

*Sanofi Presents*

Exclusive Coverage of

# EXPERT VIEWS AND OPINIONS

in Effective Management of Diabetes  
and its Complications





## Highlights of **EXPERT VIEWS AND OPINIONS** in Effective Management of Diabetes and its Complications



**Exclusive coverage of Meet-the-Experts sessions of IDF**



**Covers the latest IDF 2021 meeting updates from the experts of the field**



**Provides in-depth discussion on the landmark studies by the investigators**



**Shares views and opinions of Key Opinion Leaders related to effective management of diabetes and its complications**



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## KIDNEY COMPLICATIONS

### SESSION 1



**By:**  
**Dr. PETER ROSSING**  
Head of Complications Research, Chief Physician, Steno Diabetes Center,  
Copenhagen, Denmark

**Dr. Peter Rossing during his talk highlighted the importance of kidney and its associated complications in diabetes and updates on effective management of the same. Some of the key highlights of his talk are summarized below –**



30–40% patients with diabetes are affected by chronic kidney disease characterized by increased albuminuria or decreased glomerular filtration rate (GFR) (or diabetic kidney disease [DKD])



The presence of kidney disease increases the risk of CVD, and the combination is a deadly cocktail



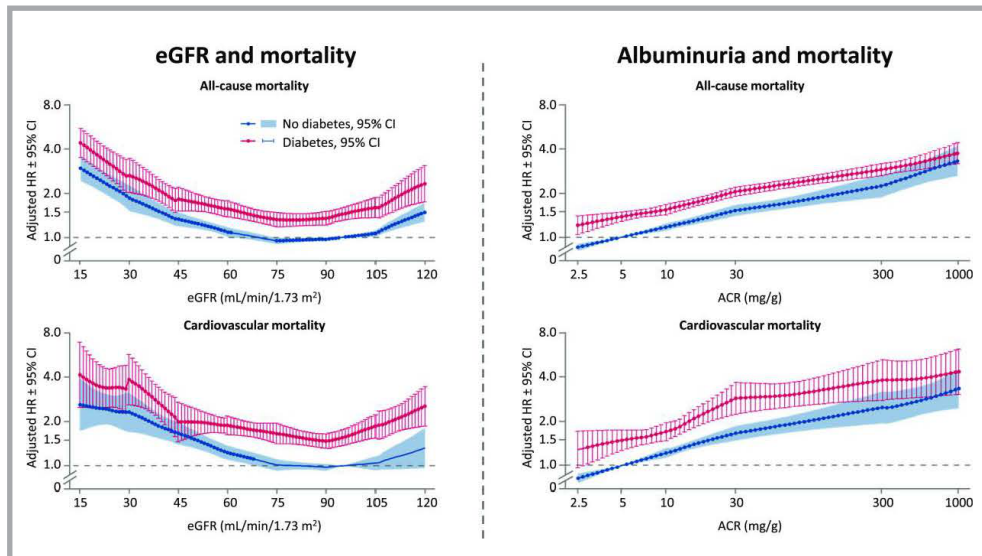
A chronic cardio-renal syndrome has been described where impaired renal function with retention of uremic solutes, hypertension, fluid retention, and anemia affect the heart



Increasing albuminuria or decreasing GFR increases the risk of CVD and mortality as well as the risk for end-stage kidney disease



On the other hand, a failing heart with low cardiac output with hypoperfusion and atherosclerosis has detrimental impact on renal function



As presented during IDF 2021

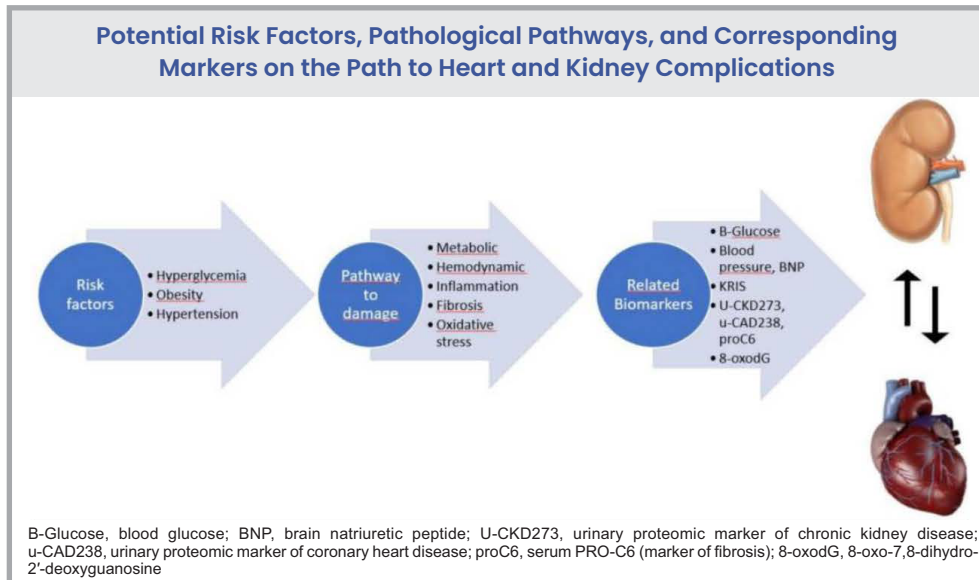
Compared with participants with normo-albuminuria, individuals with albuminuria had similar cardiac autonomic function assessed by the cardiac MIBG imaging and the heart rate variability indices in Type 1 and Type 2 diabetes

However, cardiac autonomic neuropathy was more frequent in the participants with albuminuria compared with in those with normo-albuminuria when evaluated by the cardiac autonomic reflex tests

**Myocardial Flow-Rate (MFR) was Reduced and Coronary Artery Calcium (CAC) Score Elevated in Type 1 and Type 2 Diabetes Subjects with Albuminuria Compared with Subjects with Normo-Albuminuria or Control Subjects**

Variable	Control subjects (n = 30)	Type 1 diabetes (10)		Type 2 diabetes (9)	
		Normoalbuminuria (n = 30)	Macroalbuminuria (n = 30)**	Normoalbuminuria (n = 30)	Albuminuria (n = 30)
Female (%)	40	40	43	40	27
Age (years)	59.8 ± 9.9	59.8 ± 9.1	58.2 ± 9.9	60.9 ± 10.1	65.6 ± 6.8 <sup>C</sup>
Albuminuria (mg/24 h or mg/g)*	6 (5–11)	3 (3–5) <sup>a</sup>	121 (53–283) <sup>b</sup>	7 (6–14)	146 (51–298) <sup>C</sup>
MFR	3.0 ± 0.8	3.1 ± 0.8	2.1 ± 0.9 <sup>b</sup>	2.6 ± 0.8 <sup>a</sup>	2.0 ± 0.5 <sup>C</sup>
MFR <2.5 (%)	17	23	77 <sup>b</sup>	40 <sup>a</sup>	83 <sup>C</sup>
CAC score	0 (0–81)	72 (22–247) <sup>a</sup>	263 (23–1,315)	36 (1–325) <sup>a</sup>	370 (152–1,025) <sup>C</sup>
CAC score >300 (%)	7	17	44 <sup>b</sup>	27	53 <sup>C</sup>

As presented during IDF 2021



*As presented during IDF 2021*

Elevated urinary albumin excretion reflects widespread vascular damage and predicts development of renal failure and cardiovascular events. In addition, treatment-induced reductions are associated with improved renal and cardiac prognosis

Troponin T has been used to demonstrate vascular, cardiac, and renal risk in diabetes and could be a marker of increased risk for atherosclerosis

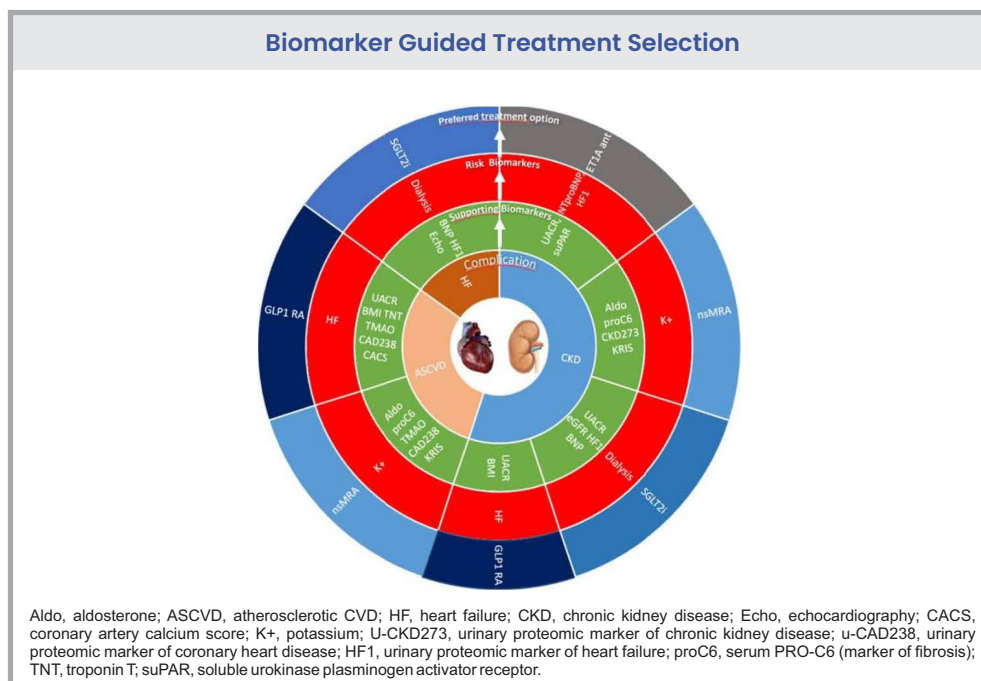
Trimethylamine-N-Oxide (TMAO), is a metabolite of phosphatidylcholine, choline, and carnitine produced by the gut microbiota from ingested animal food sources. A higher level of TMAO has been suggested as an independent risk factor for renal impairment and CVD



Another marker is serum PRO-C6 which increases hazards for cardiovascular events and all-cause mortality along with reduction of eGFR

Multiple markers have been investigated related to inflammation. These include fibrinogen, interleukin 6, and TNF $\alpha$ , which were found to be associated with risk of chronic kidney disease progression

Recently, the Kidney Risk Inflammatory Signature (KRIS) was developed with 17 inflammatory markers including TNF receptor superfamily members



As presented during IDF 2021

**Summary**

- We need to convert recent advances in diagnosis and therapy of cardiac and renal diseases in diabetes into fully individualized medicine, combining new possibilities in imaging and biomarker-based risk prediction with detailed knowledge of therapeutic avenues.
- A more detailed approach when choosing the right treatment for the right person may seem complicated and costly at first but has the potential to save both patients and the health care system considerable costs.
- The amount of information supporting design of individualized treatment is expected to grow drastically soon.
- Studies of the kidney and the heart using functional MRI and kidney biopsy studies will lead to a better diagnostic discrimination.
- At the same time, genomics, epigenomics, and metabolomics studies increase our knowledge of physiological processes. All of this will increase the complexity of the diseases but holds promise for better understanding once we learn to interpret the large amount of data available.



# DIABETIC FOOT COMPLICATIONS

## SESSION 2

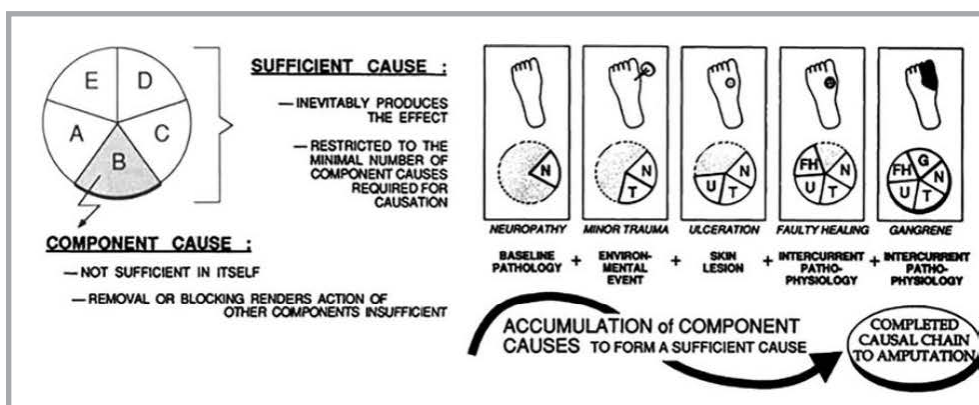


**By:**  
**Dr. EDWARD J BOYKO**

Professor of Medicine and Adjunct Professor of Epidemiology,  
University of Washington, Seattle, USA

**Dr. Boyko summarized and presented the key outcomes and analysis of the landmark Seattle Diabetic Foot Study (SDFS) which began 30 years back and till date 22 articles have been published based on that. He summarized the key take-home messages in his talk which are highlighted below –**

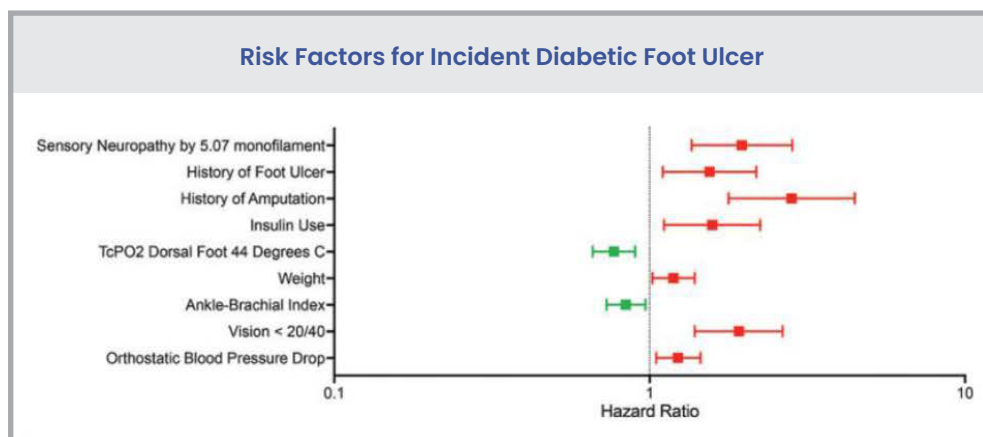
The pie diagram shown to the left represents the sufficient and component causal framework. A–E represent causes that are not sufficient in themselves but that are required components of a sufficient cause that inevitably produces an effect. The right side represents the causal pathway to amputation, which includes essential contributions from the component causes shown, all of which comprise a sufficient cause. Theoretically, amputation could have been avoided by elimination of any one component cause.



As presented during IDF 2021

## Risk factors for diabetic foot ulcers -

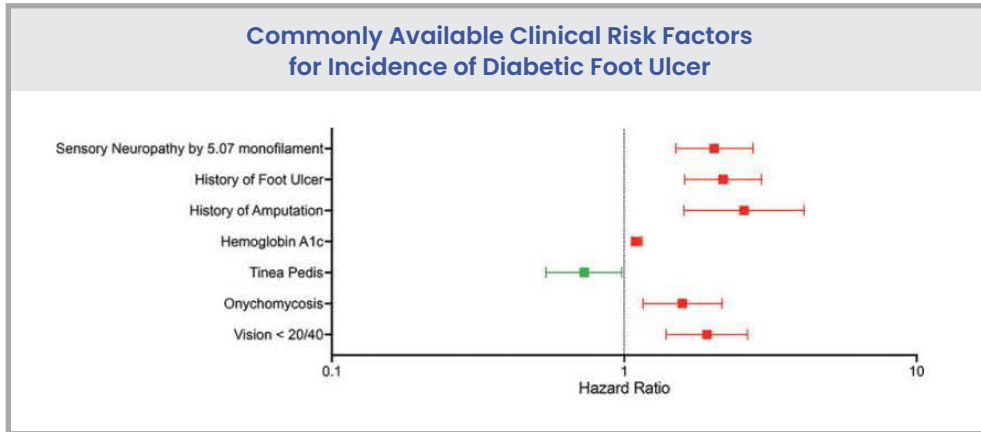
A multivariate cox regression analysis have shown that a multifactorial etiology for diabetic foot ulcer with identified factors reflecting dysfunction of autonomic and sensory nerves; poor perfusion; higher weight, perhaps reflecting greater plantar pressure or mobility limitations impairing ability to self-examine feet; poor vision, perhaps compromising self-care or signifying presence of diabetic retinopathy; insulin use indicating greater glycemia; and past history of prior diabetic foot complications.



*As presented during IDF 2021*

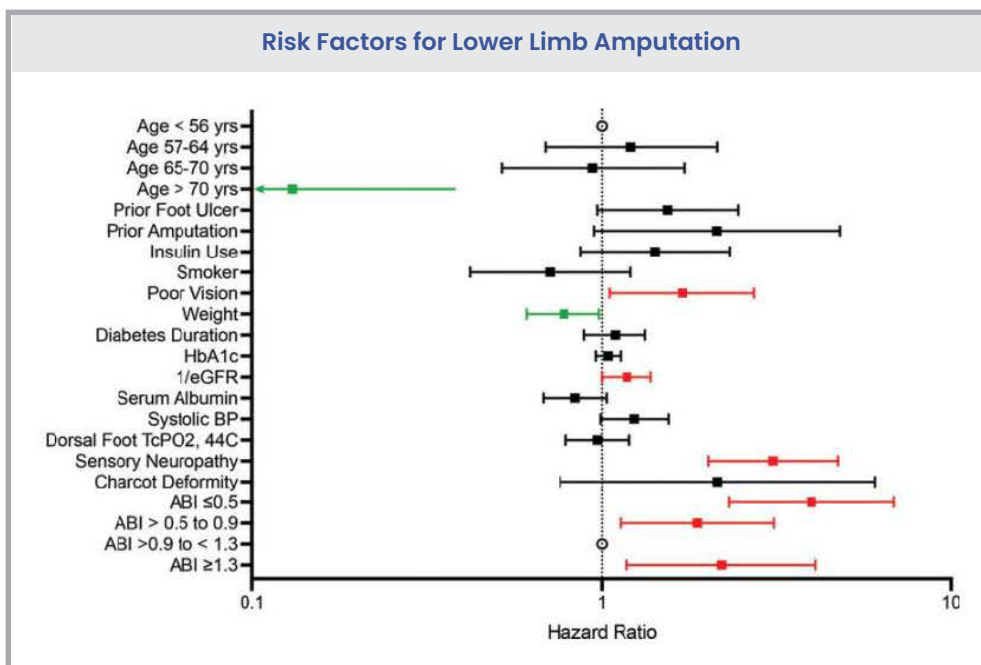
The SDFS include many readily available measurements that could be performed by any clinician. A total of 7 commonly factors emerged which are identified as significant independent risk predictors of ulcer.





As presented during IDF 2021

Factors associated with significantly higher risk included poor vision (20/70–20/200), lower estimated glomerular filtration rate, sensory neuropathy by 10-g monofilament testing, and ABI other than in the normal range of 0.91–1.29.



As presented during IDF 2021

### Plantar Pressure and Diabetic Foot Ulcer Risk

Elevated plantar pressure is thought to be a key factor in the development of diabetic foot ulcer. SDFS concluded that greater mean peak plantar pressure is associated with higher foot ulcer risk over the metatarsal heads but that this relationship is dependent on foot location.

### Diabetic Foot Ulcer and Mortality Risk

SDFS concluded that the occurrence of a foot ulcer is associated with a greater than twofold subsequent increase in mortality risk in comparison with patients with diabetes who had not developed a foot ulcer.

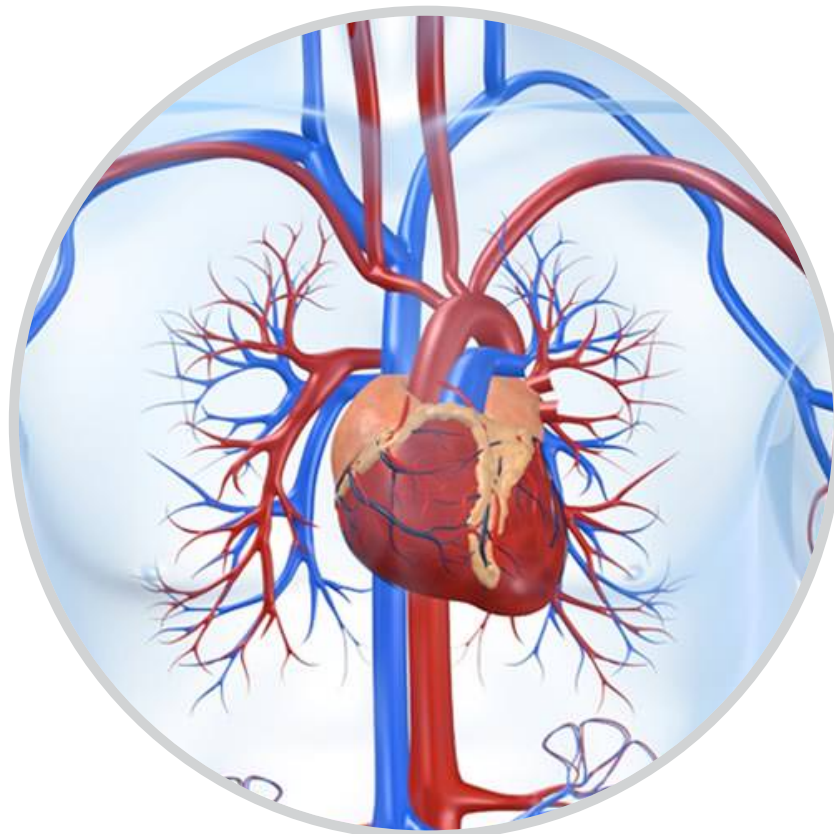
#### Summary

- SDFS has identified multiple risk factors for diabetic foot ulcer and amputation that include not only neurovascular disease capable of leading to unnoticed trauma or tissue loss due to ischemia and past history of foot ulcer and amputation but also poor vision, body weight, insulin use, and chronic kidney disease that may be markers for disease severity or impediments to effective self-care.
- Additional contributions include a validated and accurate prediction model for foot ulcer development based on readily available clinical information, which potentially can assist in targeting of patients with diabetes in need of higher intensity of foot care services.
- Although abnormal plantar pressure is considered a key component cause of foot ulcer, our research suggests that this may only apply to the metatarsal head locations.
- Our demonstration of higher all-cause mortality among individuals who develop a diabetic foot ulcer argues that this foot lesion is a marker for serious disease elsewhere limiting survival.



# CARDIOVASCULAR COMPLICATIONS

## SESSION 3

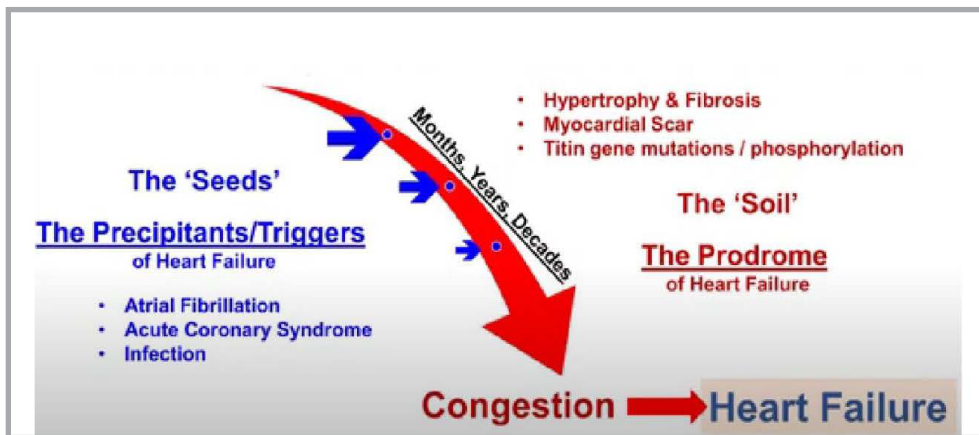


**By:**  
**Dr. JOHN CLELAND**

Consultant Cardiologist, Royal Brompton Hospital,  
Professor of Cardiology, Imperial College London, UK

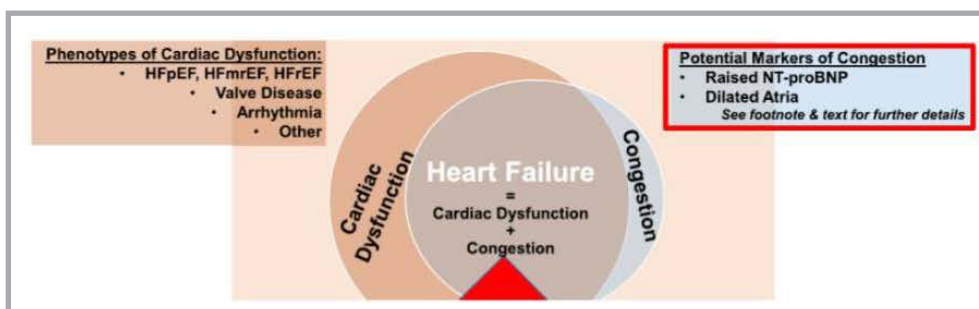
**Dr. John during his talk highlighted the role of Congestion, its role in heart failure and the clinical failure to recognize and manage it early. Few excerpts of his talk are highlighted below –**

A very small trigger over a period of long duration may cause congestion which can lead to heart failure. Thus, heart failure can be termed as a syndrome rather than disease, with a final common pathway of Congestion, which is a cardio-renal syndrome and whose early detection might be a useful strategy.



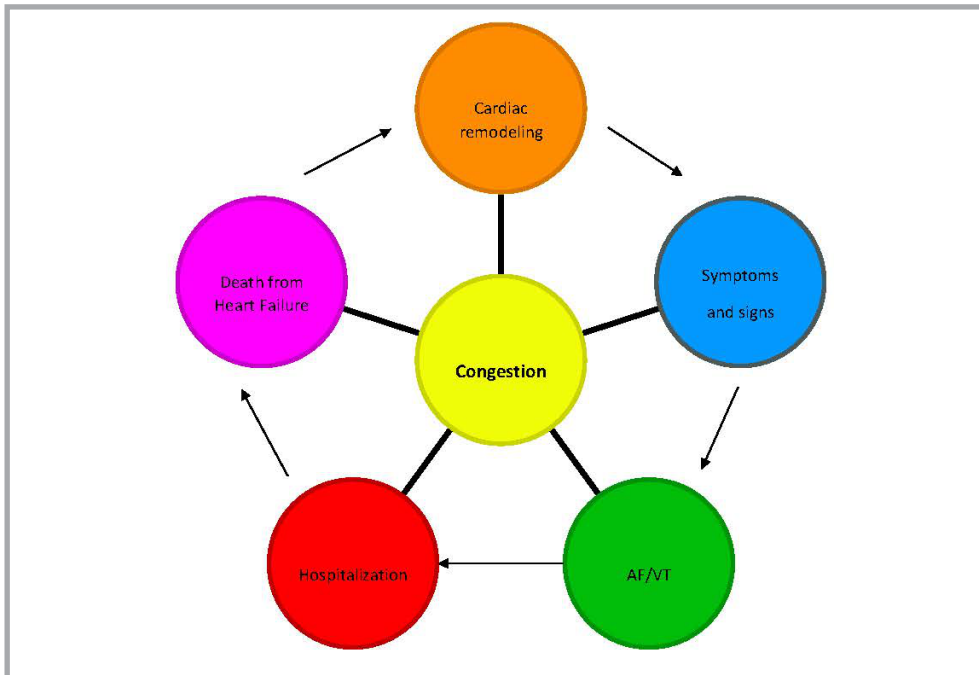
As presented during IDF 2021

A universal definition of heart failure can include congestion due to cardiac dysfunction.



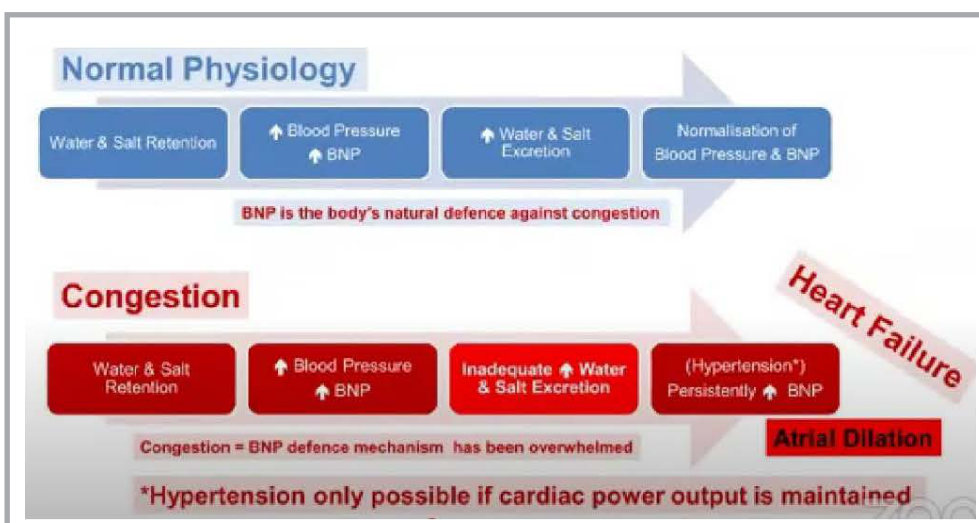
As presented during IDF 2021

There could be small group of patients with congestion who do not have heart failure. Couple of good markers for congestion are high NT-proBNP levels and dilated left atrium.



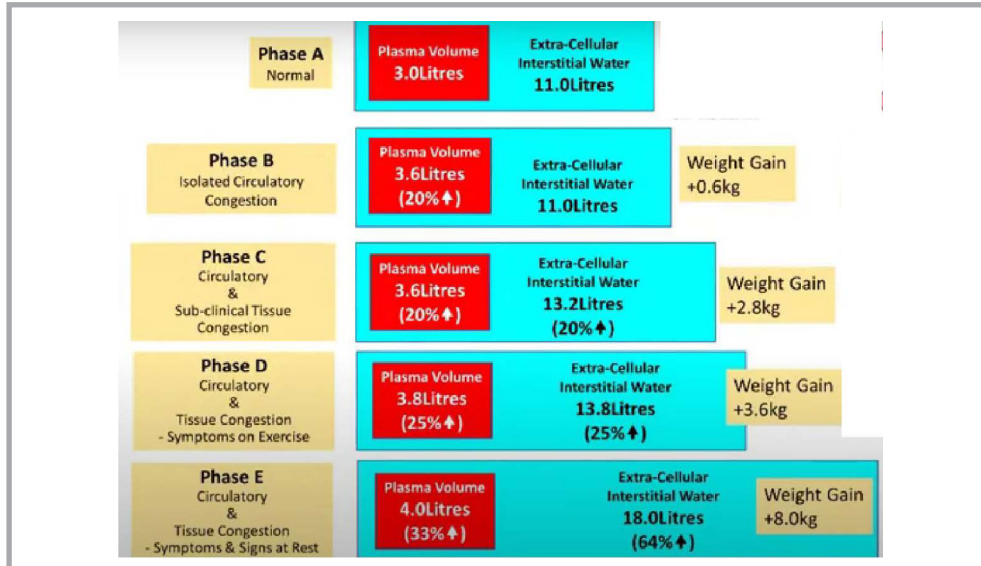
As presented during IDF 2021

Congestion is shown to increase the risk of worsening outcomes with heart failure including arrhythmia, chances of survival in case of event and overall mortality rates.



As presented during IDF 2021

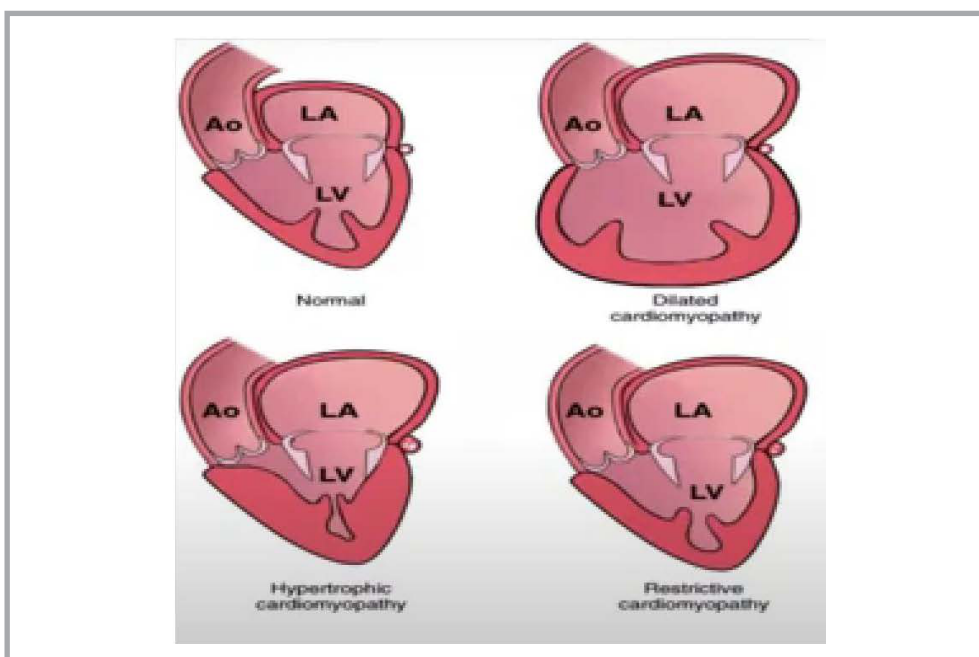




As presented during IDF 2021

A quick check at the left ventricle can give an idea about the risk of congestion (need to rule out case of mitral regurgitation or someone who is athletic or sign of atrial fibrillation).

If you want to know how left ventricle is doing, look at the left atrium.





As presented during IDF 2021

Patients have evidence of congestion on ultrasound as they have lung bee lines, dilated inferior vena cava, and dilated jugular venous.

### Potential Problem with Congestion-Based Diagnosis

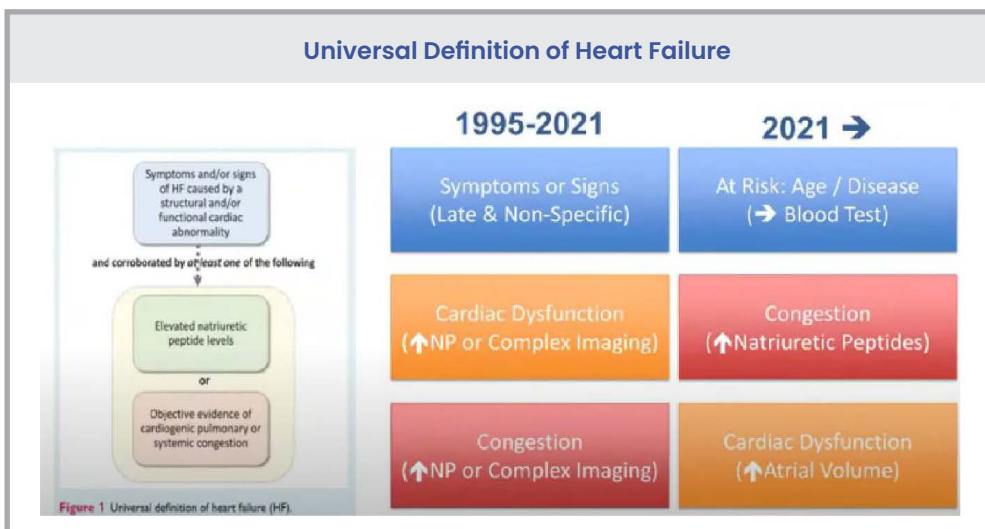
- **Cut-off for BNP / NTproBNP**
  - Age
  - Sex
  - GFR
  - AF
  - BMI

Requires data from many, many patients (millions?)


  
- **Lack of trials?**
  - STOP-HF
  - PONTIAC
  - HOMAGE
  - DECLARE

Align the definition of HF with randomised trials?  
Align the trials with a strong definition of HF?  
Evolve or Fossilize?
  
- **Increased prevalence of heart failure**
  - Need for more resources focussed on screening & (tertiary) prevention

*As presented during IDF 2021*



*As presented during IDF 2021*



## KIDNEY COMPLICATIONS

### SESSION 4

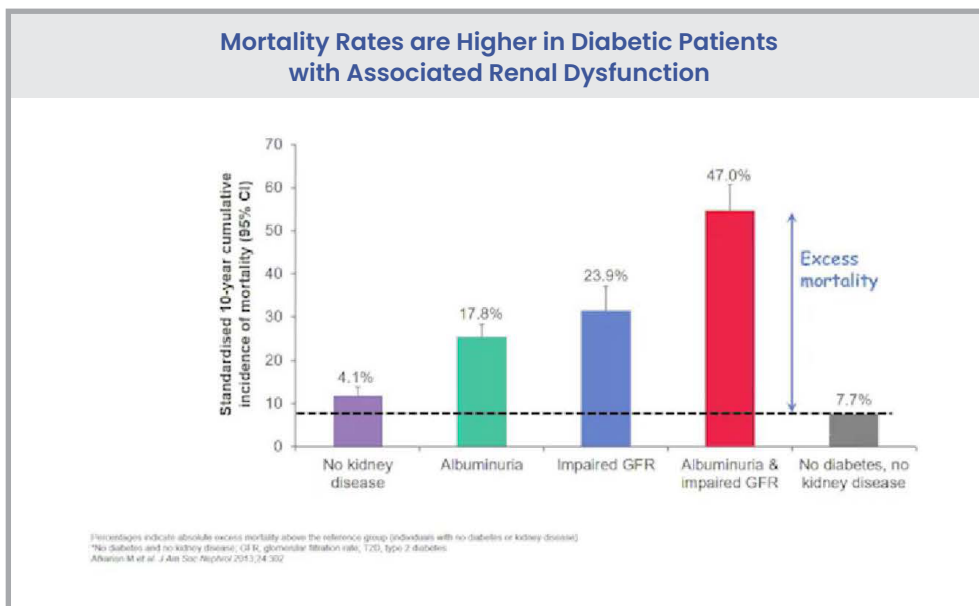


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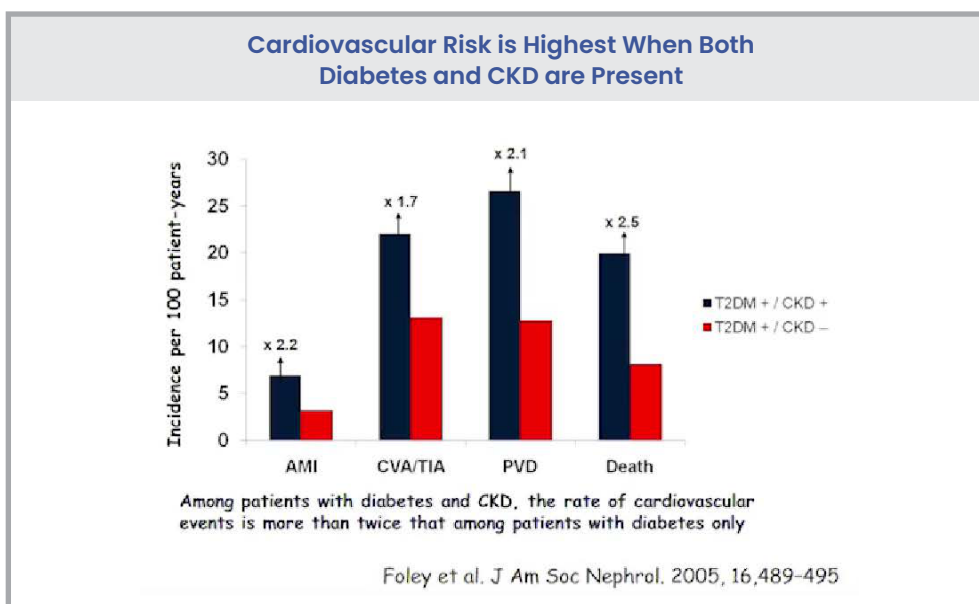
**Dr. PER-HENRIK GROOP**

Professor, University of Helsinki, Helsinki, Finland

**Dr. Henrik spoke about the kidney complications and the role of newer therapies including SGLT2i in the management of diabetic patients. Few highlighting points of his talk are summarized below –**



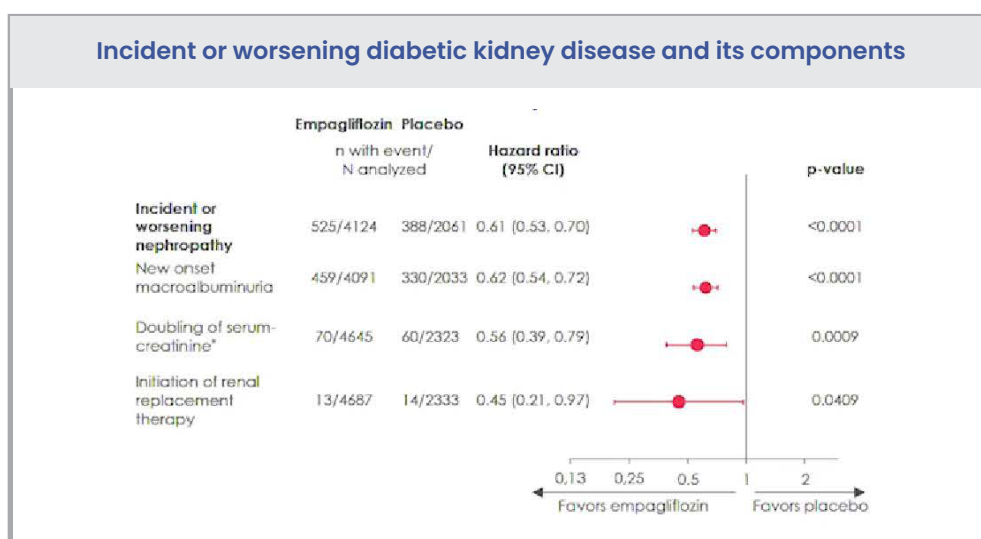
As presented during IDF 2021



**Impaired renal function is associated with multiple comorbid conditions including :**

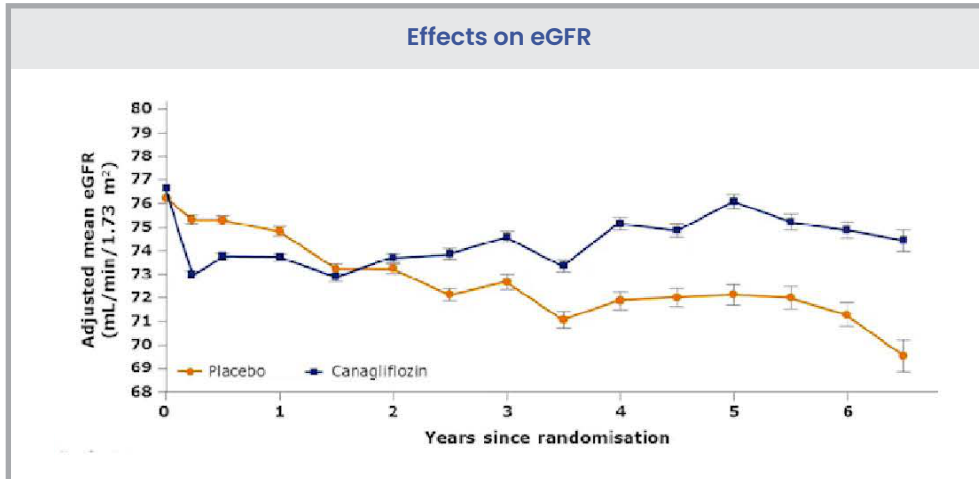
- Hypertension
- Oxidative stress
- Insulin resistance
- Arterial calcification
- Inflammation
- Accumulation of uremic toxins
- Left ventricular hypertrophy
- Endothelial dysfunction
- Activation of RAAS / SNS
- Anaemia

SGLT2i have shown to reduce the risk of renal impairment and associated comorbid outcomes.



As presented during IDF 2021

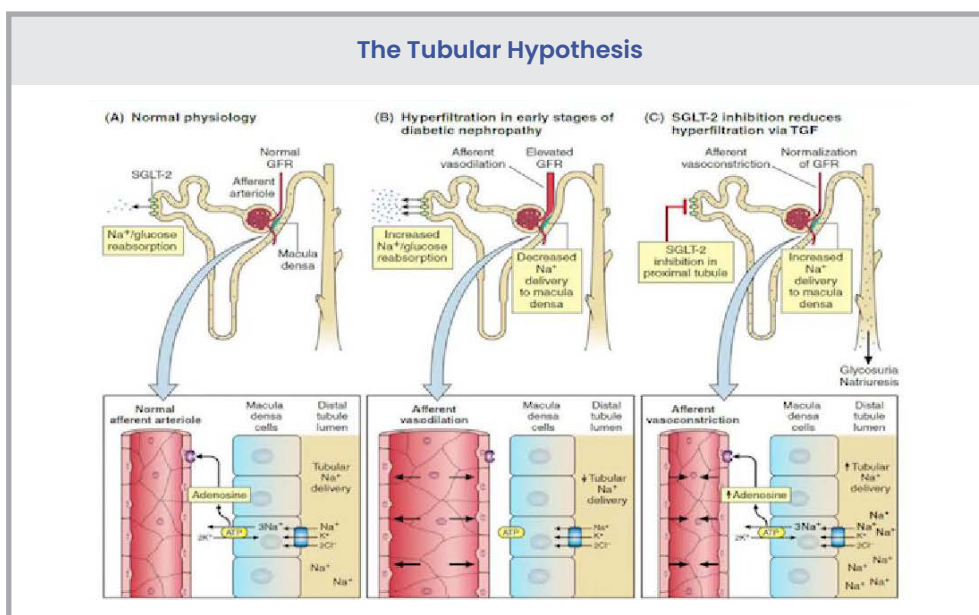




As presented during IDF 2021

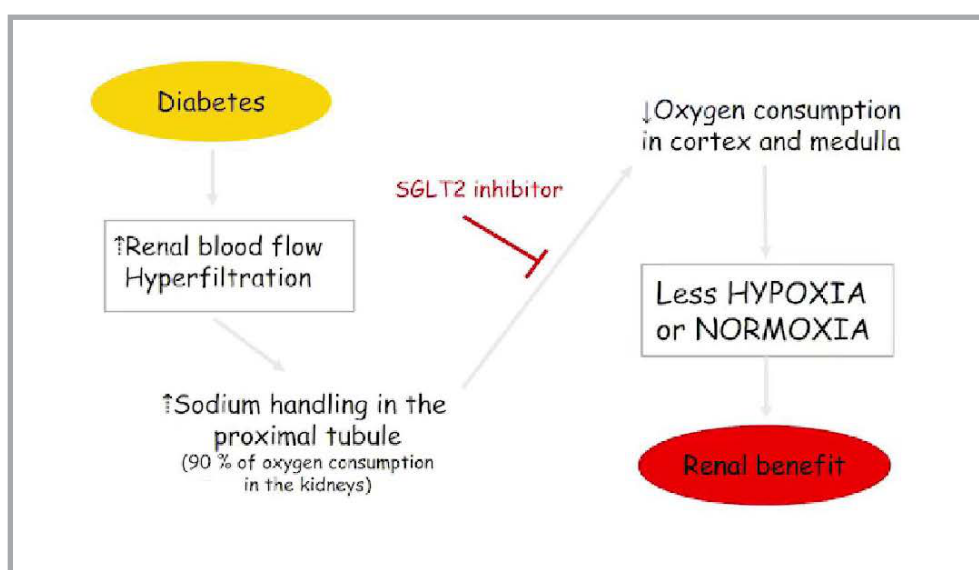
**Some of the proposed mechanisms for beneficial effect of SGLT2i therapy on kidney function includes –**

- Attenuation of glomerular hyperfiltration
- Reduction of intra-glomerular pressure
- Reduction in renal blood flow
- Increase in renal vascular resistance



As presented during IDF 2021

Empagliflozin effect on glomerular hyperfiltration shows similar magnitude as ACE inhibitor.



As presented during IDF 2021

### Summary

- Diabetic kidney disease is a common complication with grim consequences.
- SGLT2i shows cardio and reno-protective effects beyond their effect on glucose control.
- SGLT2 inhibition decreases afferent arteriole tone by impact on the tubule-glomerular feedback loop.



## DIABETIC NEUROPATHY

### SESSION 5



By:  
**Dr. NIKOLAOS PAPANAS**

Associate Professor, Internal Medicine–Diabetes Mellitus  
at Democritus University of Thrace, Greece

**Dr. Nikolaos discussed the significance of early diagnosis of neuropathy and the way it can be done. Selected excerpts from his talk are listed below –**

### **Importance of diabetic peripheral neuropathy**

- Diabetic peripheral neuropathy (DPN) is the commonest form of diabetic neuropathy and the most frequent manifestation of diabetes mellitus in the nervous system. It is chronic with a “stocking and glove distribution”. It represents a pivotal aetiological factor of diabetic foot ulcerations through three mechanisms: (a) sensory impairment or loss, leading to tissue damage through unperceived traumas; (b) impaired biomechanics with plantar pressure redistribution and abnormalities in standing and walking through muscular atrophy; (c) dry, fragile skin with reduced sweating through impaired sweat gland innervation (also called sudomotor dysfunction). Moreover, DPN may lead to chronic severe neuropathic pain with a negative impact on quality of life.

### **Importance of early diagnosis of diabetic peripheral neuropathy –**

- DPN needs to be diagnosed early for several reasons. First, patients with DPN should be offered intensified education on foot hygiene (e.g., never walking barefoot, daily foot inspection) and, ideally, podiatric care and proper footwear. These measures aim to reduce foot ulcerations as complications of DPN. Secondly, they should be instructed on avoiding other neurotoxic factors, such as excessive alcohol. Moreover, improved glycaemic control without hypoglycaemias and glucose fluctuations, management of blood pressure and dyslipidaemia, smoking cessation—all these measures, which are, indeed, necessary for every subject with diabetes—should be offered more zealously. All these therapeutic priorities render timely diagnosis of DPN very important.

## Diagnosing diabetic peripheral neuropathy

- Scientific associations of diabetes recommend that DPN is diagnosed based on careful comprehensive bedside clinical examination. The latter should assess both sensory (which are, generally, affected earlier) and motor modalities (which are thought to be affected at later stages). Moreover, it should assess both small (pain and temperature perception) and large nerve fibres (remaining functions). To do this, simple tools are required: a patella hammer, a graded 128-Hz tuning fork, a sterile test strip, a rod for hot/cold discrimination, and, secondarily, a 10-g monofilament and some cotton wool. After some training, the everyday clinician can easily carry out this examination. To promote comprehensiveness and to facilitate comparison of clinical findings, there are some clinical examination scores: among these, the most widely used is the neuropathy disability score (NDS).
- Scientific associations of diabetes also recommend that nerve conduction study is not routinely used but reserved for special circumstances, e.g., research purposes, atypical clinical manifestation, or differential diagnosis from other causes of neuropathy.

## Need for new diagnostic tests for diabetic peripheral neuropathy

- New tests aim to improve the early diagnosis of DPN. This can be accomplished in two ways: either the new tests detect signs of DPN before its clinical diagnosis or they aim to simplify the procedure, so that more subjects with diabetes can be screened, even by trained nurses. Ideally, a test should do both. Some of the new tests are highly sophisticated and demand specialised techniques and personnel, while others are very simple and can be easily and quickly carried out.

## New diagnostic tests for diabetic peripheral neuropathy

New diagnostic tests may be classified into those evaluating small nerve fibres and those evaluating large nerve fibres. Tests of small nerve fibres include the indicator test for sudomotor function Neuropad, corneal confocal microscopy of the human eye, skin biopsy for assessment of intra-epidermal nerve fibres, Sudoscan, LDIfiare, and the non-commercially available Neuroquick. Tests of large nerve fibres include automated sural nerve conduction study with a special portable device, Vibratip for vibration perception, Ipswich Touch Test, and the non-commercially available steel ball-bearing.

### 1. Tests For Small Fibre Function

- The indicator test Neuropad is a plaster assessing sweat gland function (sudomotor function). This is accomplished by evaluating the sweat produced by the feet. Indeed, sweat contains water, which reacts with the blue salt cobalt dichloride\* of the plaster and changes its colour to pink. The test is very simple: all you have to do is attach it to the plantar surface of the feet to a callus-free area between the 1st and 2nd metatarsal heads bilaterally and then wait for 10 min to read the colour change: complete bilateral colour change from blue to pink within 10 min is the normal response, while absent or incomplete colour change is abnormal. The procedure is so simple that it can be carried out by any individual, including patients themselves for self-examination. Moreover, we have shown excellent reproducibility. We have also found that the test, by virtue of its visual nature, increases motivation of subjects with diabetes to be instructed on foot care.
- Neuropad has been demonstrated to yield very high sensitivity and negative predictive value with modestly high specificity and positive predictive value. Therefore, it has been proposed as a screening tool primarily to exclude DPN. Its absolute simplicity adds to its value. We have also reported its potential utility in diagnosing DPN 5 years earlier than clinical examination in type 2 diabetes.



- Interestingly, Neuropad has been used for research purposes as well. Measurement of the absolute time until colour change has been shown to correlate with clinical and electrophysiological severity of DPN. Finally, novel automated image analysis software has been shown to improve the diagnostic performance of Neuropad.
- Corneal confocal microscopy (CCM) quantitatively evaluates small nerve fibres in the cornea of the human eye. It can study several nerve fibre parameters and requires expensive equipment and specialised personnel. Thus, it is currently used by expert groups mainly for research purposes. Generally, its sensitivity and specificity are moderate to high. It can detect nerve fibre abnormalities early in the course of diabetes. Importantly, CCM has been shown to detect improvements in DPN after therapeutic interventions, notably simultaneous pancreas and kidney transplantation or intensified glycaemic control. Therefore, it is hoped that it will improve our insights into the natural history of DPN. It is non-invasive and has high reproducibility.
- Skin biopsy is minimally invasive. It quantitatively evaluates small nerve fibres in the skin of the lower extremities. Like CCM, it can study several nerve fibre parameters, it can detect nerve fibre abnormalities early in the course of diabetes, and it is used by expert groups mainly for research purposes. Generally, its sensitivity and specificity are moderate to high. A worldwide reference study has reported useful normative data for skin biopsy parameters.
- Sudoscan again assesses sudomotor function without requiring specialised personnel. It is a device measuring the low-voltage electrical current, which attracts sodium chloride from sweat produced by palms in the hands and soles in the feet. It is non-invasive and reproducible. It has high sensitivity and moderate to high specificity.
- Neuroquick is a portable device with a fan. The latter emits cold air with adjustable fan velocity. It assesses cold air sensation on the foot dorsum. It has been suggested as a very accurate screening tool for early detection of small fibre impairment.



- LDI flare employs a modified laser Doppler imager to measure the flare size in foot dorsal skin after heating. It is simple and non-invasive. High sensitivity and specificity for DPN, as well as age-dependent normative values have been reported.

## 2. Tests For Large Fibre Function

- Automated nerve conduction study is carried out with the portable device NC-stat® DPNCheck™. It can easily and quickly record sensory nerve conduction velocity and sensory nerve action potential of the sural nerve. It does not require specialised personnel. It has very good reproducibility and shows very good correlation with gold standard nerve conduction study. We have shown high sensitivity and specificity with very high negative predictive value against clinical examination in type 2 diabetes.
- Ipswich Touch Test (ITT) is the simplest modality. The examiner touches the dorsal aspect of the 1st, 3rd, and 5th toe of the examinee bilaterally. Inability to feel at least two of these six stimuli denotes abnormal response. ITT shows good reproducibility and high correlation with the monofilament. Moreover, high sensitivity and very high specificity for DPN have been reported.
- Vibratip is a tiny battery-operated handheld device testing vibration perception on the hallux and other toes. It shows excellent agreement with the neurothesiometer, the monofilament, clinical examination, and ITT. Very good accuracy for the diagnosis of DPN has also been reported.
- Finally, the steel ball-bearing is a little globe testing protective sensation. Steel ball-bearings of varying diameters are applied on the plantar area over the second metatarsal head of each foot. The smallest ball-bearing felt by the examinee defines the ball-bearing score. We have reported high sensitivity and very high specificity for loss of protective sensation, as well as high sensitivity and specificity for detection of subjects with previous foot ulceration.

### Clinical implications

New diagnostic tests should now be more widely utilised. Skin biopsy and CCM are demanding and will continue to be used in the expert setting for research purposes. They can advance our knowledge in the early stages of the natural history of DPN, in its monitoring after therapeutic interventions etc. Conversely, the indicator test Neuropad is a brilliant and well-studied screening tool with excellent reproducibility and easiness of use, lending itself also to self-examination. It has high sensitivity and negative predictive value, being very reliable in the exclusion of DPN. It may also contribute to its early diagnosis. Automated sural nerve conduction study and Ipswich Touch Test are also easy to use and valuable for DPN screening. The other tests are also useful. It now remains to be demonstrated whether all these new diagnostic tests will, indeed, increase our diagnostic rates of DPN. At any rate, they offer an important opportunity to improve DPN diagnosis and should not be ignored.



## DIABETES COMPLICATIONS

### SESSION 6



By:  
**Dr. SARAH WILD**

Professor of Epidemiology, Usher Institute, College of Medicine and  
Veterinary Medicine, University of Edinburgh, UK

**Dr. Sarah during her presentation elaborated on the role of large diabetes registries to identify changing pattern of diabetes and its complications. Few highlighting points of her talk are summarized below –**

- Large diabetes databases with substantial population coverage can be generated from a variety of sources
- These include directly from data collected as part of routine clinical care, data collected for quality registers, administrative data such as population estimates and death registrations, and research studies using both observational and trial designs
- The Scottish approach, is to collect data on almost the whole population of people with diagnosed diabetes in Scotland and for secondary use of the data for research and compares and contrasts the approaches used for other databases
- In brief, the current Scottish Care Information (SCI)–Diabetes system has been developed over many years by clinical and technical experts to support clinical care, building on an agreed set of consistent definitions to define a core data set. SCI-diabetes has expanded over time to include call and recall for diabetic retinopathy screening and assessment of foot risk
- Relevant information is entered by clinical staff responsible for diabetes management in primary and secondary care as part of the process of care. They also gain access to information relevant to diabetes care entered by other health professionals
- An annual summary of the data in the system is provided in the Scottish Diabetes Survey. Patients have access to their records through the My Diabetes My Way patient portal
- Following approval from a national ethics committee and from the Public Benefit and Privacy Panel (a body that reviews the use of data for research for which consent has not been obtained from every individual), deidentified data are made available to researchers who have received approved data governance training

Empagliflozin effect on glomerular hyperfiltration shows similar magnitude as ACE inhibitor.

#### Advantages and Disadvantages of Using Large Databases for Research

Advantages	Disadvantages
Relatively quick and cheap to use compared to primary data collection once set up	Effort and expense required to set up and maintain
Representative if population based	Data governance issues must be addressed
Further potential from linkage to other databases and for comparisons to other databases if definitions are harmonized	Completeness and accuracy must be described
Large numbers improve power for studying rare outcomes	May lack key variables
	Potential for bias
	Statistically significant differences may not be clinically significant

### Opportunities and Challenges Relating to Use of Large Databases for Research

- The amount of time and effort required to set up such systems should not be underestimated and partly explains the limited number of population-based registers, particularly in less developed countries
- It is also important to understand the value of secondary uses of the data for research purposes if local requirements for data governance can be met
- Harmonization of data requires extensive work
- Once the challenges of ensuring that the data in diabetes databases are internally valid have been met, it becomes possible to consider the wider application of the data for research
- Database of different disease and condition like acute hospital admissions, cancer registrations, deaths and admissions to psychiatric hospitals, can be linked together
- It is also possible to link to other disease registers, such as the renal register
- Pharmaco-epidemiological studies are also possible with use of prescribing data

### Summary

- Several well-established and validated diabetes databases exist that provide the basis for valuable and efficient primary and secondary uses when data governance and methodological challenges have been addressed.
- Although setting up such databases takes a considerable amount of resources and time there are opportunities to learn from the experience of people responsible for existing databases.





## PSYCHOLOGICAL ASPECTS SESSION 7



By:  
**Dr. FRANK SNOEK**

Professor Medical Psychology, VU University Medical Center  
Amsterdam, Netherlands

**Dr. Frank elaborated on the psychological aspects on diabetes complications and the role of behavior change and mental health in improving the standard of care in diabetes. Few excerpts from his presentation are highlighted below –**

### **Contributions of Behavioral Research**

- Psychology can help us make sense of human behaviors in the context of diabetes care, and that includes not only the behaviors of people with diabetes, but also those of their significant others and of health care professionals.
- Second, behavioral science offers methodologies and measures to help capture the lived experience of individuals affected by diabetes.
- Third, psychology offers strategies and interventions to effectively promote behavior change and emotional well-being and implement effective interventions that help people with diabetes achieve optimal health outcomes.

### **Indirect Approaches**

- Most people with diabetes do not have access to a psychologist; rather, they see nurses, doctors, and sometimes dietitians or other health care professionals. These professionals on the front lines of diabetes patient care are the ones who deliver most of the care, and, with appropriate training and tools, they can indirectly offer psychological interventions as part of their routine consultations.
- We developed a procedure called MIND (Monitoring of Individual Needs in Diabetes).
- Briefly, people with diabetes are offered a short psychological assessment as part of routine consultation. This assessment includes questions to elicit patients' agenda for their consultation and questions tapping into their diabetes-related distress and emotional well-being.

- A trained diabetes nurse specialist discusses the outcomes with each patient, and together they decide whether any actions are needed, such as referral to a mental health professional.
- This approach aims to put emotional well-being at the forefront of the consultation and to promote psychologically informed diabetes care.
- Another example of indirect psychological intervention would be diabetes self-management education and support programs. Such programs, grounded in psychological theory and delivered by diabetes educators, have been shown to empower patients and improve their well-being.

### Direct Approaches to Reducing Diabetes Distress

- Diabetes distress is distinct from depression in that it is not a disorder, but rather an emotional response to the strains of living with diabetes.
- It affects 20–40% of people with diabetes and is associated with difficulties in diabetes self-management and with suboptimal outcomes.

### When and for Whom?

- Cognitive behavioral therapy offered to participants with high baseline levels of diabetes distress and elevated A1c levels effectively improves both.
- Offer interventions to those with high levels of diabetes distress, comprising ~25% of the patient population based on commonly defined cut-off scores on the Problem Areas in Diabetes (PAID) scale or the Diabetes Distress Scale (DDS).
- There are three levels of distress: low, moderate, and high. Perform repeated assessments (i.e., monitoring patients over time and responding to their changing needs rather than acting on a one-time screening). We should be cautious in interpreting a single elevated distress score as an indication for professional help; high diabetes distress at a given moment in time is not necessarily maladaptive and indeed may well be an adaptive response to a

stressful event (e.g., receiving bad news regarding the progression of a diabetes complication). It is over time that we can see whether and how well a person adapts and whether professional support is called for.

- Regarding the precision of measurement, the traditional approach of administering retrospective well-being questionnaires repeatedly over a certain period of time is helpful but not likely to be informative when it comes to identifying specific events or triggers preceding a change in distress level. So-called ecological momentary assessment (EMA), also known as the experience sampling method, is both needed and feasible with current technology.
- With EMA, patients are provided a mobile device application (app) that prompts questions on a smartphone over the course of a day and stores the data automatically. The app thus provides the opportunity to capture psychological functioning in real time without recall bias. Similar to continuous glucose monitoring, EMA can help us connect the dots and better understand the dynamics of diabetes distress in the context of a person's life.
- Moreover, “digital phenotyping” allows us to personalize psychological support and offer so-called just-in-time adaptive interventions the timing, content, and intensity of which are based on individuals' digital profile.

### What? Behavior Change and Mental Health

- The first type of intervention is aimed at promoting health behaviors (e.g., following a healthy diet, quitting smoking, getting physical exercise, and performing diabetes-specific self-care tasks), with an emphasis on beliefs and perceptions regarding health risks and future benefits.
- The second type of intervention has mood repair as its primary aim and targets negative emotions.
- The distinction between these two types of intervention is not only largely artificial, but it is also not helpful in the context of supporting people with diabetes, for whom health behavior and mood are both priorities and are closely connected.

- Particularly for people with diabetes and comorbid psychological distress, an integrated approach is warranted to help overcome potential conflicting self-regulatory demands.
- A recent study by de Groot et al. (2020) that combined depression treatment with physical activity in people with Type 2 diabetes is a good example.

### How? Reaching Those in Need

- Unfortunately, we reach only a limited number of people in need. Offering therapies via the Internet can help to expand our reach. Online interventions have been shown to be safe, patient-friendly, cost-saving, and effective in people with or without a chronic illness.
- We were among the first to develop and test a Web-based course on coping with depression specifically for people with diabetes and comorbid depression, and we showed that it effectively reduced depressive symptoms and diabetes distress even in the more severe cases.
- We are currently piloting a fully self-guided, Web-based program called MyDiamate. This app is designed to be a “buddy” for people with diabetes and to assist them in healthy coping. It offers different modules and modalities and can be used 24/7 at the discretion of the user. We hope to further develop this app and make it available to a large audience.



## EYE COMPLICATIONS

### SESSION 8



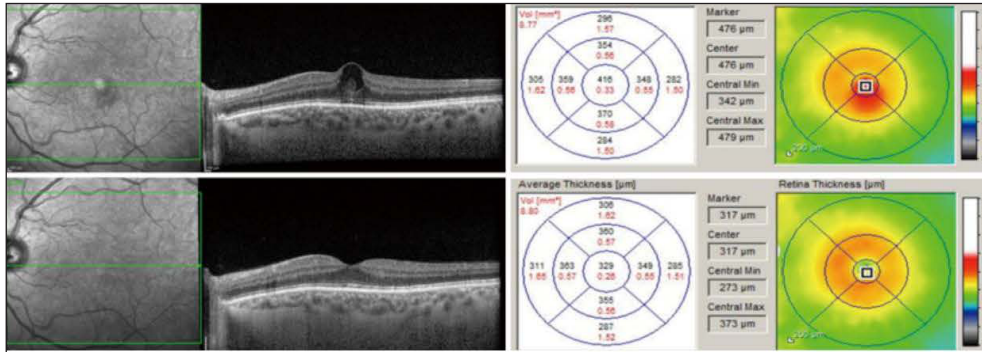
**By:**  
**Dr. NOEMI LOIS**

Clinical Professor, School of Medicine, Dentistry and Biomedical Sciences,  
Wellcome Wolfson Institute for Experimental Medicine, Queen's University Belfast, UK



**Dr. Noemi shared some insights on the management of diabetic macular edema during her talk. Few key takeaways from her presentation are listed below –**

- Diabetic macular oedema (DMO) is a major sight-threatening complication of diabetes. Based on the estimated prevalence of DMO (~7% in diabetic patients) there are at least 29.5 million people suffering from DMO worldwide
- The prevalence of DMO increases with the duration of diabetes; it has been estimated that ~20% of diabetics will have DMO after 20 years of disease
- The risk of developing DMO increases with poor glycemic control and with increased blood pressure and serum cholesterol levels
- People diagnosed at age 30 or older with diabetes and who develop clinically significant macular oedema (CSMO), as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS) criteria, seem to have increased ischemic heart disease mortality
- Although most cases of DMO will progress and fluid accumulation will worsen over time with subsequent visual loss, spontaneous resolution of DMO can occur (30–35% of cases)



As presented during IDF 2021

Optical coherence tomography (OCT) clearly demonstrated central involving diabetic macular oedema (DMO) (top row; left eye shown). The mean central subfield thickness was over 400 microns (top centre row); anti-VEGF therapy was planned to be undertaken on the following week, as per patient request. The patient failed to attend his appointment and did not return to clinic until June 2015. By then, complete resolution of the DMO was noted (bottom centre row and bottom row; left eye shown) with no change in the systemic status of the patient.

## Prevention

- Ideally, preventing the development of DMO, rather than treating it once established, should be the best option to avoid sight loss
- Given that only a small proportion of all patients with diabetes will develop DMO, identifying the people at higher risk for developing this complication would be essential to increase the likelihood for potential preventive treatments to be cost-effective
- As stated above, people with poor glycaemic control, hypertension and high serum cholesterol are at higher risk of developing DMO; controlling these systemic risk factors should be sought, although may be difficult in some patients
- Care should be taken, however, to avoid rapid changes (increase or decrease) in HbA1c and blood pressure as these may precipitate the development of DMO

- Thus, at least in people with type 1 diabetes the risk of development of DMO requiring treatment was found to be reduced when changes in levels of HbA1c, systolic and diastolic blood pressure were kept within  $\pm 0.5\%$ , 10 and 5 mmHg, respectively, during a 6-month period
- Indeed, it has been recommended that six-month changes in HbA1c should be kept below 2 percentage points to minimise progression to CSMO

## Treatment

- Macular laser photocoagulation,
- Intravitreal (anti-vascular endothelial growth factor) anti-VEGF therapies and
- Intravitreal steroids.

## Summary

- Control of systemic risk factors, macular laser, anti-VEGFs and steroids can be used to treat patients with DMO. Treatment with fenofibrate should be considered to prevent the development of complications requiring treatment (DMO and PDR).
- At least a third of patients will respond to laser treatment (very likely more if patients are selected for this treatment based on their characteristics e.g., those with localised leakage on FFA, those with  $< 400$  microns of CRT on OCT). Macular laser photocoagulation should be also performed in non-centre involving CSMO to prevent involvement of the centre and need for anti-VEGFs; the ETDRS study proved the value of laser under these circumstances. Laser should be also considered for patients with CSMO and normal or with minimal visual loss ( $> 20/32$ ) as data on anti-VEGFs is not available for this group but evidence from the ETDRS demonstrated a benefit of laser treatment.

- In clinical practice it is expected that on average ~50–60% of patients will respond to anti-VEGFs with a  $\geq 10$  ETDRS letter improvement. Around 50% of patients will still require laser treatment and ~50% will still require injections 5 years on. The reduced progression of retinopathy observed in patients on anti-VEGF may lead to reduce rates of PDR in the future.
- Licensed intraocular steroids (dexamethasone, flucinolone) may be considered as a second/third line therapy for people with DMO.
- Ideally patients with DMO should be treated in a “personalised” manner, using the treatment preferred by the patient and the one that should provide the best chance to benefit her/him. Given that Health Services do not have infinite resources, not only the clinical effectiveness but also the cost-effectiveness of the treatments should be taken into consideration when selecting therapeutic strategies for patients.
- Cancellations of all routine appointments worldwide during the ongoing coronavirus disease 2019 pandemic have exacerbated this problem to unprecedented levels. Thus, it is imperative that new ways to increase efficiency and capacity of ophthalmic clinics are identified and, if safe and acceptable, are implemented.
- The Effectiveness of Multimodal Imaging for the Evaluation of Retinal Oedema and New Vessels in Diabetic Retinopathy (EMERALD) study was conceived with the above purpose.
- It tested whether patients with DME, PDR, or both previously treated successfully (i.e., DME cleared and PDR became inactive) could be followed up through a new care pathway involving multimodal retinal imaging assessed by trained nonmedical staff (ophthalmic graders).
- Diagnostic accuracy, cost consequences, and acceptability of this new pathway to patients and health care professionals were evaluated against the current standard of care (face-to-face evaluation of patients by ophthalmologists).



## FOOT COMPLICATIONS

### SESSION 9



**By:**  
**Dr. ERIC SENNEVILLE**  
Specialist in Infectious Diseases, Gustave Dron Hospital, Tourcoing, France

## **Dr. Eric focused his talk on the medical approach of diabetic foot osteomyelitis. A summary of his presentation is listed below –**

- The invasion of bone tissues by microorganisms represents an important step in the natural history of diabetic foot infections (DFIs)
- The difficulties in obtaining a sustained remission of diabetic foot osteomyelitis (DFOs) add to the other limitations of the treatment of DFIs
- DFO can be associated with a noninfected DFU (Diabetic foot ulcer), which led the IWGDF to no longer includes osteomyelitis as one of the criteria for making a class 3 infection but designates its presence in any class 3 or 4 infection by adding “O” to the classification

### **Suspicion vs. definite diagnosis**

- Suspicion is based on clinical, biological, and imaging assessment
- Definite diagnosis is based on bone sample examination, combining it with a positive culture and histological abnormalities consistent with the diagnosis of bone infection
- In addition, definite diagnosis of DFO may be obtained by the means of clinical signs and imaging assessment

### **Clinical findings**

- Simple clinical signs can lead to suspect a DFO such as non-healing DFU despite satisfactory blood supply of the foot, appropriate nursing and off-loading of the wound
- Other clinical elements of suspicion of DFO are the characteristics of the DFU such as its size (i.e., > 2 cm), depth (i.e., > 3 mm), an inflammatory toe (“sausage toe”), drainage of synovial liquid and its location over a bony prominence
- The probe-to-bone (PTB) test is a very useful tool in order to either confirm or rule out the diagnosis of DFO



## Biomarkers

- Erythrocyte sedimentation rate (ESR) appears to be most useful of the inflammatory biomarkers available in the daily practice for diagnosing osteomyelitis

## Imaging

- Plain X-ray of the foot is widely available, not expensive and is not limited by contraindications. It can be repeated so that sequential evaluation can be easily performed
- The sensitivity of plain X-rays is, however, lower than other imaging techniques
- Combining plain X-rays with PTB results in increasing the sensitivity and specificity
- In cases where bone biopsy is not done, the interest of more sophisticated imaging techniques (i.e., MRI, scintigraphy, FDG) resides in confirming the diagnosis of DFO and help localize the site of bone infection

## Bone Biopsy

- Numerous studies have compared the results of bone and soft tissue cultures in patients with DFO
- In all studies, the best values of concordance were found with *S. aureus*
- A negative bone culture can accurately rule out the diagnosis of DFO
- Independent culture methods such as DNA-based techniques have shown their superiority over classical methods in terms of quantity and diversity of the identified bacterial strains but have not yet shown any clinical benefit for the management including the antibiotic treatment of these patients

Authors	N° patients	Diagnostic tools	% overall concordance
Lavery <sup>21</sup>	36	Deep tissues/bone biopsy	36
Kessler <sup>22</sup>	21	Swabs/deep tissues	19
Senneville <sup>23</sup>	76	Swabs/bone biopsy	23
Senneville <sup>24</sup>	31	Needle aspiration/bone biopsy	32
Elamurugan <sup>25</sup>	144	Swabs/bone biopsy	38
Malone <sup>26</sup>	34	Deep wound/bone biopsy	74 <sup>a</sup>
Couturier <sup>27</sup>	38	Per wound/percutaneous biopsy	48

<sup>a</sup>concordance defined as at least one similar organism isolated from both procedures.

As presented during IDF 2021

### Summary

- DFO is highly prevalent in patients presenting with DFI and its definite diagnosis and treatment significantly complicate the management of such patients.
- Clinical assessment including the PTB test and plain X-ray of the foot usually provide useful arguments.
- Bone sample examination taken percutaneously or surgically confirm or rule out the diagnosis of DFO and provides microbiological data to help guide the antimicrobial treatment.
- Sophisticated imaging techniques such as MRI, labelled WBC scintigraphy and <sup>18</sup>F-FDG-labelled leukocyte PET/CT should be reserved for patient in whom the diagnosis of DFO remains uncertain after first-line diagnostic tests.



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