter et al, 1996) and foot ulcer development in one prospective cohort study (Murray et al, 1996), but not in another (Boyko et al, 2006). It is important to highlight that the number of areas with callus had no significant impact in the risk of foot ulcer development in the Murray and associates (Murray et al, 1996) study (RR 11, 95% CI 2.8-43.2).

PEAK PLANTAR PRESSURE (PPP)

Since it first description in 1965, several instruments with various presentations and measurement procedures are used for the measurement of plantar pressure which is translated in the included studies by the use of different cut-offs and units among themselves. [Sing et al, 2005](See table 3)

All the retrieved studies showed that the subjects with greater PPP values presented significantly a higher risk for foot ulcer development (Caselli et al, 2002; Kästenbauer et al, 2001; Lavery et al, 2003; Murray et al, 1996; Pham et al, 2000), active or recently healed ulcer (Armstrong et al, 1998 b; Lavery et al, 1998), active or past foot ulcer history (Frykberg et al, 1998) and foot ulcer history (Bennett et al, 1996; Lott et al, 2008).

Despite the consistent results, Lavery and colleagues suggested that, using a 87.5 N/cm² cut-off, this variable alone has a low ability in predicting foot ulcer development (AUC 0.57; 95% CI 0.51-0.62). (Lavery et al, 2003) Moreover, this variable had no impact in the prediction of foot ulcer recurrence or re-ulceration (Peters et al, 2007).

A foot pressure equal or superior to 6 kg/cm² demonstrated a 59% sensitivity and a 69% specificity for the prediction of foot ulcer development, in the Pham and colleagues study. [Pham et al, 2000]

In a prospective cohort study, Caselli et al found a statistical significance association with the forefoot peak pressure and a forefoot / rearfoot ratio (F/R R) superior to 2 in the univariate analysis. However, only F/R R superior to 2 maintained statistical significance in the multivariate analysis (OR 1.8 95 CI 1.1-3.2); which is greatly related with advanced DN. [Caselli et al, 2002] This conclusion stresses the importance of foot insoles and therapeutic footwear for the correct load distribution of high risk patients. [Caselli et al, 2002]
In a very detailed analysis, Sauseng and colleagues (Sauseng et al, 1999) showed that the maximum plantar pressure, the plantar loading over time and the relative contact time in the 1st metatarsal head was significantly higher in the subjects with a neuropathic plantar ulcer. These results stress that this is a region in higher risk for ulceration.

**PEAK PRESSURE GRADIENT (PPG) AND OTHER PRESSURE MEASURES**

The PPG designates “the spatial change in plantar pressure around the location of the peak plantar pressure”. (Lott et al, 2008)

Lott and colleagues (Lott et al, 2008), in a study including only subjects with DN, observed that those with superior peak plantar gradient values presented higher foot ulcer history prevalence. They believe that a higher PPG creates an increased concentration of internal stress, which represents a superior soft tissues damage risk. In their study, they concluded that there was no statistical difference between subjects with and without foot ulcer history in what concerns pressure time integral, peak maximal shear stress (PMSS) and depth of PMSS at the forefoot. (Lott et al, 2008)

One of the pointed limitations is that for the elaboration of this study, the measures were made with subjects using the same type of footwear, which may not represent the stresses experienced in daily basis. (Lott et al, 2008)

**AVERAGE DAILY ACTIVITY**

There is almost no evidence around the effect of daily weight-bearing physical activity in diabetic foot ulceration. However, an active lifestyle has been proven to be beneficial to one person’s health, including those with diabetes. (Lemaster et al, 2003)

From the 3 retrieved studies, it was concluded that less the average daily activity was the risk for foot ulcer development (Armstrong et al, 2004), foot ulcer recurrence or re-ulceration (Lemaster et al, 2003) and foot ulcer history (Maluf et al, 2003) was significantly higher. These results are according with the “physical stress theory”, proposed by Maluf and Mueller, which affirm that a gradual increase in physical stimulation conduces to a plantar protective tissue hypertrophy, preventing skin breakdown. (Lemaster et al, 2003; Maluf et al, 2003)

**ACTIVITY VARIABILITY COEFFICIENT**

Only Armstrong evaluated the association between this variable and foot ulcer development, reporting that those subjects with higher activity variability had an increased risk. And so, they postulated that if the skin is not stressed consistently it may present an injury superior risk. (Armstrong et al, 2004)

**FISSURES**

Only a cross-sectional study (Bresäter et al, 1996) evaluated the association between the presence of fissures and active or past foot ulcer history, not achieving statistical significance.
TINEA PEDIS

In a prospective cohort study, the presence of tinea pedis was considered to be associated with a decrease in the foot ulcer development risk but only in the multivariate analysis, representing autonomic function preservation. (Boyko et al, 2006) However, for the presence of active or recently healed foot ulcer, another prospective cohort study (Lizelman et al, 1997 b) found no association in their univariate analysis.

PERIPHERAL VASCULAR DISEASE

PVD is twice more frequent in the diabetic population (Singh et al, 2005) and may lead to foot ulceration and delayed cicatization. (Boulton et al, 1999) Non-invasive testing for this condition is crucial given that the usual PVD signs are less frequent in persons with diabetes due to DN and more distal arterial stenosis localization. (Boulton et al, 1999; Irlkovská et al, 2001; Singh et al, 2005) Commonly affecting femoropopliteal and below knee vessels and paradoxally spearing pedal vessels. (Singh et al, 2005)

The 2 studies analyzing the association between PVD and foot ulcer development observed a statistical significance that was not maintained in the multivariate analysis (Abbott et al, 2002; Boyko et al, 1999). For the ulcer recurrence or re-ulceration prediction, a prospective cohort study (Peters et al, 2007) reported that those with the presence of PVD (this is with any pedal pulse missing or ankle-brachial index inferior to 0.8) significantly had a higher risk; while in a retrospective cohort study (Dionis et al, 2002) such association was not verified.

FOOT PALPABLE PULSES

In subjects with diabetes, complication in the small and large vessels frequently do not advance at an equal pace, and so one may easily observe toes with ischemic signs caused by small vessels alterations while dorsalis pedis and posterior tibial pulses remain preserved. (Boulton et al, 1999)

Although an association between the number of foot palpable pulses and foot ulcer was reported in the majority of the retrieved studies, PVD concept slightly varies from one another.

Pham et al (Pham et al, 2008) using as definition the absence of pedal pulses, Abbott et al (Abbott et al, 2002) using the presence of 0 to 2 present pulses in both feet and McGill et al (McGill et al, 2005) using the absence of the 2 pedal pulses in one or both feet concluded that those subjects in this condition had significant higher risk of foot ulcer development. In the Abbott et al study (Abbott et al, 2002), in the multivariate analysis, such association was maintained. Likewise, the 2 studies that evaluated the association between diminished foot palpable pulses (in de Sonnaville et al study (de Sonnaville et al, 1997) it was defined as dorsal pedal pulse absent, whereas in Frykberg et al study (Frykberg et al, 1998) it was not defined) and active or past foot ulcer history reported statistical significance.

Considering PVD as one or more absent pedal pulses (from a total of 4), Lavery et al observed no statistical significant association with active or recently healed ulcer. (Lavery et al, 1998)
LOWER EXTREMITY VASCULAR STUDY

In a retrospective case control study, Olmos and colleagues, in 1995, reported that subjects presenting stenosis in the lower extremity vascular study showed higher prevalence of active or past foot ulcer history.

PERIPHERAL VASCULAR SURGERY (PVS)

The 2 studies assessing the association between PVS history and foot ulcer development (Boyko et al, 1999) and active or recently healed foot ulcer (Lavery et al, 1998) demonstrated statistical significance. On the other hand, in the 2 studies for the prediction of foot ulcer recurrence or re-ulceration (Dourl et al, 2002; Faglia et al, 2001) and one of foot ulcer history (McNeely et al, 1995) such association was not verified.

CLAUSTRATION

Boyko and associates in 1999 and 2006 (Boyko et al, 1999, 2006) concluded that those subjects presenting claudication in a distance inferior to 1 block had statistical significant higher risk for foot ulcer development. However, this association was not observed in the multivariate analysis of both studies.

The remaining 3 studies assessing the association between any claudication symptom and foot ulcer development (McGill et al, 2005), foot ulcer recurrence or re-ulceration (Faglia et al, 2001) and active or recently healed foot ulcer (Lavery et al, 1998) did not demonstrated statistical significance.

HALLUX-BRACHIAL INDEX

As said before, due to the relatively frequent medial arterial calcinosis in subjects with diabetes, ABI value can be fallaciously elevated. Therefore, transmetatarsal or toe measures are considered as probably safer. (Boulton et al, 1999) However, only a cross-sectional study used this procedure and observed that subjects with a hallux brachial index equal or inferior to 0,7 demonstrated a higher risk for active or recently healed foot ulcer (Porciúncula et al, 2007)

ANKLE-BRACHIAL INDEX (ABI)

The ABI designates the ratio of the ankle systolic blood pressure with that in the brachial artery. A value superior to 0,9 and inferior to 1,1 is considered normal; inferior to 0,8 points to ischemia and superior to 1,1 may indicate medial arterial calcinosis. (Crawford et al, 2007; Singh et al, 2005)

All the studies evaluating the association between ABI and foot ulcer recurrence or re-ulceration (Faglia et al, 2001; Peters et al, 2007), active or recently healed foot ulcer (Armstrong et al, 1998 b; Lavery et al, 1998; Porciúncula et al, 2007; Sriussadaporn et al, 1997) and foot ulcer history (Maluf et al, 2003; McNeely et al, 1995) did not found statistical significance. Conversely, all of the studies having as outcome active or past foot ulcer history (de Sonnaville et al, 1997; Frykberg et al, 1998; Jirkovská et al, 2001) demonstrated that lower the ABI value higher was the risk. (See table 3)

For the prediction of foot ulcer development, one prospective case-control (McGill et al, 2005) found no association with this variable while a prospective cohort study (Boyko et al, 1999) reported a statistical significance but only in its univariate analysis.
TRANSCUTANEOUS OXGEN PRESSURE (TCPO2)

The TcPO2 value is collected placing a probe in the foot dorsum and chest wall and comparing both values, indicating the quantity of oxygen transported into the skin (Boulton et al, 1999). The performance of this test requires expensive equipment, a trained professional and time and so it is not regularly used (Singh et al, 2005).

The only study assessing the association between TcPO2 and foot ulcer development concluded that those subjects with lower values presented significantly higher risk, but only in the univariate analysis (Boyko et al, 1999). Such association did not reach statistical significance for foot ulcer recurrence or re-ulceration (Faglia et al, 2001; Peters et al, 2007) nor for active or recently healed foot ulcer (Armstrong et al, 1998 b; Lavery et al, 1998).

A value superior to 30 mmHg is considered as an indicative of adequate tissue perfusion. (Boulton et al, 1999) McNeely and colleagues (McNeely et al, 1995) observed that subjects with a TcPO2 equal or inferior to that value showed higher prevalence of foot ulcer history.

PREVIOUS FOOT COMPLICATIONS

PREVIOUS FOOT ULCER

From the 8 retrieved studies (Abbott et al, 2002; Boyko et al, 1999, 2006; Carrington et al, 2002; Margolis et al, 2008; McGill et al, 2005; Murray et al, 1996; Pham et al, 2000), all of them showed a statistical significant association between previous foot ulcer history and foot ulcer development. In those with multivariate analysis, such association remained present (Abbott et al, 2002; Boyko et al, 1999, 2006). However, for the prediction of foot ulcer recurrence a retrospective cohort study (Diouri et al, 2002) observed the same association while in a prospective cohort study (Faglia et al, 2001) statistical significance was not achieved.

PREVIOUS ULCER IN THE HALLUX

In a prospective cohort study, Peters (Peters et al, 2007) concluded that those with an ulcer history in the plantar surface of the hallux showed higher risk for foot ulcer recurrence or re-ulceration (OR 4.3; CI 95% 4.1-4.5).

PREVIOUS LOWER EXTREMITY AMPUTATION

Previous amputation was statistically associated with foot ulcer development, active or recently healed ulcer and active or past foot ulcer history in all the retrieved studies (Abbott et al, 2002; Boyko et al, 1999, 2006; Breslauer et al, 1996; Lavery et al, 1998; Margolis, et al., 2008; McGill, et al., 2005). (See table 3) On the other, for the prediction of foot ulcer recurrence or re-ulceration no study concluded that association to be statistically significant (Diouri et al, 2002; Faglia et al, 2001; Peters et al, 2007).

From the 3 retrieved studies, 2 of them (Guilford et al, 2002; Iversen et al, 2008) observed a higher prevalence of foot ulcer history in those subjects with a previous amputation history.
FOOT EDUCATION PROGRAMME

Foot education programs are proven to increase foot care habits (Soares et al, 2007) and knowledge (Valk et al, 2002). Calle-Pascual, in a prospective cohort study including only subjects with DN (based on a NDS ≥ 6); observed that those completing the educational program (4 sessions of 90 to 120 min in 1 week); changed inadequate foot care behavior during the first 6 months; came to regular visits to the podiatrist, to the at least bi-annual foot review and to the annual medical care diabetic treatment review had a significant lower risk of foot ulcer development (foot ulcer rate 3.1% vs 31.6%; RR 13; p < 0.001). (Calle-Pascual et al, 2001) It is important to say that in this study only patients with DN (NDS ≥ 6) were included and all subjects with PVD (present intermittent claudication or absence of 1 or more pedal pulses) were excluded.

In a prospective cohort study, those subjects that ever had foot care advice showed a significant higher risk for foot ulcer development. This fact is explained by the fact that they probably represented the subjects already identified as being in higher risk. (Abott et al, 2002) On the other hand, in a randomized controlled trial, the educational intervention had no effect in the prevention of foot ulcer recurrence. However, such intervention was applied to a high risk population and consisted in a single 1 hour education, handouts and a phone-call for the discussion of raised issues. (Lincoln et al, 2008)

CHIROPODIST CARE

In a randomized controlled trial, Plank et al (Plank et al, 2003) observed that subjects with monthly chiropodist care had a lower risk of foot ulcer recurrence (intention to treat RR 0.52; 95% CI 0.29-0.93).

According to McGill and colleagues (McGill et al, 2005), the number-needed-to-treat to prevent one foot ulcer per is only of: 8 patients with neuropathy and previous amputation or ulcer, 25 with neuropathy and cannot feel the SWM or 30 with neuropathy and no previous amputation or ulcer. In this study, neuropathy was defined as a VPT > 30.

MULTIDISCIPLINARY TEAM

Many centers worldwide become aware of an improvement in limb salvage rates through a multidisciplinary approach to the diabetic foot, involving a specialized team that should include a podiatrist, endocrinologist, orthopedic surgeon, vascular surgeon, internist, ophthalmologist, nephrologist and nurses. (Frykberg et al, 2006)

In a randomized controlled trial (Dargis et al, 1999), the group that received multidisciplinary care (including regular podiatric care, foot care education, extra-depth footwear and insoles) for 2 years showed a significant lower risk for foot ulcer recurrence in comparison with the standard care group, with the same appointment regularity (30.4% vs 58.4%; RR 0.51 95% CI 0.31-0.80). However, in this Lithuanian study, all the included subjects had a previous neuropathic ulcer and no PVD, Charcot deformity or previous amputation history.
DIABETES MANAGEMENT EDUCATION

In the 2 retrieved studies (CDC, 2003; McNeely et al, 1995), a diabetes management education had no statistical significant association with foot ulcer history.

DERMAL THERMOMETRY

Commonly the primary natural warning that something is wrong is pain. However, in subjects with neuropathy such alert is delayed or absent. Diabetic foot ulceration is accompanied by an inflammatory response which is characterized by a temperature increase, among other things. For this reason, a correct and easy to use foot temperature assessment can be an important helpful tool for predicting complications and leading patients to seek for medical care. (Armstrong et al, 1997, 2003, 2007; Lavery et al, 2004; Lavery et al, 2007)

In 2 studies (Armstrong et al, 2007; Lavery et al, 2004), the daily use of self-administered infrared temperature reduced significantly the risk of foot ulcer development in comparison in standard care. In Armstrong et al study, the standard therapy group presented a OR of 3 (CI 95% 1,0-8,5; p<0,05). (Armstrong et al, 2007) In Lavery et al study, ulcer occurred in 1 subject in the enhanced therapy group in comparison to 7 in the standard therapy group. (Lavery et al, 2004)

Lavery et al, in 2007, performed a randomized controlled trial distributing patients in 3 groups: standard therapy, structured foot exam twice a day and enhanced therapy, this is, perform foot exam twice daily and use digital infrared thermometer. The enhanced therapy group demonstrated a significant decrease for foot ulcer recurrence in comparison with the standard therapy and regular foot exam group. The ulcer recurrence rate was of 8,5%; 29,3% and 30,4%, respectively (p<0,01).

In a cross-sectional study (Armstrong et al, 1997), Subjects with active or recently healed neuropathic ulcers had a significantly higher skin temperature. However, in another study, Armstrong and associates (Armstrong et al, 2003) concluded that as a one-time screening tool the baseline skin temperature did not predict foot ulcer development in a 2 years prospective cohort study.
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<th>Recurrence or re-ulceration [Strength of association (number of studies)]</th>
<th>Active or recently healed ulcer [Strength of association (number of studies)]</th>
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<td>-: n=3(4,6,7)</td>
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<td>-: n=3(4,6,7)</td>
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<td>(\cdot): n= 1(^{(4)})</td>
<td>(\cdot): n= 2(^{(6, 7)})</td>
<td>(\cdot): n= 1(^{(2)})</td>
<td>(\cdot): n= 1(^{(3)})</td>
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<td>--</td>
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<td>-----------------</td>
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<td>Physical inactivity</td>
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**METABOLIC SYNDROME**

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<th>Height</th>
<th>(\cdot): n= 1(^{(13)})</th>
<th>NA</th>
<th>(\cdot): n= 1(^{(5)})</th>
<th>(\cdot): n= 1(^{(3)})</th>
<th>(\cdot): n= 1(^{(5)})</th>
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</thead>
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<td>Weight</td>
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<td>(\cdot): n= 1(^{(3)})</td>
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**BMI as a continuous variable**

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<th>BMI as a categorical variable</th>
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<tr>
<td>Waist</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>(\cdot): n= 1(^{(5)})</td>
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<td>Dislipidemia</td>
<td>NA</td>
<td>(\cdot): n= 1(^{(5)})</td>
<td>NA</td>
<td>NA</td>
<td>(\cdot): n= 1(^{(5)})</td>
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<tr>
<td>Tryglicerides</td>
<td>NA</td>
<td>(\cdot): n= 3(^{(5, 6, 8)})</td>
<td>NA</td>
<td>NA</td>
<td>(\cdot): n= 1(^{(5)})</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>NA</td>
<td>(\cdot): n= 1(^{(6)})</td>
<td>(\cdot): n= 2(^{(6, 8)})</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

| HDL | \(\cdot\): n= 1\(^{(12)}\) | NA | \(\cdot\): n= 1\(^{(6)}\) | \(\cdot\): n= 1\(^{(4)}\) | NA |
| LDL | NA | \(\cdot\): n= 1\(^{(9)}\) | \(\cdot\): n= 1\(^{(9)}\) | \(\cdot\): n= 1\(^{(9)}\) | \(\cdot\): n= 1\(^{(9)}\) |
| Hypertension history | \(\cdot\): n= 1\(^{(6)}\) | \(\cdot\): n= 1\(^{(6)}\) | \(\cdot\): n= 1\(^{(6)}\) | \(\cdot\): n= 1\(^{(6)}\) | \(\cdot\): n= 1\(^{(6)}\) |
| Mean blood pressure | NA | \(\cdot\): n= 1\(^{(8)}\) | NA | NA | NA |
| Systolic blood pressure | \(\cdot\): n= 1\(^{(6)}\) | NA | \(\cdot\): n= 1\(^{(8)}\) | \(\cdot\): n= 2\(^{(1, 2)}\) | NA |
| Diastolic blood pressure | NA | NA | \(\cdot\): n= 3\(^{(5, 6, 8)}\) | \(\cdot\): n= 2\(^{(1, 2)}\) | NA |
### DIABETES CHARACTERIZATION AND CONTROL

<table>
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<tr>
<th>Diabetes Type</th>
<th>n= 4 (8, 9, 11, 13)</th>
<th>n= 2 (2, 4)</th>
<th>n= 2 (2, 7)</th>
<th>n= 1 (1)</th>
<th>n= 1 (2)</th>
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</thead>
<tbody>
<tr>
<td><strong>Diabetes Treatment</strong></td>
<td>+: n= 1 (13)</td>
<td>+: n= 1 (10)</td>
<td>-: n= 2 (2, 3)</td>
<td>-: n= 1 (4)</td>
<td>+: n= 4 (1, 2, 6, 8)</td>
</tr>
<tr>
<td><strong>Diabetes duration as a continuous variable</strong></td>
<td>+: n= 2 (2, 4)</td>
<td>-: n= 2 (2, 7)</td>
<td>+: n= 2 (2, 7)</td>
<td>+: n= 2 (2, 3)</td>
<td>+: n= 2 (2, 3)</td>
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<tr>
<td><strong>Diabetes duration as a categorical variable</strong></td>
<td>-: n= 1; CO: 10 years (5)</td>
<td>-: n= 1; CO: 10 years (4)</td>
<td>-: n= 1; CO: 10 years (7)</td>
<td>+: n= 1; CO: 5 years (4)</td>
<td>+: n= 1; CO 10 years (5)</td>
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<tr>
<td><strong>Blood sugar monitoring</strong></td>
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<td>-: n= 1 (2)</td>
<td>NA</td>
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<tr>
<td><strong>Fasting blood glucose</strong></td>
<td>+: n= 1 (13)</td>
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<td>-: n= 2 (2, 4)</td>
<td>+: n= 1 (13)</td>
<td>-: n= 2 (2, 4)</td>
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<tr>
<td><strong>HbA1C as a continuous variable</strong></td>
<td>+: n= 3 (10, 11, 13)</td>
<td>-: n= 2 (2, 4)</td>
<td>+: n= 2 (4, 8)</td>
<td>+: n= 1 (15)</td>
<td>-: n= 2 (2, 4)</td>
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<tr>
<td><strong>HbA1C as a categorical variable</strong></td>
<td>+: n= 1; CO: 7 (4)</td>
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<td>-: n= 1; CO 9 (7)</td>
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### MACRO-VASCULAR COMPLICATIONS

| Any macro-vascular complication | NA | NA | NA | NA | +++: n= 1 (5) |
| Stroke | NA | -: n= 1 (5) | NA | NA | +: n= 1 (12) |
| Myocardial infarction | +: n= 1 (12) | NA | NA | NA | -: n= 1 (4) |
| Angina pectoris | NA | NA | NA | NA | -: n= 1 (5) |
### MICRO-VASCULAR COMPLICATIONS

<table>
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<th>NA</th>
<th>NA</th>
<th>NA</th>
<th>NA</th>
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<tbody>
<tr>
<td>Nephropathy</td>
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<tr>
<td>ESRD</td>
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<tr>
<td>Microalbuminuria</td>
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<td>Macroalbuminuria</td>
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<td></td>
<td></td>
<td>+: n= 1 (^{(8)})</td>
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<tr>
<td>Serum creatinine</td>
<td>+: n= 1 (^{(13)})</td>
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<td>-: n= 1 (^{(2)})</td>
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<td>Retinopathy</td>
<td></td>
<td>+: n= 2 (^{(3, 4)})</td>
<td>+: n= 2 (^{(6, 7)})</td>
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<tr>
<td>Visual acuity</td>
<td>+++: n= 2 (^{(10, 13)})</td>
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<td>Laser photocoagulation</td>
<td>+: n= 2 (^{(10, 12)})</td>
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<td>-: n= 1 (^{(7)})</td>
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### DIABETIC NEUROPATHY

<p>| Clinician diagnosed diabetic neuropathy | +: n= 1 (^{(13)}) | -: n= 2 (^{(2, 4)}) | NA | NA | NA |
| Neuropathy symptoms               | +: n= 1 (^{(13)}) | -: n= 2 (^{(2, 4)}) | NA | +++: n= 1 (^{(4)}) | NA |
| VPT hallux                        | NA | -: n= 1 (^{(5)}) | NA | NA | +: n= 2 (^{(3, 10)}) |
| VPT malleolli as a continuous variable | +++: n= 2 (^{(11, 13)}) | +: n= 1 (^{(2, 4)}) | -: n= 2 (^{(2, 7)}) | +: n= 3 (^{(1, 5, 6)}) | +: n= 5 (^{(1, 3, 6, 7, 8)}) |
| VPT malleolli as a categorical variable | +++: n= 1; CO: 25V (^{(7)}) | NA | +++: n= 1; CO 25V (^{(7)}) | +++: n= 1; CO 25V (^{(1)}) | +: n= 1; CO 25V (^{(10)}) |
| Achilles reflex                    | +: n= 3 (^{(2, 6, 10)}) | NA | -: n= 1 (^{(5)}) | -: n= 1 (^{(4)}) | -: n= 1 (^{(4)}) |
| Rotulian reflex                   | NA | -: n= 1 (^{(5)}) | NA | +: n= 1 (^{(4)}) | NA |
| SWM                              | +++: n= 4; CO 1/9 (^{(10, 13)}); CO Hallux 10 g (^{(10)}); CO NR (^{(12)}) | +: n= 1; CO 1/NR (^{(7)}) | +: n= 2; CO score 0 to 6 (^{(14)}); CO NR (^{(8)}) | +++: n= 2; CO 2/3 (^{(1)}); CO 2/8 (^{(4)}) | +: n= 3; CO 1/2 (^{(7)}); CO 1/4 (^{(5)}); CO 1/4-8 (^{(6)}) |</p>
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### FOOT DEFORMITY

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<td>Hallux rigidus</td>
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<td>Hallux limitus</td>
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<td>HAV</td>
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<td>Pes cavus and planus</td>
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</table>

### PRESSURE, SHEAR STRESS AND ACTIVITY

<table>
<thead>
<tr>
<th>Condition</th>
<th>++: n= 1</th>
<th>-: n= 1</th>
<th>+: n= 1</th>
<th>-: n= 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Callus present</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of callus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPP as a continuous variable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPP as a categorical variable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activity variability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### FISSURES

<table>
<thead>
<tr>
<th>Fissures</th>
<th>NA</th>
<th>NA</th>
<th>NA</th>
<th>(++: n = 1^{(5)})</th>
<th>NA</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinea Pedis</td>
<td>(++: n = 1^{(8)})</td>
<td>NA</td>
<td>NA</td>
<td>(++: n = 1^{(8)})</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

### PERIPHERAL VASCULAR DISEASE

<table>
<thead>
<tr>
<th>PVD</th>
<th>(+: n = 2^{[2,13]})</th>
<th>NA</th>
<th>NA</th>
<th>NA</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foot palpable pulses</td>
<td>(+: n = 3^{(3,9)})</td>
<td>NA</td>
<td>(+: n = 1^{(7)})</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>PV study</td>
<td>NA</td>
<td>(+: n = 1^{(4)})</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>PV surgery</td>
<td>(+: n = 2^{[2,3]})</td>
<td>(+: n = 1^{(7)})</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Claudication</td>
<td>(+: n = 2^{(7,16)})</td>
<td>(+: n = 1^{(7)})</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hallux-Brachial Index</td>
<td>NA</td>
<td>(+: n = 1^{(8)})</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>ABI as a continuous variable</td>
<td>(+: n = 1^{(8)})</td>
<td>(+: n = 2^{(3,4)})</td>
<td>(+: n = 3^{(5,6,7)})</td>
<td>(+: n = 3^{(1,4,5)})</td>
<td>(+: n = 2^{(2,6)})</td>
</tr>
<tr>
<td>ABI as a categorical variable</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>TcPO2 as a continuous variable</td>
<td>(+: n = 1^{(13)})</td>
<td>(+: n = 2^{(3,4)})</td>
<td>(+: n = 3^{(1,7)})</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>TcPO2 as a categorical variable</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>(+: n = 1^{1}; CO 30 \text{ mmHg}^{(1)})</td>
</tr>
</tbody>
</table>

### PREVIOUS FOOT COMPLICATIONS

<table>
<thead>
<tr>
<th>Previous foot ulcer</th>
<th>(+++: n = 2^{[12,13]})</th>
<th>(+: n = 1^{(6)})</th>
<th>NA</th>
<th>NA</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous hallux ulcer</td>
<td>(+: n = 1^{(5)})</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Previous LE amputation</td>
<td>(+++: n = 2^{[2,4]})</td>
<td>(+: n = 3^{(2,3,4)})</td>
<td>(+++: n = 1^{(7)})</td>
<td>(+: n = 1^{(3)})</td>
<td>(-: n = 1^{(2)})</td>
</tr>
</tbody>
</table>
**PREVENTIVE MEASURES**

<table>
<thead>
<tr>
<th>Preventive Measure</th>
<th>+: n= 2 (12, 20)</th>
<th>-: n= 1 (10)</th>
<th>NA</th>
<th>NA</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foot education</td>
<td>+: n= 1 (14)</td>
<td>-: n= 1 (6)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Chiropractor care</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>-: n= 2 (9)</td>
<td>NA</td>
</tr>
<tr>
<td>Multidisciplinary team</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Diabetes education</td>
<td>+: n= 1 (1)</td>
<td>-: n= 1 (1)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Dermal thermometry</td>
<td>-: n= 1 (22)</td>
<td>+: n= 2 (3, 21)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Abbreviations in alphabetical order**

Cat: categorical variable; Cont: continuous variable; CO: Cut-off; ESRD: End-stage renal disease; HAV: Hallux Abductus Valgus; HbA1C: Glycated hemoglobin; LE: lower extremity; MNCV: Motor Nerve Conduction Velocity; MNSS: Michigan Neuropathy Screening Score; n: number of studies; NA: Association not assessed between the variable and outcome in any of the included studies NDS: Neuropathy Disability Score; NR: Not Reported; NSS: Neuropathy Symptoms Score; PPP: Peak Plantar Pressure; PV: peripheral vascular; SSEPS: Short Latency Somatosensory Evoked Potentials; SWM: Semmes-Weinstein monofilament; VPT: Vibration Perception Threshold

**Symbols**

+++: variable with statistically significant association with the outcome in both univariate and multivariate analysis; ++: variable with statistically significant association with the outcome only in multivariate analysis; +: variable with statistically significant association with the outcome only in univariate analysis; --: variable with no statistically significant association with the outcome in both univariate and multivariate analysis; -: variable with no statistically significant association with the outcome only in univariate analysis

**Table references**


c. FOOT ULCER RISK STRATIFICATION SYSTEMS: STUDIES’ DESCRIPTION

In our SR we retrieved 5 stratifications systems, discussed in 11 papers:

1. University of Texas Foot Risk Stratification (UTFRS)
2. International Working Group on Diabetic Foot (IWGDF)
3. Scottish Intercollegiate Guideline Network (SIGN) Risk Assessment
4. American Diabetes Association (ADA)
5. Boyko et al

A detailed analysis of each stratification system will be performed through this segment.

In a previous review (Singh et al, 2005) it was reported that 3 more groups proposed foot ulcer risk stratifications systems (although their effectiveness was never assessed): the United States Veterans Health Agency and Department of Defence, the Collaborative Group from the United Kingdom and the American College of Foot and Ankle Surgeons. The first 2 were not available in full text version. The last group used the IWGDF classification.

In the studies where crude data was not expressed it was requested to authors. (Boyko et al, 2006; Lavery et al, 1998, 2008) Unfortunately, it was not possible to retrieve them.

Examining table 4, which expresses the variables included in each stratification system, we recognize that almost all have the same core variables: DN, PVD, foot deformity, previous ulcer and previous lower extremity amputation.

The stratification system proposed by Boyko and colleagues (Boyko et al, 2006) was the only one including HbA1C, which we believe it is of prime importance.

All stratification systems stand just about in the same evidence level: first systems’ or respective modification effectiveness evaluation.

The study with the biggest sample size was Leese 2006 et al (Leese et al, 2006). Boyko 2006 and associates (Boyko et al, 2006) had the longest follow-up. (See table 5)

With the STROBE checklist, the 2001 Peters’ et al and the 2006 Boykos’ et al studies had the best scores (both with 18 points out of 22). With the READER checklist proposal it was the Lavery 1998 (Lavery et al, 2008) study that had the highest score (20 points out of 29). (See table 5)

It was only possible to calculate the diagnostic accuracy measures in 2 studies: Peters et al, in 2001, evaluating the effectiveness of an IWGDF stratification system modification and Leese et al, in 2006, assessing a modification of the SIGN stratification system. (See table 5)

Comparing both systems, the SIGN stratification showed a significantly higher validity value analyzing the patients in the highest risk group. However, in all the other measures and evaluating the subjects in moderate and high risk groups the statistical significance is lost. (See table 6)

In the Boyko and colleagues study (Boyko et al, 2006), only the AUC and cut-off values are available, which does not allow a direct comparison between the other stratification systems’ effectiveness.
### TABLE 4: VARIABLES INCLUDED IN THE DIVERSE STRATIFICATION SYSTEMS

<table>
<thead>
<tr>
<th>Variables</th>
<th>DN</th>
<th>PVD Foot deformity</th>
<th>Previous ulcer</th>
<th>Previous amputation</th>
<th>Visual Impairment</th>
<th>Physical Impairment</th>
<th>HbA1C</th>
<th>Callus</th>
<th>Tinea Pedis</th>
<th>Onychomycosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTRFS</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IWGDF</td>
<td>O/R</td>
<td>O/R</td>
<td>O/R</td>
<td>O/R</td>
<td>O/R</td>
<td>O/R</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIGN</td>
<td>O/R</td>
<td>O/R</td>
<td>O/R</td>
<td>O/R</td>
<td>O/R</td>
<td>O/R</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADA</td>
<td>O/R</td>
<td>O/R</td>
<td>O/R</td>
<td>O/R</td>
<td>O/R</td>
<td>O/R</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boyko et al</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

O: Present in the Original stratification, R: Present in the Revised stratification

### TABLE 5: STRATIFICATION SYSTEMS STUDIES’ CHARACTERIZATION AND CLASSIFICATION

<table>
<thead>
<tr>
<th>Articles</th>
<th>Stratification</th>
<th>Creation method</th>
<th>Step</th>
<th>Sample size (n)</th>
<th>Mean Follow-up</th>
<th>Ulcer prevalence (%)</th>
<th>STROBE score</th>
<th>READER score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lavery et al, 1998</td>
<td>UTRFS</td>
<td>Logistic regression model</td>
<td>Derivation</td>
<td>225</td>
<td>Cross-sectional</td>
<td>34</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Apelqvist et al, 2000</td>
<td>IWGDF</td>
<td>International Consensus</td>
<td>Description</td>
<td>NAp</td>
<td>Nap</td>
<td>NAp</td>
<td>NAp</td>
<td>NAp</td>
</tr>
<tr>
<td>Peters et al, 2001</td>
<td>IWGDF</td>
<td>International Consensus</td>
<td>Modification proposal and evaluation</td>
<td>213</td>
<td>30 months</td>
<td>25</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Lavery et al, 2008</td>
<td>IWGDF</td>
<td>International Consensus</td>
<td>Modification proposal and evaluation</td>
<td>1666</td>
<td>27 months</td>
<td>15</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Apelqvist et al, 2008</td>
<td>SIGN</td>
<td>Literature review</td>
<td>Description</td>
<td>NAp</td>
<td>Nap</td>
<td>NAp</td>
<td>NA</td>
<td>NAp</td>
</tr>
<tr>
<td>SIGN, 2001</td>
<td></td>
<td></td>
<td>Description</td>
<td>NAp</td>
<td>Nap</td>
<td>NAp</td>
<td>NA</td>
<td>NAp</td>
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<tr>
<td>Leese et al, 2006</td>
<td>SIGN</td>
<td>Literature review</td>
<td>Modification proposal and evaluation</td>
<td>3526</td>
<td>20 months</td>
<td>5</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Mayfield et al, 2003</td>
<td>ADA</td>
<td>Literature review</td>
<td>Description</td>
<td>NAp</td>
<td>Nap</td>
<td>NAp</td>
<td>NAp</td>
<td>NAp</td>
</tr>
<tr>
<td>Mayfield et al, 2004</td>
<td>ADA</td>
<td>Literature review</td>
<td>Modification proposal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boulton et al, 2008 a</td>
<td>ADA</td>
<td>Literature review</td>
<td>Modification proposal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boulton et al, 2008 b</td>
<td>ADA</td>
<td>Literature review</td>
<td>Modification proposal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boyko et al, 2006</td>
<td>Logistic regression model</td>
<td>Derivation</td>
<td>1285</td>
<td>40 months</td>
<td>17</td>
<td>18</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

NAp: Not applicable
## TABLE 6: DIAGNOSTIC ACCURACY MEASURES CALCULATION OF EACH FOOT ULCER RISK STRATIFICATION SYSTEM

<table>
<thead>
<tr>
<th>Measures/Stratifications</th>
<th>Groups</th>
<th>Sensitivity (IC 95%)</th>
<th>Specificity (IC 95%)</th>
<th>LR+ (IC 95%)</th>
<th>LR- (IC 95%)</th>
<th>PPV (IC 95%)</th>
<th>Validity (IC 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTRFS</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NA</td>
</tr>
<tr>
<td>IWGDF</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Apelqvist et al, 2000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IWGDF 3</td>
<td>74</td>
<td>62-86</td>
<td>86</td>
<td>5.35</td>
<td>0.30</td>
<td>64</td>
<td>83</td>
</tr>
<tr>
<td>Peters et al, 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IWGDF 3+2</td>
<td>87</td>
<td>78-96</td>
<td>58</td>
<td>2.10</td>
<td>0.22</td>
<td>NA</td>
<td>66</td>
</tr>
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<td>Lavery et al, 2008</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NA</td>
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<tr>
<td>Apelqvist et al, 2008</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td>SIGN 2001</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>SIGN 3</td>
<td>84</td>
<td>79-90</td>
<td>90</td>
<td>8.41</td>
<td>0.17</td>
<td>31</td>
<td>90</td>
</tr>
<tr>
<td>Leese et al, 2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Boyko et al, 2006</td>
<td>ROC Curve</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>81</td>
</tr>
</tbody>
</table>

NP: Not possible with the available data; NA: Not applicable (Only foot ulcer risk stratification system description)
This stratification system was described for the first and only time in 1998, by Lavery and colleagues, in a transversal case-control study. Two hundred and thirteen (213) subjects with diabetes were enrolled: 76 (cases) with a present or recently healed (< 4 weeks) foot ulcer and 149 (controls) without active or previous foot ulcer.

First, the association between foot ulceration and several variables was evaluated through univariate analysis. They observed that male gender, diabetes duration longer than 10 years, subjective symptoms of neuropathy, loss of protective sensation, increased plantar pressure, foot deformity, limited joint mobility, lower extremity amputation or bypass, concomitant nephropathy, retinopathy and poor glucose control were significantly associated with foot ulceration. However, using a stepwise logistic regression model to assess possible interactions between variables, several variables were no longer significant: limited joint mobility, lower extremity bypass, concomitant nephropathy and retinopathy.

Next, they analyzed the cumulative risk associated with the significant variables more frequently available in daily practice: loss of protective sensation, foot deformity and ulcer or amputation history - which resulted in the following stratification system.

**TABLE 7: UTRFS RISK STRATIFICATION SYSTEM**

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Definition</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Intact protective sensation</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Loss of protective sensation, no deformity, and no history of ulceration or amputation</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Loss of protective sensation and deformity, but no history of ulceration or amputation</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Loss of protective sensation, deformity, plus a history of ulceration or amputation</td>
<td></td>
</tr>
</tbody>
</table>

For each added variable the cumulative risk enlarged. For category 1 the odds ratio for foot ulceration was 1,7 (CI 95% 0,7-4,3), for category 2 was 12,1 (CI 95% 5,2-28,3) and for category 3 was 36,4 (CI 95% 16,1-82,3) in comparison with category 0 (reference category).

Loss of protective sensation was evaluated using a Biothesiometer. A vibration perception threshold superior to 25V indicated peripheral sensory neuropathy. PVD was assessed through Rose Intermittent Claudication Scale, absence of palpable dorsalis pedis and posterior tibial pulses, transcutaneous oxygen tension and the ankle-brachial systolic blood pressure index. None of these variables were considered significant neither in univariate nor in multivariate analysis.

It was not possible to calculate any diagnostic accuracy measures due to a lack of a cross-tabulation with the number of cases and controls in each risk stratification group and to retrieve them when contacting the article’s first author (Dr. Lavery).
The IWGDF stratification differs from previous systems as it was created through consensus involving 45 expert clinicians and researchers from varied areas of work, from 23 countries. (Apelqvist et al, 2000; Peters et al, 2001)

APELQVIST, 2000 AND 2008

Although they have an 8 year interval, both papers are very similar with only minor differences. In both articles, the following risk stratification system is described:

**TABLE 8: IWGDF ORIGINAL DIABETIC FOOT RISK STRATIFICATION SYSTEM**

(Apelqvist et al, 2000; 2008)

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Without sensory neuropathy</td>
</tr>
<tr>
<td>1</td>
<td>Sensory neuropathy</td>
</tr>
<tr>
<td>2</td>
<td>Sensory neuropathy and/or foot deformities or bony prominences and/or signs of peripheral ischemia and/or previous ulcer or amputation.</td>
</tr>
</tbody>
</table>

They recommend the use of the 10 g SWM, tuning fork and/or cotton wisp for the detection of sensory neuropathy. (Apelqvist et al, 2000, 2008) However, to our knowledge, there is no study analyzing the cotton wisp ability to perform such diagnostic and the use of just one or three tests simultaneously present different diagnostic accuracy values.

This stratification system, as it is, was never validated for the prediction of foot ulcer development. In 2001, its effectiveness was evaluated though already with small modifications. (Peters et al, 2001)

PETERS, 2001

In a prospective cohort study with 213 subjects followed for a mean period of 30 months, the following stratification system (see table 5) was evaluated for the prediction of diabetic foot ulceration, this is, skin lesions distal to the ankle:

**TABLE 9: IWGDF DIABETIC FOOT RISK STRATIFICATION SYSTEM**

(Peters et al, 2001)

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Without neuropathy</td>
</tr>
<tr>
<td>1</td>
<td>Neuropathy but without foot deformity or PVD</td>
</tr>
<tr>
<td>2</td>
<td>Neuropathy and with foot deformity or PVD</td>
</tr>
<tr>
<td>3</td>
<td>History of foot ulceration or a lower-extremity amputation</td>
</tr>
</tbody>
</table>

PVD: Peripheral vascular disease

In this study, subjects with previous amputation due to an ulcer were excluded.

With this stratification system, in the higher risk groups there was a statistically significant increase in ulcerations and amputations ($X^2 p<0.001$). Subjects in group 3 (higher risk) were 34,1 (IC 95% 11,0-105,8) times more prone to foot ulcer occurrence, during the follow-up period. (Peters et al, 2001) Although this results indicate a good effectiveness, no diagnostic accuracy measures were reported although it was possible to calculate them. (See table 6)
Neuropathy was defined as one or more insensitive sites to the 10 g Semmes Weinstein monofilament or a vibratory perception threshold superior to 25V (with a Biothesiometer). (Peters et al., 2001) A ABI inferior to 0.8 or any non-palpable pedal pulsation was defined as PVD. (Peters et al., 2001)

It is important to highlight, that in daily clinic practice the ankle brachial index is infrequently performed due to material and training costs. Additionally, due to the frequent arterial calcifications in patients with diabetes its results are often deceiving. (Leese et al, 2006)

The Biothesiometer is not commonly available due to its cost. However, the authors stressed that a 128 Hz can be used as an alternative, alleging good correlation (based on a single study). (Peters et al, 2001)

Peters and colleagues proposed a subdivision in group 3, separating into different subgroups those with history of foot ulceration from those with history of lower-extremity amputation.

LAVERY, 2008

In 2008, Lavery and colleagues included this modification in the stratification system and also proposed a subdivision for group 2, expressed in the following table:

**TABLE 10: IWGDF REVISED DIABETIC FOOT RISK STRATIFICATION SYSTEM**

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Without neuropathy or PVD</td>
</tr>
<tr>
<td>1</td>
<td>Neuropathy but without foot deformity or peripheral vascular disease</td>
</tr>
<tr>
<td>2A</td>
<td>Neuropathy and foot deformity, no PVD</td>
</tr>
<tr>
<td>2B</td>
<td>PVD</td>
</tr>
<tr>
<td>3A</td>
<td>History of foot ulceration</td>
</tr>
<tr>
<td>3B</td>
<td>Lower-extremity amputation</td>
</tr>
</tbody>
</table>

PVD: Peripheral vascular disease

This prospective cohort study included 1666 consecutive subjects followed for an average of 27 months. (Lavery et al, 2008) An increase in the group risk was associated with more foot ulcerations (X^2 for association and trend p< 0.001) and more complications were observed in group 2B in comparison with 2A (p<0.001). (Lavery et al, 2008)

For group 1 the odds ratio for foot ulceration was 2.4 (IC 95% 1.1-5.0), for group 2A was 1.2 (IC 95% 0.8-2.7), for group 2B was 9.3 (IC 95% 5.7-15.2), for group 3A was 50.5 (IC 95% 30.5-87.0) and for category 3B was 52.7 (IC 95% 27.2-98.0) in comparison with category 0 (reference category). (Lavery et al, 2008) No diagnostic accuracy measures were calculated and due to lack of data their determination is impossible.

Foot ulcer defined a full-thickness wound involving the foot or ankle. (Lavery et al, 2008)

Neuropathy was assessed using the 10 g Semmes Weinstein monofilament and the Biothesiometer, although it is not expressed how the diagnostic is made. (Lavery et al, 2008) One non-palpable foot pulse and an ankle brachial index inferior to 0.8 indicated PVD. (Lavery et al, 2008)
This stratification system was created, in parallel time with the IWGDF, through an evidence-based SR performed by a multidisciplinary group, although methodology and results are poorly detailed. Such SR resulted in the following stratification system:

**TABLE 11: SIGN STRATIFICATION SYSTEM AND RESPECTIVE GENERAL RECOMMENDATIONS**

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Definition</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>Normal Sensation AND good pulses, no previous ulcer, no foot deformity AND normal vision</td>
<td>No specific regular chiropody input needed (except in exceptional circumstances) Annual foot check</td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>Loss of sensation OR absent pulses (or previous vascular surgery) OR significant visual impairment OR physical disability</td>
<td>Regular (4-12 weekly) general chiropody input advised.</td>
</tr>
<tr>
<td>High Risk</td>
<td>Previous ulcer due to neuropathy/ischemia OR Absent pulses and neuropathy OR callus with risk factor (neuropathy, absent pulse, foot deformity) OR previous amputation</td>
<td>Chiropodist with interest and expertise in diabetes</td>
</tr>
<tr>
<td>Active Foot Disease</td>
<td>Active foot ulceration, painful neuropathy</td>
<td>Suggest making contact with local specialist</td>
</tr>
</tbody>
</table>

It also revealed that the available evidence goes from expert opinion for the importance and regularity of foot examination to only well-conducted case control or cohort studies with a low risk of confounding or bias for the importance and diagnostic of diabetic peripheral neuropathy and vascular insufficiency. *(SIGN, 2001)*

This stratification system was never validated in this form. In 2006, Leese and colleagues validated it with slight modifications in a prospective cohort study.

**TABLE 12: REVISED SIGN STRATIFICATION SYSTEM**

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>Able to detect at least one pulse per foot AND able to feel 10g monofilament AND no foot deformity, physical or visual impairment</td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>Unable to detect both pulses in a foot OR unable to feel 10g monofilament OR foot deformity OR unable to see or reach the foot</td>
</tr>
<tr>
<td>High Risk</td>
<td>Previous ulceration or amputation OR Absent pulses AND unable to feel 10 g monofilament OR one of above with callus or deformity</td>
</tr>
</tbody>
</table>

In sum, subjects with no risk factors were considered at low risk of foot ulcer occurrence, subjects with one risk factor at moderate risk and subjects with two or more risk factors or with foot ulcer history at high risk. *(Leese et al, 2006)*

In this study peripheral neuropathy was detected through the 10g Semmes-Weinstein monofilament. The inability to feel the monofilament on more than 1 of 10 pre-defined sites was considered as altered sensation. *(Leese et al, 2006)*

This study was the only one, in this review, assessing the inter-observer agreement of a stratification system in 50 subjects by 2 healthcare professionals, resulting in a kappa value of 0,95. *(Leese et al, 2006)* It was also the single one calculating diagnostic accuracy measures. The main quality of this stratification system is to identify the subjects at really low risk of developing a foot ulcer, this is, those categorized in the low risk group had a 99,6% (CI 95% 99,5-99,7) probability of not developing a foot ulcer during follow-up. *(Leese et al, 2006)*
This stratification system was created through a literature review (Mayfield et al, 2003, 2004), although we could not access to the full text article where methods and detailed results are expressed. Initially, some variables were recognized as related with foot ulcer development and whoever presented any of these conditions was considered as a high-risk patient.

**TABLE 13: ADA STRATIFICATION SYSTEM AND RESPECTIVE GENERAL RECOMMENDATIONS**

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Definition</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>No risk for foot ulcer</td>
<td>Frequent evaluation, reinforce patient education, foot inspection by professional in every appointment</td>
</tr>
<tr>
<td>High Risk</td>
<td>Peripheral neuropathy, altered biomechanics, evidence of increased pressure, bony deformity, peripheral vascular disease, history of ulcers or amputation and/or severe nerve pathology</td>
<td></td>
</tr>
</tbody>
</table>

In 2008 a modification was proposed. Using the same variables, Boulton and colleagues, proposed a stratification system grading by estimated cumulative risk:

**TABLE 14: REVISED ADA STRATIFICATION SYSTEM AND RESPECTIVE GENERAL RECOMMENDATIONS**

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Definition</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No risk for foot ulcer</td>
<td>Patient education, follow-up annually</td>
</tr>
<tr>
<td>1</td>
<td>Loss of protective sensation (LOPS) and/or foot deformity</td>
<td>Consider prescriptive footwear, prophylactic surgery for foot deformity, continue education, follow-up every 3-6 months</td>
</tr>
<tr>
<td>2</td>
<td>PVD and/or LOPS</td>
<td>Consider prescriptive footwear, consider vascular consultation, follow-up 2-3 months</td>
</tr>
<tr>
<td>3</td>
<td>History of ulcer or amputation</td>
<td>Same as category 1, consider vascular consultation if PAD present, every 1-2 months</td>
</tr>
</tbody>
</table>

DN screening was recommended using the 10g Semmes Weinstein monofilament and one other test: 128 Hz tuning fork, pinprick sensation, ankle reflex or vibration perception threshold. An altered result in one or more tests suggests lost of protective sensation. (Boulton et al, 2008 a, 2008 b) The absence of the posterior tibial and/or dorsalis pedis pulses indicated PVD. (Boulton et al, 2008 a, 2008 b)

However, none of the ADA stratification systems were validated for the prediction of ulcer development. (Peters et al, 2003) This stratification system was described in 4 articles. Nonetheless the Mayfield 2003 and Mayfield 2004 (Mayfield et al, 2003, 2004), published in Diabetes Care, are identical, as with both articles published by Boulton and colleagues in 2008, in Diabetes Care and Endocrine Practice. (Boulton et al, 2008 a, 2008 b)
In this study, 1285 veterans were prospectively followed over more than 3 years with re-evaluations at 12 to 18 months, to study “individual and combined effects of commonly available clinical information in the prediction of diabetic foot ulcer occurrence” in order to create a logarithmic model. (Boyko et al, 2006)

Several available and pertinent variables were assessed at baseline: age; race; weight; current smoking; diabetes duration and treatment; HbA1C; visual acuity; history of laser photocoagulation treatment, foot ulcer, and amputation; foot shape; claudication; foot insensitivity to the SWM; foot callus; pedal edema; hallux limitus; tinea pedis; and onychomycosis.

Using a Cox proportional hazard regression, the association between baseline subjects’ variables and foot ulcer occurrence was evaluated through univariate and multivariate analysis, which resulted in the following score equation:

\[
\text{Score} = \text{HbA1C} \times 0.0975 + \text{DN present} \times 0.7101 + (\text{poor vision}) \times 0.3888 + (\text{tinea pedis present}) \times 0.3206 + (\text{onychomycosis present}) \times 0.4579 + (\text{past history of foot ulcer}) \times 0.7784 + (\text{past history of lower limb amputation}) \times 0.943\]

A subject with a resultant score inferior to 1.48 at the lowest risk group for foot ulceration, with a score between 1.48 to 1.99 at the next to lowest risk, between 2.00 to 2.61 at the next to highest risk and with a score superior to 2.62 at the highest risk group. (Boyko et al, 2006)

This was the only study that included HbA1C as a predictive variable and that assessed the stratification systems’ ability to predict foot ulcer occurrence through a ROC curve at 1 and 5 years from the start of follow-up, resulting in AUCs of 0.81 and 0.76 respectively. (Boyko et al, 2006)

Analyzing the ROC curve, at 1 year, a specificity of 86% corresponds to a 60% sensitivity; while a 80% sensitivity corresponds to a 60% specificity. (Boyko et al, 2006) Nevertheless, it was not possible to calculate any other diagnostic accuracy measures for the different groups or the AUC confidence intervals due to lack of data.

Foot ulcer was defined as a full-thickness skin defect that needed more than 14 days to heal. (Boyko et al, 2006) DN was diagnosed applying a 10 g Semmes Weinstein monofilament in nine sites in each foot. Insensitivity in one or more sites indicated altered sensation. (Boyko et al, 2006) In this stratification system, PVD was not considered, only the presence of claudication. (Boyko et al, 2006)
4. DISCUSSION

a. PREDICTIVE VARIABLES

Various studies affirmed that diabetic foot examinations in general practice and in hospitalized patients is uncommon and unsatisfactory. This may be partly due to an inaccurate comprehension of which variables to incorporate in the regular screening. (Lavery et al, 1998) We believe that to change that fact a SR creating a list of all the possible predictors of foot ulceration is essential.

With such SR, we found that there is considerable evidence available about the association between isolated variables and foot ulcer development (however with several drawbacks).

The reported prevalence of foot ulcer development in the retrieved studies varies greatly. Only 2 studies included only patients with no active, recently healed or past foot ulcer history. In the Abbott et al study (Abbott et al, 1998) the outcome’s prevalence was of 7,2% while in the Kästenbauer and collaborates (Kästenbauer et al, 2001) was of 5%. The inclusion criteria were not well defined in the Caselli et al and Calle-Pascual et al studies. (Calle-Pascual et al, 2001; Caselli et al, 2002)

In the remaining studies, the foot ulcer rate varied from 2,1% (Margolis et al, 2008) to 37,3% (Carrington et al, 2002). While foot ulcer recurred in 15,5 (Lemaster et al, 2003) to 60,5% (Peters et al, 2001) of the patients. The foot ulcer history prevalence fluctuated from 10,4 (Vosien et al, 2008), in a community based study, up to 57,9% (Lott et al, 2008).

The most frequently assessed variables were age, gender, BMI, diabetes duration, HbA1C, VPT at malleolli and SWM. Of the more than 100 variables assessed, the presence of nephropathy; DN diagnosed with VPT at malleolli, Achilles reflex, SWM, tuning fork, thermal sensitivity or MNCV; edema; use of therapeutic footwear; rigid toe deformity, hallux rigidus, abnormal foot shape, limited STJ and 1st MPJ mobility; presence of callus and tinea pedis; absent foot palpable pulses, previous foot ulcer, previous LE amputation and dermal thermometry were significantly and consistently associated with foot ulcer development in more than one study. (See table 3)

Nonetheless, we must highlight that the association between each predictive variable and foot ulcer development was assessed only by 2 or less studies in 82% of the cases, with foot ulcer recurrence or re-ulceration in 95%, with active or recently healed foot ulcer in 86%, with active or past foot ulcer in 93% and with foot ulcer history in 91% of the cases. This underlines the striking necessity of more research in this field. (See table 3)

Most of the retrieved studies were observational. Conversely, half of them were RCT or well conducted prospective cohort studies which represent a reasonably high evidence level and the reporting quality, assessed through the respective checklists, was moderate. In the observational studies, evaluated with the STROBE checklist, a higher disparity was verified (from 7 up to 21 points).

One of the most important results of this SR is that a foot ulcer definition is absent in 47% of the retrieved studies and that the 32 remaining studies presented around 20 different definitions.

Several variables presented different cut-offs which turned difficult their analysis and standardization (eg. foot pulses, VPT, SWM, PPP…) and can be considered as a shortcoming.
These different definitions, cut-offs and results demonstrate that there is still a long work to be done for a universal language and research standardization. One of the ex-libris and more important variables with this setback is SWM. One systematic review, evaluating this test diagnostic accuracy for DN (using MNCV as gold-standard) concluded that little can be said due to a lack of methodologically adequate studies and future research must be made to define the best procedure and threshold (Dios et al, 2009) and other (Feng et al, 2009) even affirms that in the original studies the selection of the number and sites of application seemed arbitrary.

On the other some frequently discussed variables were not addressed in any study, such as physical impairment, cotton-wisp test, pinprick test, neuropad, stasis signals, Rose criteria for PVD detection, etc.

In addition, one can observe a great void in foot ulcer development preventive measures’ impact research – a extremely important thematic. Less than 10 studies evaluated the association between foot ulcer development and therapeutic footwear, foot education, chiropodist care, multidisciplinar team care, diabetes education and dermal thermometry altogether.

One of the limitations that can be pointed to this review is the fact that articles that needed to be purchased were excluded (n=8). On the other hand, primary and secondary authors were contacted requesting those missing articles and this research had no financial support.

Another weakness of this study is the fact that the quality assessment, data analysis and extraction were performed only by one reviewer (Matilde Monteiro-Soares).

A previous meta-analysis [Crawford et al, 2007] performed included only 16 studies. This can be explained by the fact that their original search retrieved 1752 articles (in comparison to 2094 in ours) and they included only studies where all subjects were free of active foot ulceration. Although these studies may present a blinding bias we believed that their results should be reported. Additionally, we believe that for now a meta-analysis cannot effectively translate all the evidence available due to the outcome selection and definition, variables measurements and respective cut-offs and study methodology disparities.

The results of this SR emphasize that a small amount of easy to collect variables can be used in the regular diabetic foot screening exam. A complete exam can be made through a simple questionnaire around diabetic complications, a foot observation, the application of one or more DN tests and foot pulses palpation. However, some of the assessed variables are more difficult to collect due to excessive time or capital costs: VPT, thermal sensitivity and dermal thermometry.
b. STRATIFICATION SYSTEMS

Stratification systems are an essential tool to classify patients according to a cumulative risk for foot ulcer development category and consequently to distribute the limited existing resources to those at most need (Frykberg et al, 2006; Lavery et al, 1998; Leese et al, 2006). Doing so diminishes the unreasonably high level of foot related morbidity. (Boulton et al, 2008 a, 2008 b) However, no system was unanimously adopted (Frykberg et al, 2006) and their implementation in clinical practice is scarce (Leese et al, 2006).

From the proposed variables included in the different stratification systems (HbA1C, visual acuity, DN, onyihcomycosis, tinea pedis, callus, PVD, physical impairment, previous foot ulcer and previous amputation) almost all tended to be associated with foot ulcer development in our SR. Only HbA1C, callus and ABI did not show a statistical significance in all studies and physical impairment was not assessed in any of them. (See table 3)

On the other hand, there is a lack of articles applying these results into stratification systems.

Only 5 stratification systems were retrieved and it was possible to determine the effectiveness in 3 of them through diagnostic accuracy measures.

The UTRFS stratification system study did not allow calculation of diagnostic measures. This is a transversal case-control and therefore has a very low evidence level and has some possible bias. We believe that having as outcome the presence or recently healed ulcer (without a definition) could represent a blinding bias and that the sample size could be insufficient. This study assessed, in univariate analysis, the association between 27 different variables with ulceration in a sample of 213 subjects. However, according to recommendations one needs to include 10-15 subjects for each variable analyzed, meaning in this case a sample of 270 to 405 subjects. Another disadvantage of this classification is the diagnosis of peripheral neuropathy with a Biothesiometer, which is an expensive and unavailable instrument in the daily clinic.

We have retrieved 4 articles related to the IWGDF stratification system, 2 describing it and 2 evaluating its effectiveness. However, each study presents modifications (without statistical fundamentation), which maintains this stratification in the fourth evidence level. On the other hand, ulcer definition and diagnosis of DN and PVD are somewhat different in each study.

The SIGN stratification system was validated in a prospective cohort of 3526 subjects. It is based on 8 easy to use and inexpensive variables and has great value on detecting those who will not develop a foot ulcer.

Comparing the IWGDF stratification system with the one proposed by the SIGN group, one can observe that the last presents a significantly higher LR+ for the prediction of foot ulcer development in the high with the moderate risk group and a significantly higher validity in the high risk group. On the other parameters, no statistical significant difference occurred. However, we must highlight that this results were retrieved from 2 different populations.

The ADA stratification system was never validated for foot ulcer development, only for amputations. (Peters et al, 2001) However, the variables included are the same of the IWGDF.
All of these stratification systems studies are reasonably well conducted and have great value in the prediction of foot ulcer development. However, none of them has passed to external validation which grounds them to almost the same evidence level (level 4). On the other hand, due to lack of data and to concept differences (AUC (Boyko et al., 2006) versus diagnostic measures for static groups (Leese et al., 2006; Peters et al., 2001) the results between the IWGDF and SIGN stratification systems with Boyko’s are unfeasible to compare. (Ling, et al., 2003)

We have selected the Boyko et al system for validation due to several reasons.

First, we believe that the inclusion of the HbA1C variable (despite the evidence discrepancy) is of major importance and that all the included variables were carefully well defined and intentionally selected those easier to collect, inexpensive and usually available in daily practice. Moreover, only Boyko and coworkers (Boyko et al., 2006) and Lavery and coworkers (Lavery et al., 1998) have selected which variables to include through statistical methods in spite of consensus (which always involve subjective values and therefore are considered as a lower evidence level).

Second, this stratification systems assigns, as with the majority of CDRs, a score to the presence of each variable associated with foot ulcer development which allows an impact evaluation of each variable (versus a group of variables) in the resulting risk degree. This property is crucial for the patients’ education, awareness and for a focused prevention planning by health professionals.

Third, it was the study with the longest follow up period and the only one including the time factor in their analysis, assessing the stratification system effectiveness at 1 and 5 years, and reporting their results under an AUC form; which is considered as the best way to express a model’s discriminatory ability (Reynolds, 2001).

And last, due to a personnel interest on the development and optimization of logarithmic predictive models.
IV. EXTERNAL VALIDATION AND OPTIMIZATION OF A MODEL FOR PREDICTING FOOT ULCERS IN PATIENTS WITH DIABETES
A. \textit{INTRODUCTION}
Even though not all diabetic foot complications can be prevented, a significant reduction is possible through an appropriate evidence-based preventive programme. (Frykberg et al, 2006)

Prevention is the key element to avoid ulcers, ulcer recurrence and, in last instance, lower extremity amputation. Actually, guidelines consider essential to include a direct and sustained follow-up, patients’ and its family education, treatment of non-ulcerative lesions and an early discrimination of feet at risk. (Apelqvist et al, 2000; Peters et al, 2001) Being the last essential to plan the prevention program and establish the usually limited resource allocation. (Lee et al, 2006)

In the background (Chapter III, section A) it was strongly stressed that CDRs are one of the most effective ways of translating original research results into daily clinical practice. (Beattie et al, 2006) CDR’s, under the foot ulcer risk stratification system form, allow us to analyze the impact of each variable present in the ulcer development pathophysiology as well as the effect of their modifications on ulceration risk, which represents a key stone for a well structured preventive programme. (Crawford et al, 2007)

Several risk stratification systems were proposed. But, by the reasons explicated in the previous section we have developed a particular interest in the system proposed by Boyko et al, in 2006 (Boyko et al, 2006). (Chapter III, section B)

The authors developed a risk stratification model to predict foot ulceration in diabetic patients, using seven commonly available variables, with good results. However, to our knowledge, no external validation of the model was performed. Thus the aims of this study were to validate and to optimize the diagnostic accuracy of the model mentioned above in a different population from the original study.

To assure a correct methodology in the development of this study, we have used the stepwise and checklist for the reporting and assessment of CDRs proposed in the chapter III (section A) of this thesis.
B. MATERIAL AND METHODS
1. TYPE OF STUDY AND SELECTION OF PARTICIPANTS

We conducted a retrospective cohort study on all patients with diabetes attending to the Podiatry section of a Diabetic Foot Clinic, at a public northern tertiary Hospital in Portugal (in Vila Nova de Gaia), from February 2002 to October 2008. Patients (n=435) were previously diagnosed with diabetes and classified as type 1 or 2 according to the World Health Organization (WHO) criteria.

Patient exclusion (n=75) was due to inability to walk, incomplete data and/or less than 3 appointments in Podiatry.

This study has been approved by the Ethic Committee of the referred institution.

2. DATA COLLECTION METHODS

During the first Podiatry’s appointment all variables were assessed and registered through a structured interview and thorough foot examination, performed by 2 podiatrists (with 10 and 6 years of experience in evaluating diabetic foot) not included in the Boyko’s and colleagues derivation process. Predictive and outcome variables were then collected from the patients’ clinical files until May 2009. No adverse events occurred due to any part of the study.

A. VARIABLES PRESENT IN BOYKO’S ET AL STUDY

Original prediction model variables (HbA1C, visual impairment, monofilament insensitivity, tinea pedis, onychomycosis and history of foot ulcer and/or amputation) were collected in the following way:

- We collected the HbA1C value closest to the date of the first appointment (median time: 2 months, range: 0 to 3 months).

- In Boyko’s study visual impairment was assessed using a Snellen chart. In the present study, this condition was assessed only through interview and subjectively analyzing the patient ability to inspect his own feet. If the subject affirmed that he could not perform by himself the regular foot care and exam due to visual inability and/or presented lesions caused by improper nail trimmer, he was considered as visual impaired. Although this is not the most correct form of collecting this variable it was the only way possible due to impossibility of ophthalmologic observation and to the study retrospective character.

- Sensory testing was evaluated, with the patient’s foot supported, applying the SWM perpendicularly and briefly (for approximately 2 seconds), in 4 non-queratotic points of each foot: hallux, 1st, 3rd and 5th metatarsal heads. The patient was asked, while he/she was with his/her eyes closed, if he/she felt the filament. A negative answer to one or more applications was classified as altered sensation. As one can see in the foot ulceration predictive variables RS, there is a very low consistence in the sensory testing procedure and there is no selected standard method. We have chosen this cut-off, proposed by Smieja et al, since it presented 94% accuracy for the detection of patients with abnormal 16-site monofilament examination – developing this way a shortened version for this examination. On the other hand, the sites were selected based on the literature and resulting most common ulceration locations.
• Tinea pedis and onychomycosis presence was assessed during foot examination.

• History of previous ulcer and/or foot amputation history were collected through patients’ clinical history and foot evaluation.

Variables that were analyzed in the original study but not included in the final model were also collected. Demographic data (age and sex); diabetes type, treatment and duration; smoking habits; the presence of intermittent claudication and previous laser photocoagulation were collected through a structured interview. During foot inspection, the presence of callus, foot deformity (any foot alteration augmenting the pressure in one or several sites of the foot that consequently can contribute to callus and/or ulcer development), hallux limitus and edema were also assessed.

B. OTHER VARIABLES

Some variables that were not analyzed in Boyko’s study were also collected at baseline due to their clinical sense, availability and evidence pointing towards an association with ulcer development.

Eye problem due to diabetes (Iversen et al, 2008; Sriussadaporn et al, 1997), physical impairment defined as patient’s difficulty in reaching their own feet (Keese et al, 2008), reported myocardial infarction (Margolis et al, 2008) and stroke (Iversen et al, 2008), education degree, nephropathy (Abbott et al, 2002; Margolis et al, 2008) and neuropathic symptoms (Armstrong et al, 1998 a; Boyko et al, 1999; Gulliford et al, 2002; Lavery et al, 1998) were collected during the anamnesis.

PVD was defined as the presence of only 2 or less of the 4 pedal pulses (Abbott et al, 2002) and it was collected during foot examination as well as foot care habits (Gulliford et al, 2002; Suico et al, 1998; Sriussadaporn et al, 1997): nail care and skin moisturizing. We believe that the absence of two palpable pulses in one foot or the absence of pedal or posterior tibial pulses in both feet represented a noteworthy vascular supply alteration, and so we have chosen the designation used in the Abbott prospective cohort study. (Abbott et al, 2002)

Footwear, brought to the appointment, was evaluated and classified as low risk if they were all closed, with laces and correctly sized; moderate risk if they didn’t have laces, were slippers or made with an inadequately soft material; high-risk if they were too small, sandals or flip-flops. (Abbott et al, 2002) To all patients it was also asked to describe the most frequently used shoes. The attributed classification was made taking in consideration those that presented a higher risk. In those patients presenting lesions, callosities or reddened sites due directly to footwear were immediately classified has wearing high-risk footwear; independently of the shoes described or worn in the appointment.

3. OUTCOMES

The outcome analyzed was foot ulcer development; this is, a full-thickness skin defect distal to the malleolli that required more than 14 days healing. (Boyko et al, 2006) Follow-up on both limbs ended as soon as the first foot ulcer occurred.

All limb-specific measurements were considered, in each subject, as present or absent if they occurred in at least one foot (taking into consideration that this study intends to predict foot ulcers at patient-level). Readers were blinded to stratification score during predictive variables and outcome collection.
Subjects were reevaluated with a periodicity varying from 1 to 12 months, according to the IWGDF guidelines (Apelqvist et al, 2000; Peters et al, 2001) but were instructed to contact the clinic if any ulcer or any complication appeared before the next scheduled appointment (scheduling an emergency appointment to the same or next day). Additionally, ulcers’ primary cause was also registered.

4. **STATISTICAL ANALYSIS**

Risk factor distribution was compared between the group of patients with ulcer and those without ulcer, during follow-up. Continuous variables (HbA1C, age and diabetes duration) were compared using student t-test or Mann-Whitney U test for independent samples according to the variable’s distribution. The remaining dichotomic variables were compared using chi-square test or exact Fisher’s test, when applicable. Distribution normality was assessed by evaluation of the histogram and the Kolmogorov-Smirnov test. Significance was defined as a \( p \) less than 0.05.

Each variable, not included in Boyko’s original model, significantly associated with ulcer development in the multivariable analysis was included separately or in groups in the model. To understand the impact of each alteration in the models’ optimization, the AUC was recalculated for each variable inclusion.

Multivariable analysis and model modifications were performed using logistic regression. The same procedure was made backwards, removing each Boyko’s original model variable with no significance in the multivariate analysis, to see if it was possible to simplify it.

Only for this study’s purpose, the risk score \[ \text{score} = \text{HbA1C (continuous)} \times 0.0975 + 0.7101 \text{ (neuropathy present)} + 0.3888 \text{ (poor vision present)} - 0.3206 \text{ (tinea pedis present)} + 0.4579 \text{ (onychomycosis present)} + 0.7784 \text{ (present past history of foot ulcer)} + 0.943 \text{ (present past history of lower limb amputation)} \] was calculated using the downloadable spreadsheet for its calculation from http://www.eric.seattle.med.va.gov/downloads. Subsequently, patients were stratified according to the described risk degree stratification in Boyko study (Boyko et al, 2006): lowest risk if the score was inferior to 1.48; next to lowest risk between 1.48 and 1.99; next to highest risk between 2.00 and 2.61 and highest risk if the score was superior to 2.61.

Original and optimized stratification model’s sensitivity, specificity, LR, predictive values and AUC with 95% confidence intervals were calculated. Due to the predictive values high dependence on prevalence condition (Fritz et al, 2001), they were calculated using the different prevalence reported in the 5 articles assessing the effectiveness of foot ulcer risk stratification systems retrieved in our SR (Chapter III, section B) (Boyko et al, 2006; Lavery et al, 1998, 2008; Leese et al, 2006; Peters et al, 2001). Values varied from 5 % in the SIGN study (Leese et al, 2006) up to 34% in the Lavery and coworkers study (Lavery et al, 1998).

All statistical analysis was performed using the SPSS version 17.0.
C. RESULTS
1. PARTICIPANTS DESCRIPTION

The study included 360 participants, with a median follow-up of 25 months (range 3 to 86). Subjects had a median age of about 65 years, a median of 15 years of diabetes evolution, were mainly patients with type 2 diabetes (98%) with a low level of education (86% up to primary school) and 45% were male. Each subject had a median of 8 appointments (Minimum 3, Maximum 20). Ulceration occurred in 94 (26%) subjects. The main direct cause was inadequate footwear (60%), followed by self-treatment injury (9%) and direct trauma (7%). There were no indeterminate results or outliers. As explained in the participants’ selection section, cases with missing responses were excluded from the study.

2. VARIABLES ASSOCIATION WITH ULCER DEVELOPMENT

In our study six out of the seven variables included in Boyko’s original model were statistically associated with ulcer development in the univariate analysis: HbA1C, visual impairment, previous foot ulcer, previous amputation, monofilament insensitivity and onychomycosis. (See table 15) However some variables analyzed in the original study but not included in the model revealed association in our study: gender; intermittent claudication; foot deformity; hallux limitus.

From the variables not analyzed in Boyko’s study only eye problem due to diabetes, peripheral vascular disease, physical impairment and the use of moderate to high risk footwear were considered as possible predictive variables of foot ulceration. (See table 15)

Only the variables with statistically significant association and those included in the original model were evaluated in the multivariate analysis. Results showed that only HbA1C, previous foot ulcer, tinea pedis, gender, hallux limitus and footwear were statistically significant in the multivariable analysis. (See table 15) Therefore, we assessed if the inclusion of gender, hallux limitus and footwear and/or the extraction of the visual impairment, previous amputation, monofilament insensitivity and onychomycosis variables improved the models’ accuracy for the prediction of diabetic foot ulceration.
TABLE 15: PARTICIPANTS BASELINE CHARACTERISTICS, UNIVARIATE AND MULTIVARIATE ANALYSIS FOR THE ASSOCIATION WITH FOOT ULCER DEVELOPMENT

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total n= 360</th>
<th>Without ulcer development n= 266 (74%)</th>
<th>With ulcer development n= 94 (26%)</th>
<th>Univariate analysis (p value)</th>
<th>Multivariate analysis (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INCLUDED IN BOYKOS’ STUDY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1C (in % units)*</td>
<td>7,4</td>
<td>7,1</td>
<td>8,1</td>
<td>&lt; 0,001&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0,001</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>155</td>
<td>103 (39)</td>
<td>52 (55)</td>
<td>&lt; 0,001&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0,807</td>
</tr>
<tr>
<td>Previous foot ulcer</td>
<td>137</td>
<td>68 (26)</td>
<td>69 (73)</td>
<td>&lt; 0,001&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt; 0,001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Previous amputation</td>
<td>48</td>
<td>21 (8)</td>
<td>27 (29)</td>
<td>&lt; 0,001&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0,532</td>
</tr>
<tr>
<td>Monofilament insensitivity</td>
<td>166</td>
<td>101 (38)</td>
<td>65 (69)</td>
<td>&lt; 0,001&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0,124</td>
</tr>
<tr>
<td>Tinea pedis</td>
<td>19</td>
<td>17 (6)</td>
<td>2 (2)</td>
<td>0,177&lt;sup&gt;a1&lt;/sup&gt;</td>
<td>0,047</td>
</tr>
<tr>
<td>Onychomycosis</td>
<td>206</td>
<td>144 (54)</td>
<td>62 (66)</td>
<td>0,046&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0,981</td>
</tr>
<tr>
<td><strong>NOT INCLUDED IN ORIGINAL MODEL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (in years)*</td>
<td>65</td>
<td>65</td>
<td>66</td>
<td>0,697&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>164</td>
<td>110 (41)</td>
<td>54 (57)</td>
<td>0,007&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0,01</td>
</tr>
<tr>
<td>Diabetes type 2</td>
<td>354</td>
<td>261 (98)</td>
<td>93 (99)</td>
<td>0,465&lt;sup&gt;a1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Insulin use</td>
<td>150</td>
<td>115 (43)</td>
<td>35 (37)</td>
<td>0,311&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Diabetes duration (in years)*</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>0,422&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>18</td>
<td>14 (5)</td>
<td>4 (4)</td>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>107</td>
<td>67 (25)</td>
<td>40 (43)</td>
<td>0,002&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0,204</td>
</tr>
<tr>
<td>Callus</td>
<td>147</td>
<td>104 (39)</td>
<td>43 (46)</td>
<td>0,360&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Foot deformity</td>
<td>265</td>
<td>182 (68)</td>
<td>83 (88)</td>
<td>&lt; 0,001&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0,147</td>
</tr>
<tr>
<td>Hallux limitus</td>
<td>124</td>
<td>83 (31)</td>
<td>41 (44)</td>
<td>0,029&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0,017</td>
</tr>
<tr>
<td>Edema</td>
<td>101</td>
<td>72 (27)</td>
<td>29 (31)</td>
<td>0,483&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Laser photoocoagulation</td>
<td>128</td>
<td>89 (34)</td>
<td>39 (42)</td>
<td>0,162&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>OTHER VARIABLES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical impairment</td>
<td>148</td>
<td>98 (37)</td>
<td>50 (53)</td>
<td>0,006&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0,527</td>
</tr>
<tr>
<td>Eye problem due to diabetes</td>
<td>177</td>
<td>121 (46)</td>
<td>56 (60)</td>
<td>0,019&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0,512</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>56</td>
<td>40 (15)</td>
<td>16 (17)</td>
<td>0,624&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Reported stroke</td>
<td>73</td>
<td>52 (20)</td>
<td>21 (22)</td>
<td>0,554&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Nephropathy</td>
<td>62</td>
<td>44 (17)</td>
<td>18 (19)</td>
<td>0,565&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Neuropathic symptoms</td>
<td>212</td>
<td>151 (57)</td>
<td>61 (65)</td>
<td>0,169&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>130</td>
<td>77 (29)</td>
<td>53 (56)</td>
<td>&lt; 0,001&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0,453</td>
</tr>
<tr>
<td>Education degree ≤ to 4th year</td>
<td>308</td>
<td>226 (85)</td>
<td>82 (87)</td>
<td>0,733&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Good nail care</td>
<td>149</td>
<td>118 (44)</td>
<td>31 (33)</td>
<td>0,054&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Moisturized skin</td>
<td>268</td>
<td>202 (76)</td>
<td>66 (70)</td>
<td>0,274&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Moderate or high risk footwear</td>
<td>173</td>
<td>100 (38)</td>
<td>73 (78)</td>
<td>&lt; 0,001&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt; 0,001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*Median; ± Chi-square test; ± Fisher’s exact test; ± T-test for independent samples; * Mann-Whitney U test

Univariate analysis was performed using the adequate methods for all variables present in the Boyko et al study (Boyko et al, 2006) and other pertinent and clinical available variables. Multivariate analysis was performed using the variables present in the original model and those with a statistical significant association with foot ulcer development in the univariate analysis (p<0,05).

3. MODELS’ OPTIMIZATION

Only the inclusion of present hallux limitus variable (AUC of 0.84) and the use of moderate or high risk footwear variable (AUC of 0.88) improved the original models’ accuracy, however it was not statistically significant. When included simultaneously the improvement was equal to the one observed with the inclusion of the footwear variable alone (AUC of 0.88).

With the exclusion of the monofilament insensitivity variable the models’ accuracy diminished (AUC of 0.82) while with the exclusion of visual impairment, previous amputation and onychomycosis variables; separately, in pairs or all together, it remained the same (AUC 0.83). (See table 16)
The inclusion of the footwear variable excluding, at the same time, any or all the variables suggested for extraction of the original model, maintained the models’ AUC in 0,88 (results not shown).

### TABLE 16: ORIGINAL MODEL AREA UNDER THE CURVE AND OPTIMIZATION PROCESS (THROUGH THE ADDICTION OR EXTRACTION OF SELECTED VARIABLES BASED ON THE MULTIVARIABLE ANALYSIS RESULTS)

<table>
<thead>
<tr>
<th>Variables</th>
<th>AUC</th>
<th>CI 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORIGINAL MODEL (OM)</strong></td>
<td>0,83</td>
<td>0,78-0,88</td>
</tr>
<tr>
<td><strong>ADDITION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>0,83</td>
<td>0,79-0,88</td>
</tr>
<tr>
<td>Hallux limitus</td>
<td>0,84</td>
<td>0,80-0,89</td>
</tr>
<tr>
<td>Moderate or high risk footwear</td>
<td>0,88</td>
<td>0,84-0,91</td>
</tr>
<tr>
<td>Hallux limitus &amp; moderate or high risk footwear</td>
<td>0,88</td>
<td>0,85-0,92</td>
</tr>
<tr>
<td><strong>EXTRACTION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monofilament insensitivity</td>
<td>0,82</td>
<td>0,78-0,87</td>
</tr>
<tr>
<td>Visual impairment and/or previous amputation and/or onychomycosis</td>
<td>0,83</td>
<td>0,79-0,88</td>
</tr>
</tbody>
</table>

Analyzing the results from table 14, we have attempted to simplify and/or increase the original models’ AUC. We have addictioned variables with a statistical significant association in the multivariable analysis that were not present in the OM and extracted those variables that did not maintained statistical significance in the multivariable analysis. New models were created with this alterations using logistic regression and corresponding AUCs calculated.

Analyzing the resulting AUC (excluding the proposed variables) we verified that the model’s accuracy remained the same and the respective confidence interval did not allow us to affirm how it may be affected. Therefore, we chose to adopt a conservative position and maintain them in our final model proposal, which resulted in the following model equation: score = 0,373 x (HbA1C in % units) + 0,217 x (presence of visual impairment) + 2,037 (presence of previous ulcer history) + 0,593 x (presence of previous amputation) +0,637 x (presence of monofilament insensitivity) – 1,256 x (presence of tinea pedis) + 0,217 x (presence of onychomycosis) + 1,905 x (use of moderate or high risk footwear).

Assessing the resulting ROC curves and respective AUC, best stratification was achieved using the following cut-offs: score under 3,87 (lowest risk); between 3,87 and 5,66 (next to lowest risk); between 5,67 and 6,81 (next to highest risk); score over 6,81 (highest risk). (See figure 3)
Ulcer development in each group of the original and optimized model risk stratification is shown in table 3 (p< 0,001 X² for association and trend in both models).

For the original model the risk of foot ulcer development was 4-fold greater in the next to lowest group (13%), 7-fold in the next to highest group (23%) and 11-fold in the highest group (39%) when compared to subjects in the lowest risk group (3,5%). While in the optimized model subjects in next to lowest risk group had a 7-fold (11%), subjects in the next to highest a 19-fold (28%) and in those in highest group a 27-fold (41%) higher risk of foot ulcer development when compared to those in the lowest risk group (1,5%).

In both models, the specificity value of the highest risk group and the sensibility value of the highest plus next to highest plus the next to lowest risk groups are excellent. (See table 16) The optimized model tended to produce higher specificity and positive LR at all levels, i.e., to show better results in the prediction of patients that will develop foot ulceration (the most needed ability in the tertiary care context). It also tended to produce higher values for all diagnostic accuracy measures for the detection of patients in or above the next to highest risk and in or above the next to lowest risk groups. However none of the referred differences were statistically significant. (See table 17)
Foot ulcer prevalence varies greatly from one study to another which results in diverse predictive values. For a low prevalence (community setting) both models produced a 91% negative predictive value (NPV), with low positive predictive values (PPV) in both models (20% in the original model and 25% in the optimized model). As expected, increasing the outcome prevalence NPV values dropped up to 51% in a high risk setting where foot ulcer development occurred in 34% of the subjects. Conversely, PPV rose up to 71 and 75% for the original and optimized model, respectively.

With our study prevalence, moderate NPV and PPV resulted for both models. (See table 18) The optimized model tended to generate higher PPV, although without statistical significance, and similar negative predictive values NPV to the original model. (See table 18)

5. SUBGROUP ANALYSIS

One of Boyko’s study limitations is the fact that their sample was composed mainly by men. In our sample, we verified that gender was equally distributed and therefore we performed a subgroup analysis. The original model stratification in male subjects had a AUC of 0.84 (CI 95% 0.78-0.90) while in female had a AUC of 0.80 (0.72-0.87). The optimized model stratification in male subjects had a AUC of 0.89 (0.85-0.94) while in female had a AUC of 0.83 (0.77-0.90).

As one can observe, there were no statistical significant differences between genders (although both models tended to perform better in males) nor between the original model and the optimized model in both genders (although the optimized tended to produce better results).

Both models presented good classification accuracy for the prediction of foot ulcer development at patient-level in both genders. The optimized model tended to produce higher AUC values.
### TABLE 17: ORIGINAL AND OPTIMIZED MODELS’ RISK STRATIFICATION, ULCER DEVELOPMENT DISTRIBUTION AND ACCURACY MEASURES FOR DIFFERENT CUT-OFFS

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Original model</th>
<th>Optimized model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cutoff</td>
<td>Se (95%CI)</td>
</tr>
<tr>
<td>Highest risk</td>
<td>91 (25)</td>
<td>61 (51-70)</td>
</tr>
<tr>
<td>Next to highest risk</td>
<td>67 (18)</td>
<td>84 (75-90)</td>
</tr>
<tr>
<td>Next to lowest risk</td>
<td>65 (18)</td>
<td>95 (88-98)</td>
</tr>
<tr>
<td>Lowest risk</td>
<td>137 (38)</td>
<td>20 (16-24)</td>
</tr>
</tbody>
</table>

**Legend:** Se – sensitivity; Sp – specificity; LR+ - positive likelihood ratio; LR - - negative likelihood ratio; CI confidence interval

Diagnostic accuracy measures and respective 95% CI were calculated for the distinct risk levels for both original and optimized model.

### TABLE 18: ORIGINAL AND OPTIMIZED MODELS’ RISK STRATIFICATION PREDICTIVE VALUES FOR DIFFERENT FOOT ULCER PREVALENCE

<table>
<thead>
<tr>
<th>Foot ulcer prevalence (%)</th>
<th>Original model</th>
<th>Optimized model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PPV (95%CI)</td>
<td>NPV (95%CI)</td>
</tr>
<tr>
<td>5</td>
<td>20 (16-24)</td>
<td>91 (88-94)</td>
</tr>
<tr>
<td>[Leese et al, 2006]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>49 (44-54)</td>
<td>72 (67-77)</td>
</tr>
<tr>
<td>[Boyko et al, 2006; Lavery et al, 2008]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>62 (57-67)</td>
<td>60 (55-65)</td>
</tr>
<tr>
<td>[our study, Peters et al, 2001]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>71 (66-76)</td>
<td>51 (46-56)</td>
</tr>
<tr>
<td>[Lavery et al, 1998]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Legend:** PPV positive predictive value, NPV negative predictive value, CI confidence interval

PPV was calculated for the highest risk group and NPV for the lowest risk group, using different foot ulcer prevalence values present in several stratification systems evaluation studies.
D. DISCUSSION
An unhealed foot ulcer is the most frequent precursor of a diabetes-related lower limb amputation. Therefore ulcer prevention is vital. Ideally specialized foot care should be given to all patients with diabetes. However, in reality no health-care system has sufficient resource for this universal approach. Therefore, preventive and treatment resources for the diabetic foot must be distributed in a cost-effective and rational manner (McGill et al, 2005) ideally through foot ulcer risk stratification systems.

This tool is crucial for distributing patients among the different care level institutions standardize concepts and procedures among professionals, control preventive care efficacy, determine the needed appointment periodicity and allocate resources (namely therapeutic footwear and insoles). However, few risk stratification systems exist, fewer were validated and that we are aware of none has been externally validated.

This study evaluated the validity and proposed an optimization of the first logarithmic model for risk degree stratification in what concerns the development of foot ulcers in patients with diabetes, using the READER checklist (See chapter III, section A).

The logarithmic models have an advantage when compared with simple stratification systems. Knowing the effect of each variable in the risk degree simplifies the detection of risk variables, allows a more personalized approach and improves patient’s perception. For example, in a patient with a high HbA1C, one can show him the changes that may occur in his risk group only by achieving a better glyceamic control.

We confirmed that the commonly available and easy to collect variables chosen by Boyko et al in their study have excellent capacity for predicting foot ulceration in patients with diabetes. The achieved AUC of 0.83 (CI 95% 0.78-0.88) includes the value obtained in their study of 0.81 at 1 year. (Boyko et al, 2006)

Our results suggest that the inclusion of a variable regarding footwear could improve it (AUC 0.88). Nevertheless, it was not statistically significant although this might be explained by the sample’s size. The same explanation can be applied to the variables that were considered for exclusion in the model. And so, we choose to adopt a conservative attitude and maintain them in the model. Ideally 10 to 15 subjects should be enrolled for each variable analyzed (Stiell, 2000) and therefore sample size should be between 300 and 450 subjects. However, we included all patients available (n=360).

We must highlight that 60% of ulcer occurrence had as main cause the use of inadequate footwear, which underlines the importance of this variable. This is a simple to collect variable that is considered as one of the 5 pillar stones of foot ulcer prevention by the IWGDF (Apelqvist et al, 2000) and it was significantly associated with foot ulcer development in several studies assessing this variable. (Abbott et al, 2002; Boyko et al, 1999; Busch et al, 2003; Chantelau et al, 1990, 1994; Maluf et al, 2003)

One of the referred limitations of Boyko’s study was the fact that their sample was composed mainly by men. In our sample, gender was equally distributed. Subgroup analysis revealed no statistically significant differences in the AUC between genders and between the original model and the optimized model in both genders. This indicates that the two models can be applied in both women and men with good results. On the other hand our population included, as in Boyko’s study, mainly patients with type 2 diabetes (98%) and elderly people (average age of 65 years) which may affect models’ generalizability. Nonetheless type 2 diabetes’ prevalence is around 90% (WHO, 1994) and the model should be applied in a sample with similar distribution as the general diabetic population.
As mentioned above, all variables analyzed in the Boyko et al study (Boyko et al, 2006) were collected in the first appointment, except for race, due to the fact that all of our patients were Caucasian, and weight, because of space, material and time restrictions (and so we have no available data regarding this variable). However, both variables were not considered as statistical significant in the prediction of ulcer development in their study.

The visual acuity was collected in a less formal way; however that did not seem to affect the models’ discriminatory abilities. The visual impairment is often collected using specific eye evaluation charts. However, due to the impossibilities described in the methods section, we have chosen to collect this variable in the same way Leese and colleagues (Leese et al, 2006) in their study evaluating the SIGN stratification system effectiveness (the only alternative form of collecting this variable).

In our study (as in Boyko’s), tinea pedis was associated with foot ulcer development only in the multivariable analysis. Although no former studies evaluated this association, Boyko et al suggested that tinea pedis could be a clinical marker for intact autonomic function. (Boyko et al, 2006)

At our SR light, all the original models’ variables are statistically associated with foot ulcer development in all the retrieved studies except for HbA1C (2 studies did not achieve statistical significance). Tinea pedis and onychomycosis’ association were only assessed in this study.

The selection of variables for multivariate analysis was made upon an association with a p inferior to 0,05 and/or the presence in the original model. The strict use of these criteria, and not including all empirical based variables, may contribute to a lack of information. On the other hand, we must simplify to the maximum the optimized model.

Foot deformity and PVD (according to pulses palpation) showed a statistical significant association with foot ulcer development in all the retrieved studies in our SR (but only with univariate analysis) and are present in the majority of the stratification systems. However, both variables’ definition varies from study to study and in our study statistical significance was also only present in univariate analysis. In Boyko’s original study (Boyko et al, 2006) only claudication was assessed.

Another limitation is the fact that we did not analyze time’s factor effect. Therefore statistical analysis was made by logistic regression, in spite of the Cox proportional hazards modeling, due to the fact that very few patients were followed for 5 or more years (second end line used by Boyko et al). (Boyko et al, 2006)

It is important to stress that the population studied may present a risk bias, being this study performed in a tertiary referral center. However, in Portugal there are no secondary care institutions and still little resources are allocated for the prevention of diabetic foot complications in the primary care setting (as in several other countries). And so, for now, it is the Hospital’s responsibility to fill this gap, develop strategies and spread a higher awareness about this extremely important health and social problem to the remaining institutions. However, outcome’s prevalence was superior in our study (26%) when compared with Boyko’s study (17%).
On the other hand, it is not possible to define a cut-off prevalence to designate low, moderate or high risk contexts. If one labels it as superior to 5%, then all studies (Boyko et al, 2006; Lavery et al, 1998, 2008; Peters et al, 2001) except one (Leese et al, 2006) that assessed the effectiveness of a foot ulcer risk stratification system were performed in high risk settings. In the Peters and colleagues paper (Peters et al, 2001) the reported prevalence was similar to ours (25%) and in the Lavery and coworkers (Lavery et al, 1998) it was as high as 34%.

Subjects unable to walk were excluded from this study because we consider they represent a specific subpopulation and to respect the exclusion factors from the Boyko’s study. This patients’ group include those in prosthetics adaptation, hospitalized patients and patients with severe physical limitations. We believe that these patients are in higher risk for pressure ulcer development which has a considerably different pathophysiology, and so their inclusion could affect our results.

In comparison to the IWGDF stratification system (Peters et al, 2001) both models (original and optimized) had similar results in the detection of patients at highest risk of foot ulcer development. Nevertheless, the SIGN stratification system study (Leese et al, 2006) reported statistically significant better sensitivity, positive and negative LR to identify patient at higher risk in comparison to the original model, and better sensitivity and negative LR in comparison to the optimized model.

For the detection of patients at highest and next to highest risk the IWGDF system showed statistically significant inferior specificity and positive LR in comparison to the optimized model, and again no difference in comparison with the original model. The SIGN system reported once more higher sensitivity than the original model, but similar results with the optimized model.

NPV value (99,6 CI 95% 99,5-99,7) was higher in the SIGN study (2006) when compared with both models in our study. PPV value was also higher but statistical significance was not maintained when compared to the optimized model. In comparison with the IWGDF study (Peters et al, 2001), NPV value (60 CI 95% 54-66) and PPV value had no statistical difference in both the original and optimized model. (see tables 6 and 18).

We must emphasize that these results were obtained on very different population and neither the IWGDF nor the SIGN systems were externally validated. A comparison with the 1998 and 2008 Lavery and coworkers papers (Lavery et al, 1998, 2008) was not possible due to a lack and impossibility to calculate diagnostic accuracy measures.

Our results demonstrated that Boyko’s model in its original or in the optimized form has a very low negative LRs and 91% NPVs, i. e., in a low prevalence context those subjects in the lowest risk group have 91% probability of remaining free of ulcer development. In addition, both models resulted in a low proportion of false positives in the highest risk group, i. e., in a high specificity and moderate positive LRs; which is vital for tertiary care institutions.

Analyzing LR values (for both models) most of them generate only small alterations in the outcome odds, although it can be sometimes important. (Fritz et al, 2003) But it is imperative to stress that the positive LR in the highest risk group has a moderate impact and the negative LR in the lowest risk group has a large impact in the outcome odds.
Our results indicate that in countries with truly 3 different care levels, tertiary institutions should follow patients at the highest risk level (since this group presented a high specificity and positive LR), secondary institutions should follow those at next to lowest and next to highest risk and primary institutions should screen all new subjects and follow those at the lowest risk group (given that this group presented a high NPV). However in countries where there are no intermediate care institutions, tertiary institutions should follow patients at the highest and next to highest risk groups, given that they present a high sensibility (84% in the original model and 88% in the optimized model) at the expense of around 25% of patients that will no develop ulcer but were included in those groups. Primary care institutions should screen and follow the remaining subjects.

Although with a retrospective design, this study represents the first attempt of external validation and optimization of the model, therefore improving this clinical decision rule to a level 2 of evidence.

In addition, we have performed this validation respecting 25 of the 29 proposed items in the READER checklist for a good methodology, being 3 items not applicable in this study (abstract and time interval between predictor variables and gold-standard). Reproducibility was not evaluated because variables were collected through interview or blood analysis (HbA1C). For the variables collected through foot examination there was no way to know which of the 2 podiatrist realized it, due to the retrospective design.

In conclusion, the stratification by risk of foot ulceration is a key issue in the allocation of scarce resources; the common reality in what concerns to podiatric services. This internet available and easy to use stratification can be used to identify the patients at higher risk of foot ulceration; those to whom the most specialized care, orthotic resources, structured educational programs and more frequent examinations should be provided. (Armstrong et al, 1998; Leese et al, 2006; Peters et al, 2001)

We conclude that Boyko’s model, based on seven easily available variables, is an excellent discriminating instrument for foot ulcer prediction in patients with diabetes of both genders and that the inclusion of a variable concerning footwear may improve the model.
V. CONCLUSIONS AND FUTURE RESEARCH
A. **Creation of a stepwise and checklist (READER) for the development and critical analysis of clinical decision/prediction rules.**

Clinical decision rules are a valuable, although rather recent, clinical decision support tool created to reduce clinical decision making uncertainty, simplify and increase the clinicians’ diagnostic and prognostic accuracy (Beattie et al., 2006; Childs et al., 2006; Jaeschke et al., 2002; Lijmer et al., 1999; Neilly et al., 2006; Sackett et al., 1996; Stiell, 2000; Stiell, 2007; Wasson et al., 1985) - providing a standardized approach for the probability estimation of an outcome development (Reynolds, 2001).

Due to its relative newness, we have verified that insufficient efforts for its development methodology and reporting standardization have been made - one of the most important features for a more widespread utilization and implementation.

With our work, we have proposed for the first time a structured stepwise for clinical decision rule’s derivation (in 10 steps), validation (in 8 steps) and impact analysis (in 9 steps) and a checklist, with 29 items, to help guiding in their creation and analysis.

Therefore, we wish, as a future project, to perform a systematic review around the clinical decision rule’s development and assessment topic and, if possible, to develop a more definitive checklist and stepwise through an expert consensus.

After that essential step, we wish to apply the resultant checklist to a randomized sample of clinical decision rules developed since the beginning of its development until nowadays in order to assess if occurred any improvement in the reporting quality and the most common missing items. That way, we can verify the impact of the 2 clinical decision rule’s development methodology proposal publications (Laupacis et al., 1997; Wasson et al., 1985) and highlight the most common faults in order to improve their development and reporting in the future. Due to time restrictions, and to the fact that this subject matter was not this thesis core, it was not possible to perform it before the time limit.

B. **Pathophysiology of diabetic foot ulcer development.**

Through a literature review, we have concluded that diabetic foot ulceration has an intricate pathophysiologic process in which diabetic neuropathy, peripheral vascular disease and trauma frequently have special roles (Boulton, 2004a, 2006; Boulton et al., 2008a, 2008b; Bowring, 2001; Frykberg et al., 2006; Khanolkar et al., 2008; Morbach, 2003; SIGN, 2001).

C. **Systematic review of predictive factors for diabetic foot ulcer development.**

In the systematic review we have performed (chapter III, section B), with the aim of retrieving a list of all possible predictive variables of ulceration, 60 studies assessing more than 100 variables were included.

The performed systematic review points to a similar conclusion of the pathophysiology section - the most consistently associated variables with foot ulcer development were: nephropathy, several diabetic neuropathy tests, edema, therapeutic footwear, foot deformities, callus, tinea pedis, absent foot palpable pulses, previous foot complications and dermal thermometry.

Despite the large quantity of studies available, the presented evidence showed various limitations. Something as simple and vital as foot ulcer definition was absent in half of the studies or presented an enormous variety.
The retrieved studies were agglomerated into 5 different outcomes and they presented various study designs with a diverse range of quality. Additionally, several variables collection and diagnostic cut-offs showed inconsistency (foot pulses, vibration perception threshold, Semmes-Weinstein monofilament, plantar peak pressure...) and the association of various variables revealed to be not consistent among studies or was assessed only by one study (in more than 90% of the variables).

As a result, we believe that there is a long way to run in order to improve research development in this field, such as performing a consensus for selecting the most appropriate foot ulcer definition and carrying out studies to better outline the best cut-offs for the most essential variables (HbA1C, diabetic neuropathy tests, foot pulses, plantar peak pressures, ankle brachial index...) and to evaluate the true impact of preventive measures (education, therapeutic footwear, multidisciplinary team care, chiropodist care).

D. Systematic review of the existing stratifications of risk degree for diabetic foot ulcer development.

Foot ulcer risk stratification systems are an indispensable tool for the patient with diabetes screening. The core variables of the 5 retrieved stratification systems are very similar (diabetic neuropathy, peripheral vascular disease, foot deformity, previous ulcer and previous lower extremity amputation) and are in agreement with the systematic review results. However, little has been done in their validation. Only 4 articles evaluate the effectiveness of a determined stratification system in separate and expressed it in different forms (odds ratio; diagnostic accuracy measures as sensitivity, specificity, likelihood ratios; area under the receiver operating curve); which has difficult their results’ comparison. Additionally, all the stratification systems are only at a level 4 of evidence.

E. Validation and optimization of the Boyko’s foot ulcer development risk stratification system.

We have chosen to validate and optimize the Boyko’s et al proposed stratification system (choice justification present in chapter III, section B discussion) and concluded that this is an excellent tool to identify patients at high-risk, in both gender, and that the inclusion of a variable regarding footwear could improve it.

As a major limitation this study presents its retrospective nature and the high-risk context were it was developed. However, this was the first and only attempt to externally validate and optimize this stratification system elevating it to a level 3 of evidence.

Therefore we particularly aspire to validate the original model proposed by Boyko prospectively and in a larger population (if possible with a higher representation of patients with type 1 diabetes) and establish if the inclusion of a variable concerning the footwear and other variables resulting from the systematic review (such as other diabetic neuropathy tests, limited joint mobility, peripheral vascular disease tests...) can in fact improve it.
A foot ulcer risk stratification system choice and validation is also essential to a future project: a risk perception study comparing the patients’ risk auto-perception with the one retrieved by the selected stratification system.

With this research we aim to create a protocol, to standardize concepts and procedures, and a database of all the diabetic patients followed in the hospital and health centers connected to our hospital in order to promote a better communication, resource allocation and guarantee an improvement in the diabetic foot prevention in our impact area.
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