

Sanofi Presents

Exclusive Coverage of

CLINICAL PEARLS IN DIABETES CARE

for Implementation in Your
Diabetes Practice





Highlights of **CLINICAL PEARLS IN DIABETES CARE** for Implementation in Your Diabetes Practice



Exclusive coverage of specific clinical updates presented during the latest IDF 2021 meeting



Covers the latest global updates on the clinical pointers



Presents Key takeaways to improve standard of care in clinical setting



Highlights the latest trends presented during the IDF 2021 conference in prevention and management of diabetes and its complications

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PATHOGENESIS AND PATHOPHYSIOLOGY OF DIABETIC EYE DISEASES

SESSION 1



By:

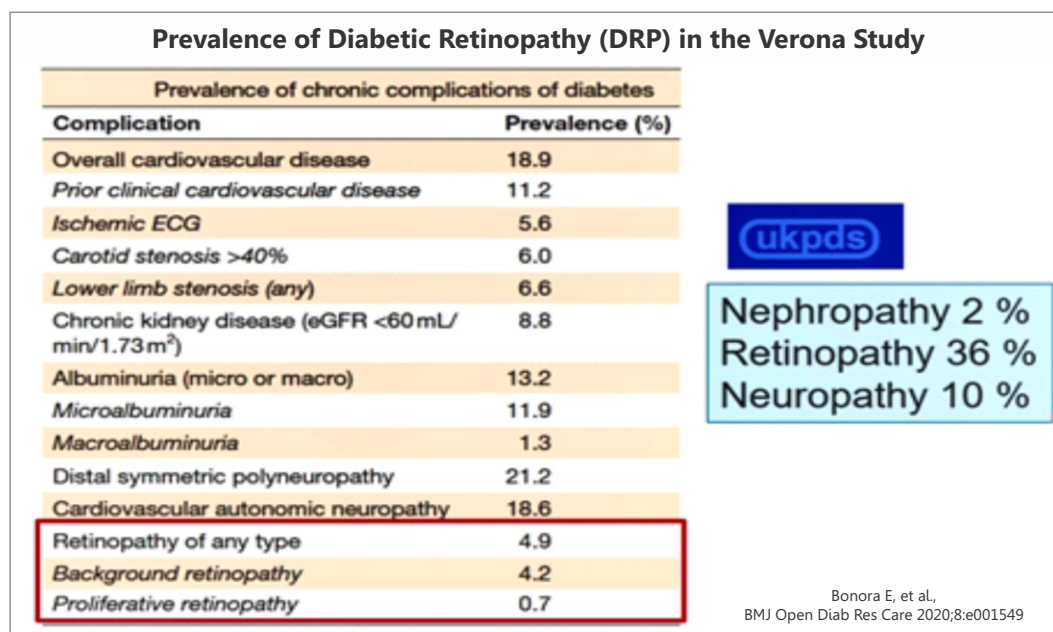
DR. HANS-PETER HAMMES

Section Head Endocrinology, V. Medical Clinic, Medical Faculty Mannheim Heidelberg University, Germany

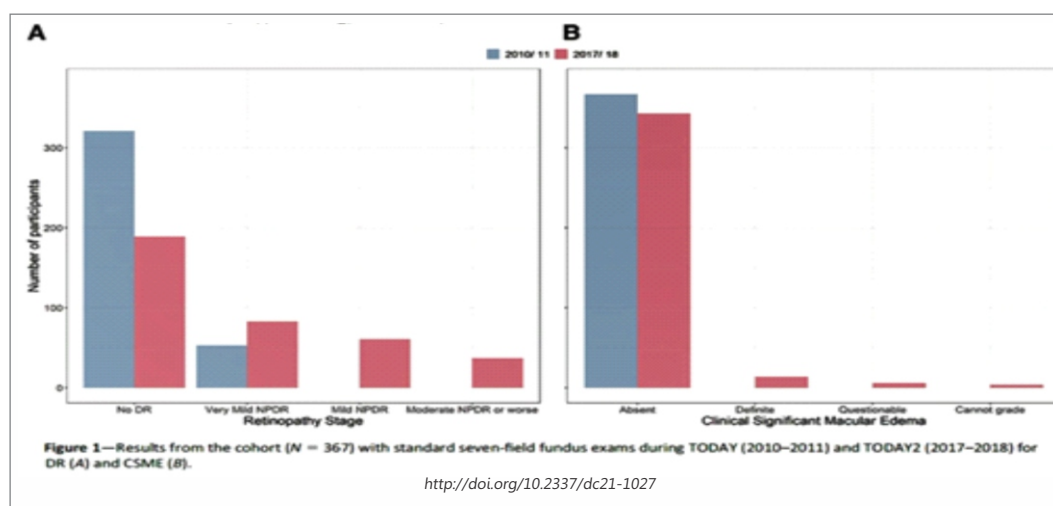
DR. ALAN SITT

Professor, Dean of Innovation and Impact, School of Medicine, Dentistry and Biomedical Sciences,
Queen's University Belfast, UK

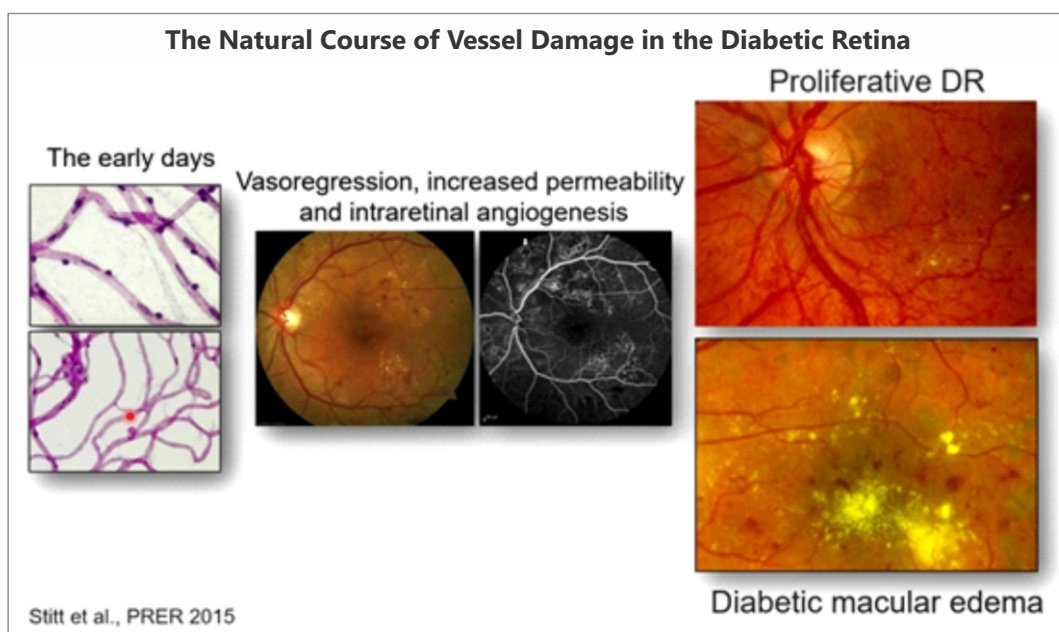
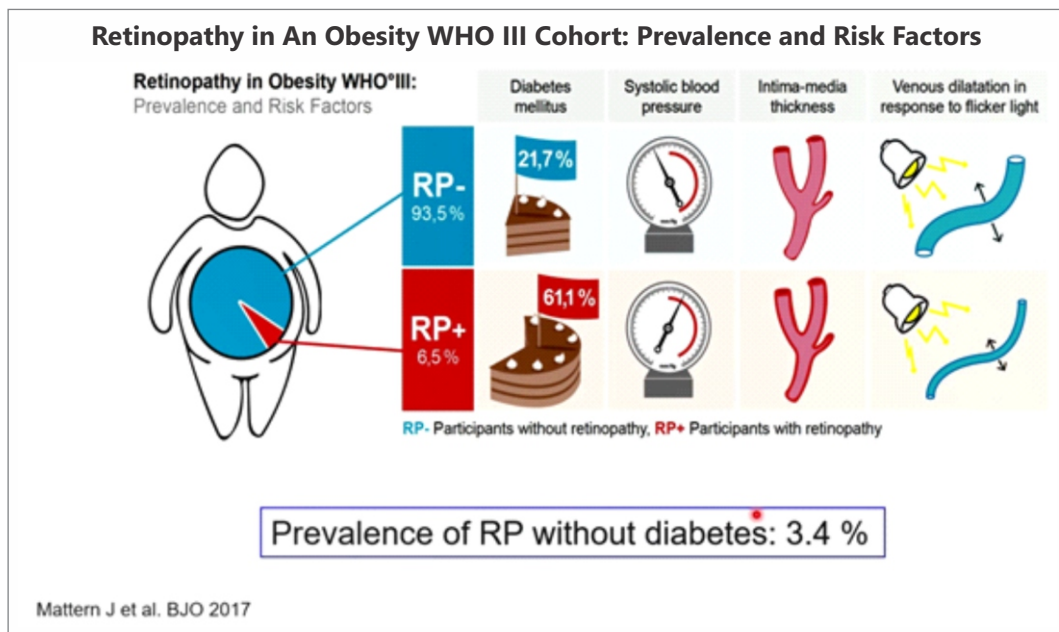
Dr. Hans summarized the natural history and classification of diabetic eye disease:

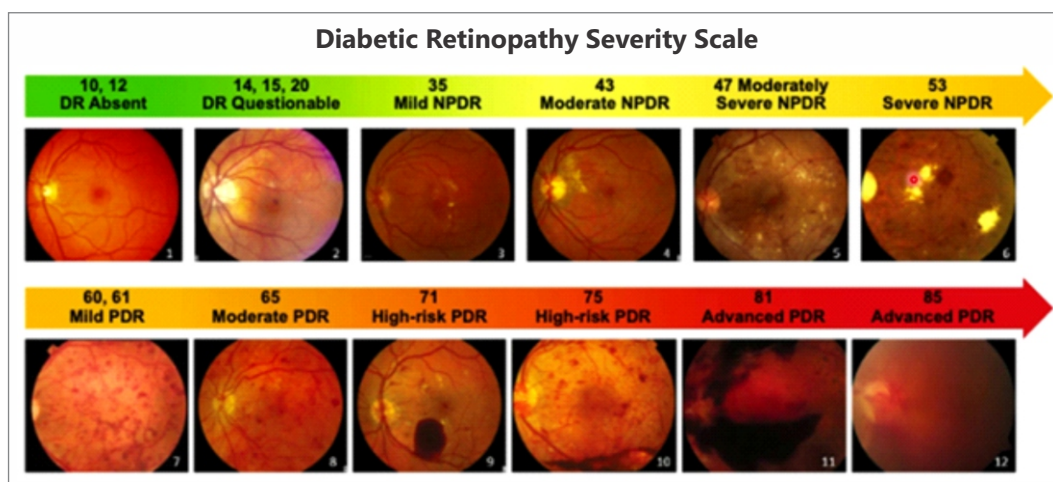


Also as highlighted in the outcomes of TODAY study, the development and progression of diabetic retinopathy is increasing in adolescents and young adults.

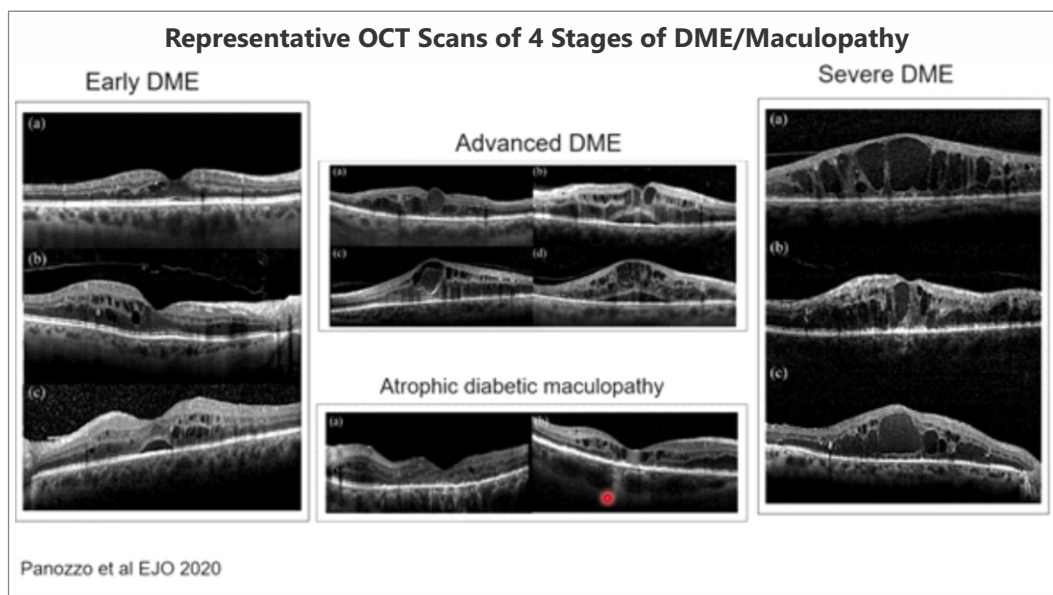


Univariate analysis shown that the progression of retinopathy is associated with lower BMI, higher HbA1c (even multivariate), higher BP, higher triglycerides, decreased C-peptide and presence of multiple comorbidities.





As presented during IDF 2021

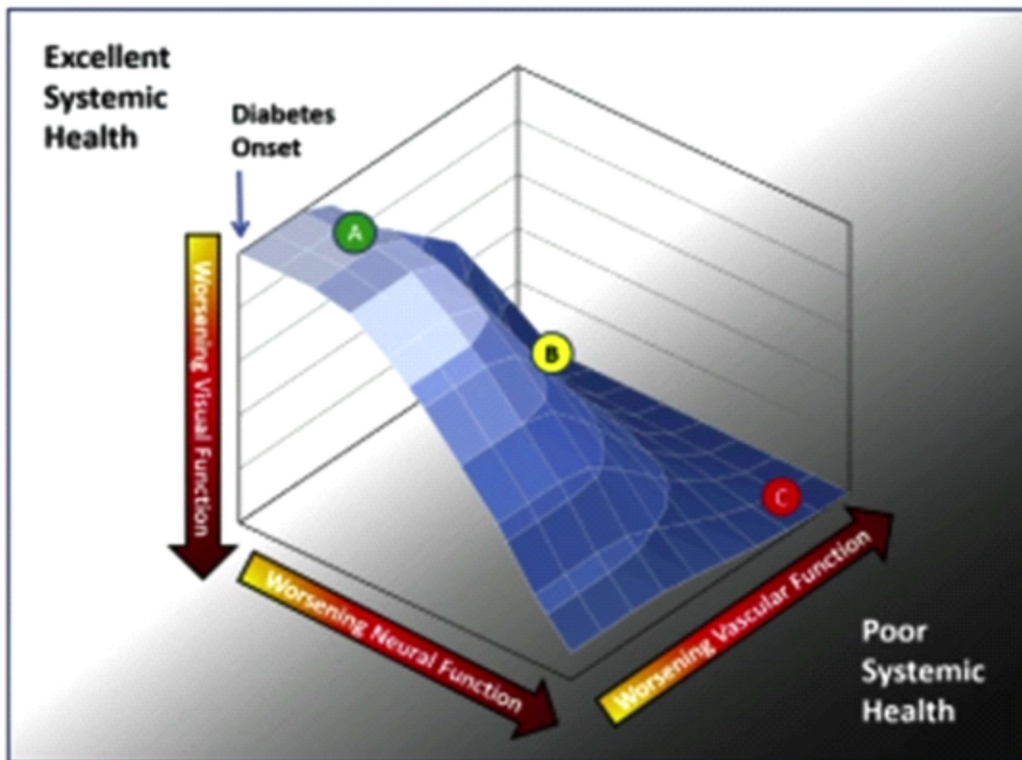


WHO Short Guide on Screening of Diabetic Retinopathy



As presented during IDF 2021

Relationship Between Retinal, Neural and Vascular Pathology with Visual Function – Need for a Revised Severity Scale for Diabetic Retinal Disease



Sun et al. Ophthalmology 2021 128(4) 490-493

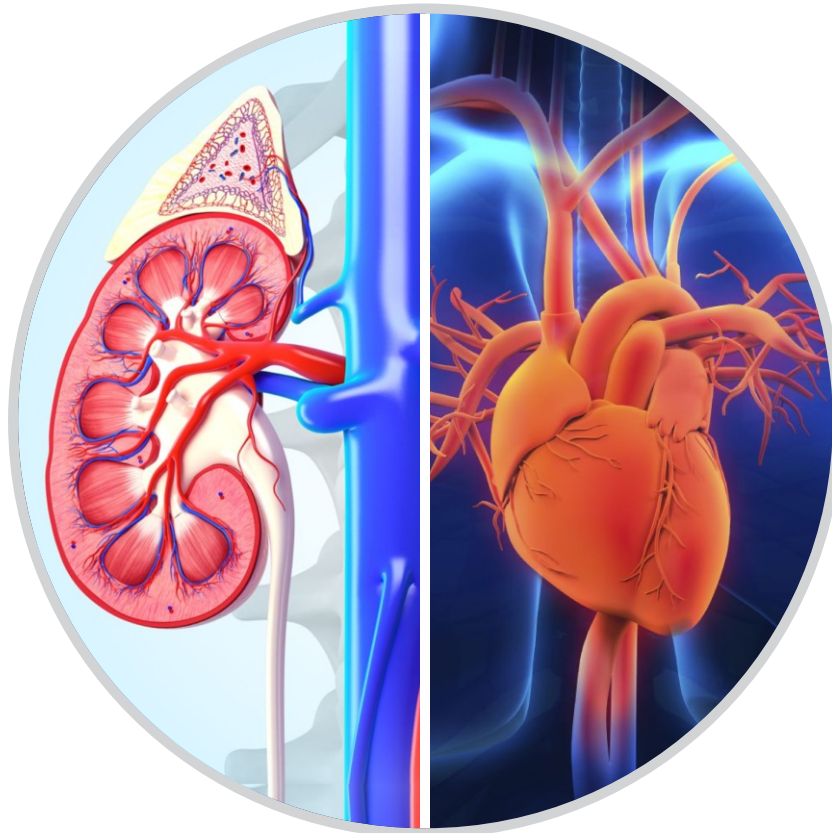
Summary

- Retinopathy is a predictor of CVD
- Diabetes care should acknowledge different DRP courses
- Retina is the most glucose-sensitive target tissue
- Currently classification is mainly based on vascular lesions
- DRP is a disease of the neurovascular unit and should be treated accordingly

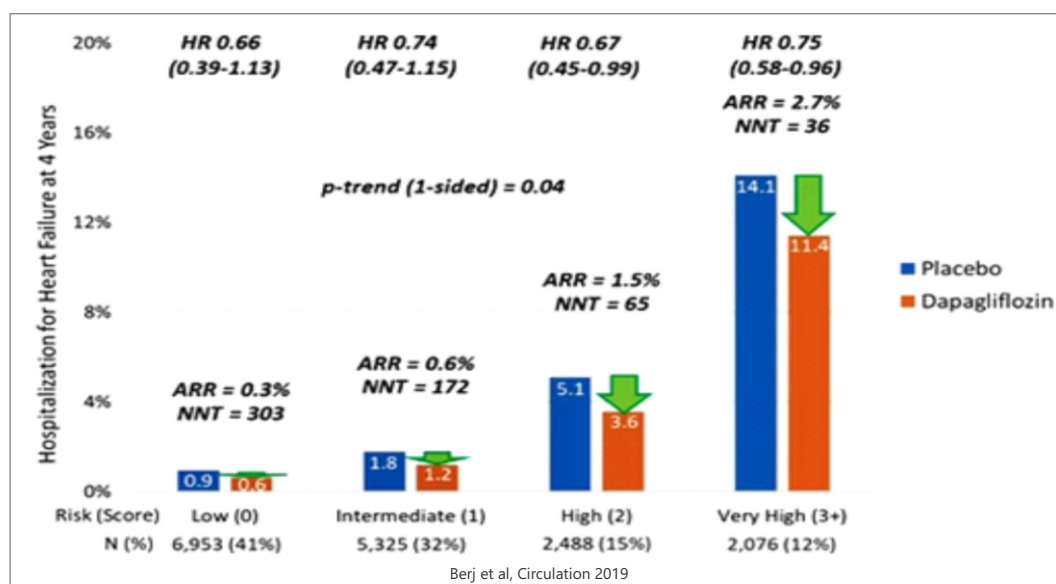


ROLE OF GLYCEMIC CONTROL IN AN ERA OF GLUCOSE-LOWERING MEDICATIONS WITH PROVEN CARDIORENAL BENEFITS

SESSION 2



- Recent data on newer drug therapies including SGLT2i and GLP-1 RAs has shown a positive effect of these drugs in diabetic patients with associated cardiovascular or renal comorbidities
- However, these drugs have shown a positive outcome even in diabetic patients with normal renal or cardiac function
- A subgroup analysis of DECLARE study with dapagliflozin has shown a reduction in risk scores in diabetic patients with normal renal or cardiac function



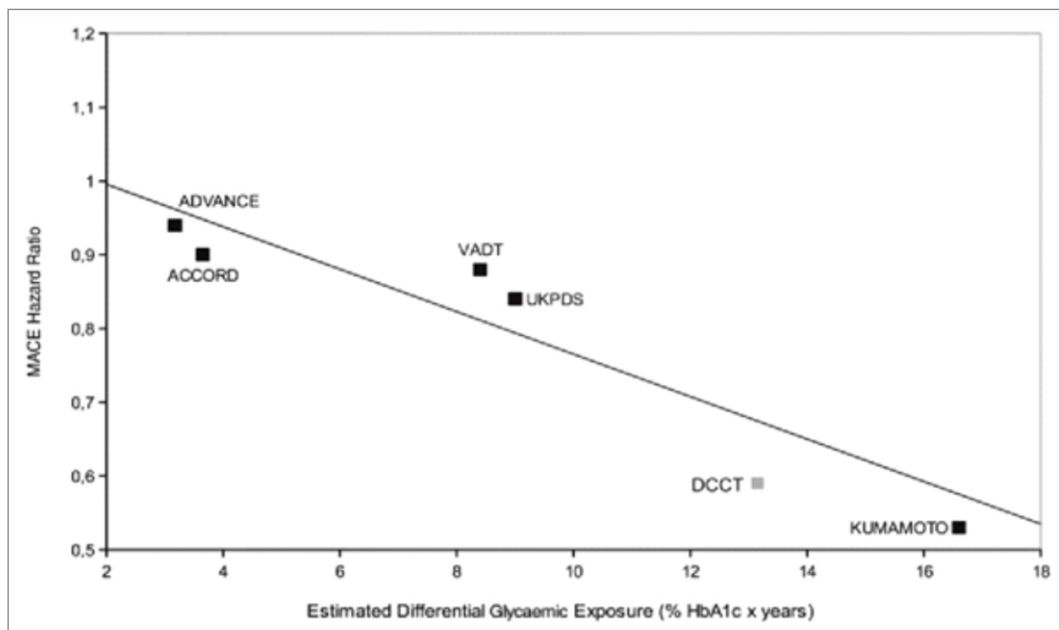
- An optimal glycemic control in Type 2 diabetes can reduce the adverse CV outcomes

		Standard therapy		Intensive therapy					
	Diabetes duration (years)	n	HbA _{1c} achieved (%)	n	HbA _{1c} achieved (%)	Intervention period (years)	Follow-up (years)	Cardiovascular outcome, hazard ratio (95% CI)	
UKPDS ⁵	0	1,138	7.9	2,729	7.0	10.0	10.0	0.84 (0.71-1.00)	
							16.8	0.85 (0.74-0.97)	
ACCORD ⁷	10	5,123	7.5	5,128	6.4	3.4	3.4	0.90 (0.78-1.04)	
							8.8	0.95 (0.87-1.04)	
ADVANCE ¹⁷	7.9-8.0	5,569	7.3	5,571	6.5	5.0	5.0	0.94 (0.84-1.06)	
							9.9	1.00 (0.92-1.08)	
VADT ^{14,18}	11.5	899	8.4	892	6.9	5.6	5.6	0.88 (0.74-1.05)	
							9.8	0.83 (0.70-0.99)	
							13.6	0.91 (0.78-1.06)	

0.5 Intensive therapy better 1.0 Standard therapy better 1.5

Kershaw V et al, Nat Rev Cardiol 2019

- Similar outcomes are reported in post-hoc analysis of various landmark trials to assess the risk of MACE with glycaemic exposure by Ronan et al (2018)



As presented during IDF 2021



OHAS FAST CHECKING – ADJUSTING TREATMENT OPTIONS TO REAL-WORLD PRACTICE

SESSION 3



By:
DR. SIEW PHENG

Honorary Professor, Visiting Consultant Endocrinologist, University of Malaya Medical Center, Malaysia

Dr. Siew Pheng Chan emphasized the need for evaluating approach for management of Type 2 diabetes (glucocentric or cardiocentric) during her talk. Few highlighting discussion points are summarized below:

Points to consider before finalizing treatment approach

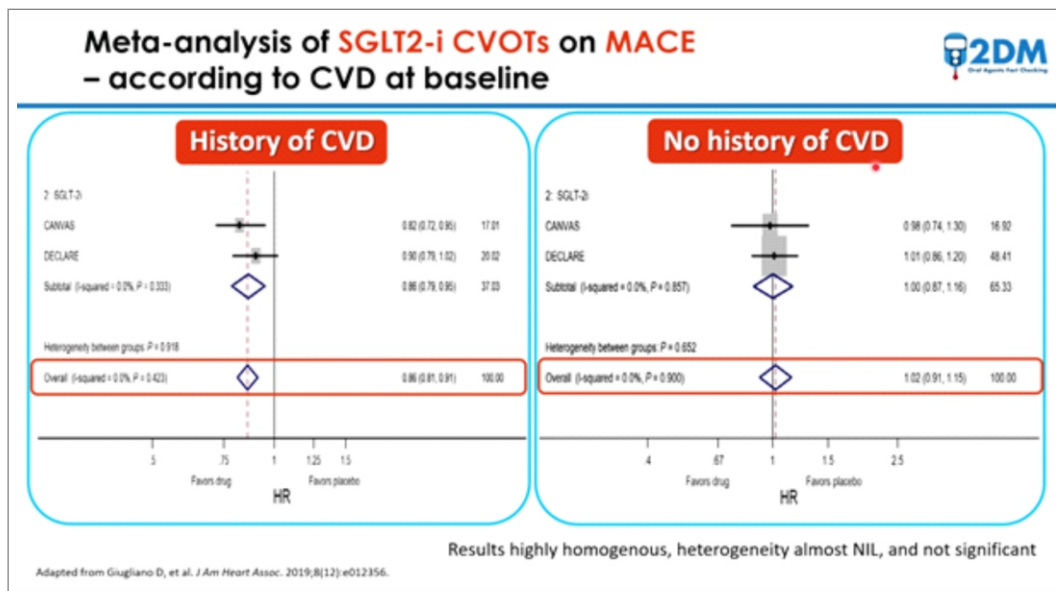
- Discuss the risks and benefits of glucocentric and cardiocentric treatment approaches in Type 2 diabetes
- Adopt an individualized approach to Type 2 diabetes management that balances potential benefits and harms in the context of patient preferences, goals, and barriers to treatment

Benefits of a glucocentric approach

- Trials like UKPDS and ADVANCE have shown the merit in glucocentric approach with reduction of slight HbA1c translating in risk reduction of multiple comorbid conditions
- At the same time there is a legacy effect shown by glucocentric approach

Benefits of a cardiocentric approach

- A significant reduction in MACE has been observed by therapies that provide cardiovascular benefits however these benefits are mainly exhibited in case of patients with history of CVD



Limitation of a cardiocentric approach

- Lack of generalizability as current CVOTs include participants who are having high CV risk and thus not accurate representative of the larger population
- The timeline is short to access long-term potential harm

The key is to strike the right balance and forming an individualized treatment approach to provide best care including the realities of cost and affordability

During the session, Dr. Lee Ling Lim presented the interim data of the new real-world evidence on sulfonylurea (SU) use in Asia – The JADE registry (Joint Asia Diabetes Evaluation)

- JADE registry will throw light on treatment patterns in Asian Type 2 diabetic patients with respect to SU usage pattern
- The study will provide new regional, real-world data on pattern of SU use and effectiveness and safety of SU
- JADE has more than 100,000 patients from 11 Asian countries (including more than 35,000 patients from India)

Study population

- ◆ Asian patients with type 2 diabetes (T2D)
- ◆ Treated with oral glucose-lowering drugs (OGLDs)
- ◆ Aged ≥18 years
- ◆ Enrolled in the JADE Register between **January 2007 and December 2019**

Primary objectives

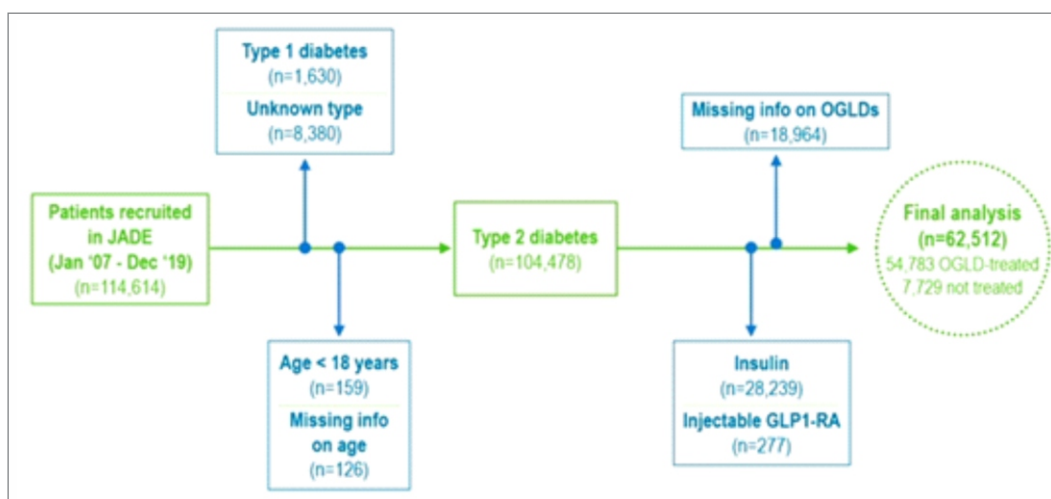
- ◆ To describe the **pattern of OGLDs use** (as well as SU and non-SU-based therapy)
- ◆ To evaluate the **effectiveness and safety* of SU-based therapy**

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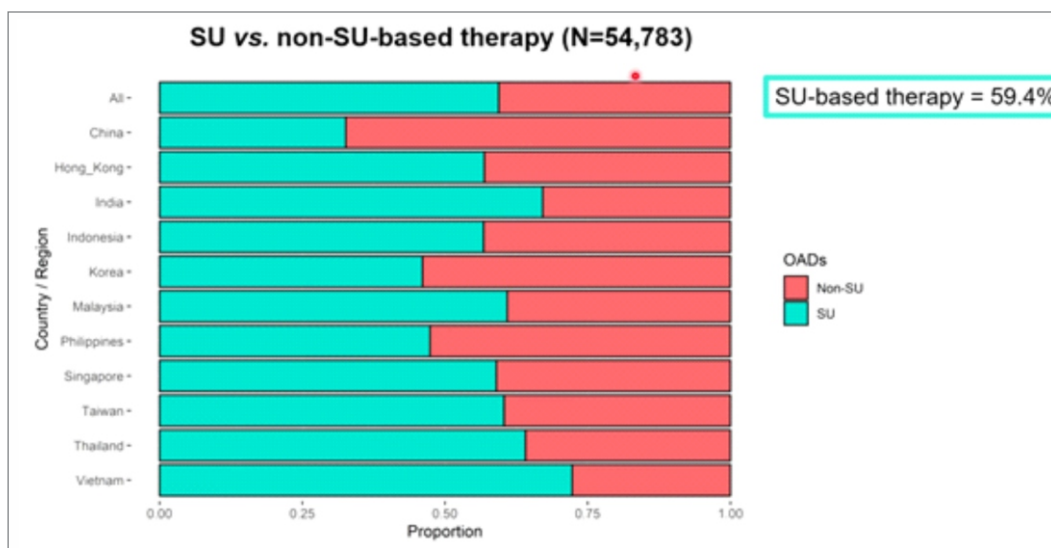
Secondary objectives

- ◆ To describe the patterns of different SU (including gliclazide) in monotherapy or combination therapy
- ◆ To compare the proportion of patients with ≥ 1 episode of self-reported hypoglycemia event
 - SU vs. non-SU
 - Gliclazide vs. non-gliclazide
- ◆ To describe the clinical profiles between treatment-naïve group and SU-treated group in newly diagnosed patients (<1 year of diabetes duration)

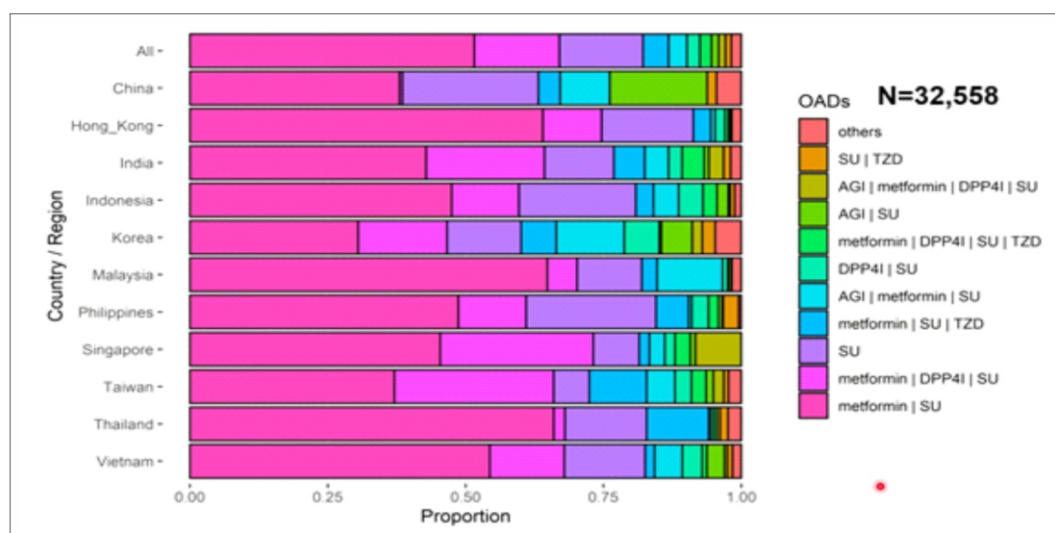
As presented during IDF 2021



As presented during IDF 2021



As presented during IDF 2021



As presented during IDF 2021

- The interim data has shown that the use of SU in Asian countries is very common with nearly 60% of patients on OADs currently being treated with SU based therapies
- Among the SU based therapies, SU+Metformin is most commonly prescribed treatment regiment, followed by triple combination (with DPP-4i) and plain SU respectively



PAINFUL DIABETIC NEUROPATHY (PDN)

SESSION 4



By:
MS. ERUM

Consultant Diabetes Educator, Pakistan

DR. ANA COSTA

Assistant Professor at Higher Education College of Setúbal
(Escola Superior de Educação do Instituto Politécnico de Setúbal), Portugal

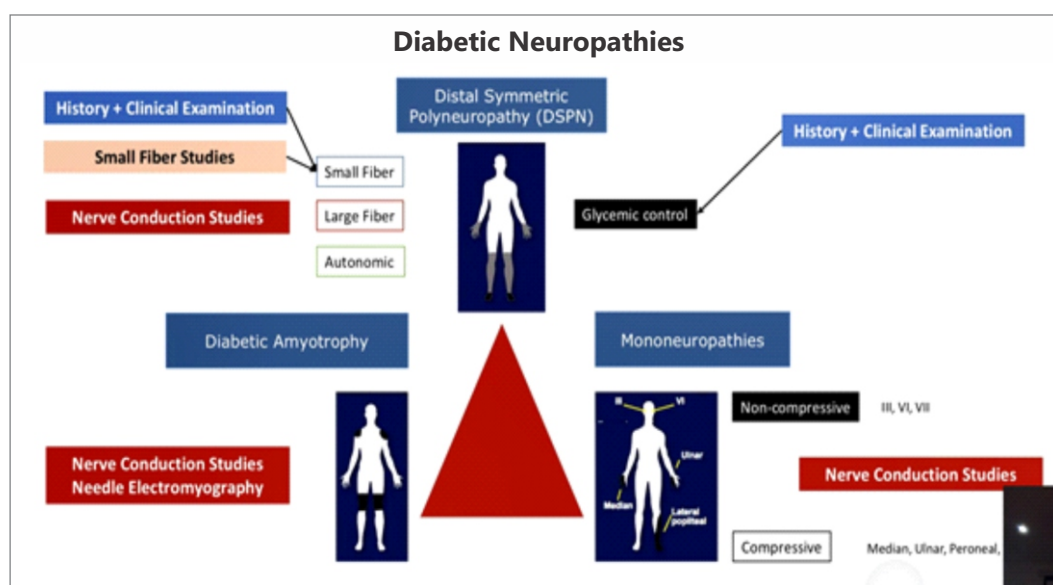
PROF. KARA MIZOKAMI

Assistant Professor, Internal Medicine, University of Michigan Health, USA

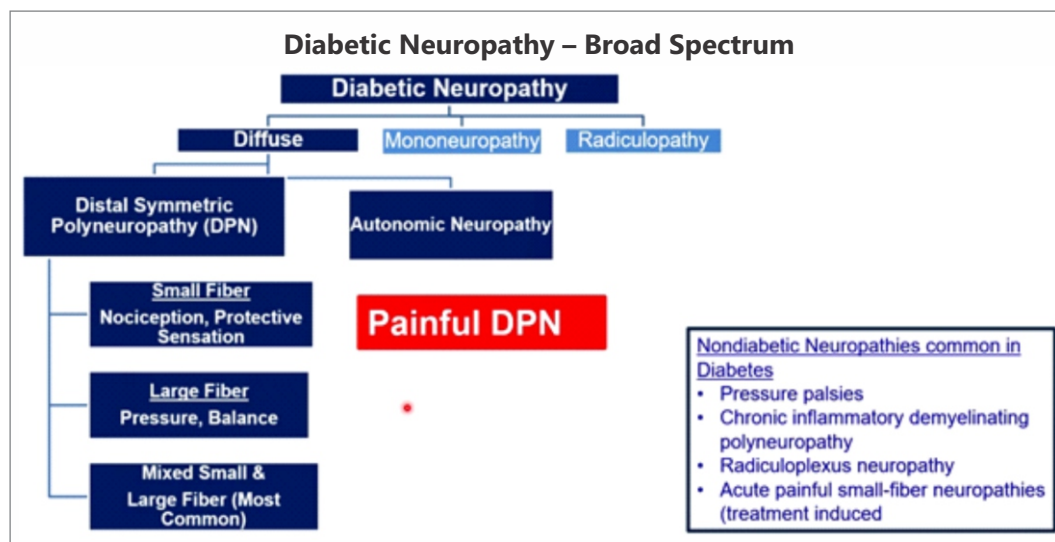
The session included talk by Ms. Erum, a diabetic educator herself, and patient of diabetic neuropathy. She shared her personal experiences and tips of managing the condition, including:

- Individualizing treatment plan
- Making right meal choices
- Balancing insulin with carb intake
- Having strict control on diabetes
- Understanding the disorder and complications better
- Having peer support
- Continuous education
- Positive attitude

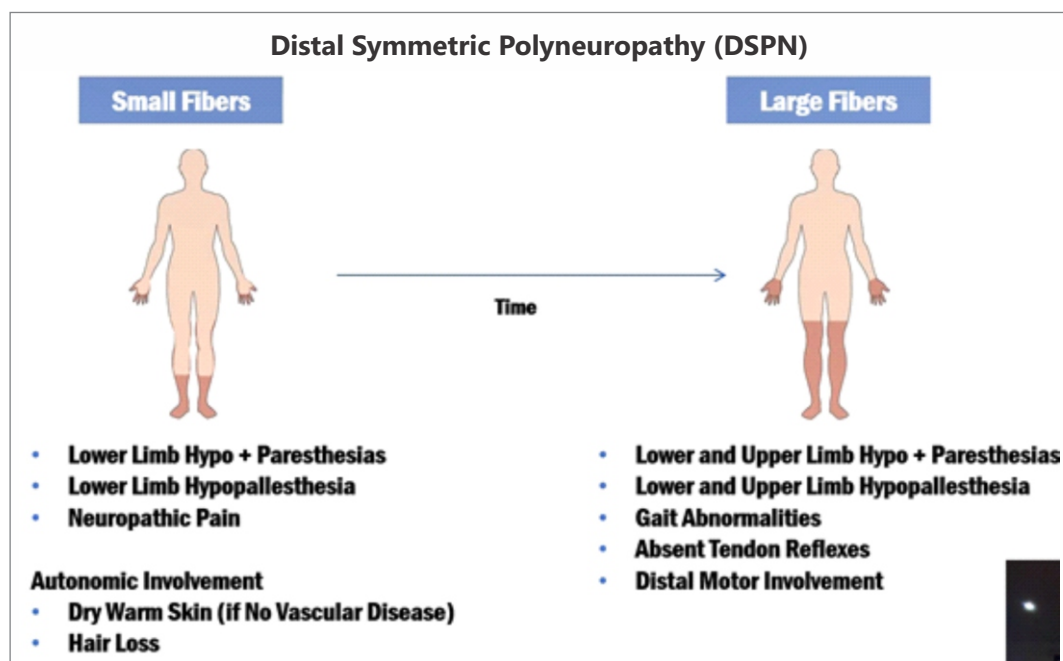
The session was followed by talk of Dr. Ana Costa on pharmacological therapies in PDN. Few excerpts of her presentation are highlighted below:



As presented during IDF 2021



As presented during IDF 2021



As presented during IDF 2021

The impact of neuropathic pain

- DSPN prevalence is estimated to be between 7-10% and it grows with ageing, incidence of diabetes and cancer (Colloca et al, Nat Rev Dis Prim 2017)
- Neuropathic pain can cause substantial impact on the patients' Quality of Life (QoL)
- QoL is affected being the loss of functionality, cognitive impairment, sleep disorders, anxiety, and depression

Signs and symptoms of pain in PDN includes

- Reduction or complete loss of sensitivity
- Spontaneous symptoms – burning, itching
- Evoked symptoms – Hyperalgesia, allodynia

Risk factors for painful DSPN

- Degree and duration of uncontrolled diabetes
- Body weight
- Gender (woman are at higher risk)
- Gain of function variants in gene encoding and several genetic polymorphisms

Treatment of DNP

- The primary objective of treatment is pain reduction and its clinical manifestation (30% reduction – moderate relief, 50% reduction – substantial relief)
- Pharmacological treatment is typically first step in treating DNP
- The pharmacological approach to NP consists of gradual process to identify the drug combinations that provide the greatest pain relief with fewest adverse events
- Examination and assessment of chronic pain requires a detailed history of each patient including –
 - Pain history
 - General medical history
 - History of the pain treatment (pharmacological and non-pharmacological)
 - Psychosocial history (sleep quality, mood, ability to cooperate)
 - Physical exam
 - Additional diagnostic assessments (if required)
- Diagnosis of DNP usually consists of physical examination as well as specific questionnaire (like NPSI – Neuropathic Pain Symptom Inventory)

Guidelines	First-line recommendations	Second-line & posterior recommendations	Oral therapies are often used in the treatment of DNP; however, the specific limitations and complications associated with different pharmacological classes as well as the limitations of systemic therapy must be taken into account: ³
Neuropathic Pain Special Interest Group of the International Association for the Study of Pain (NeuPSIG, 2015) ¹	<ul style="list-style-type: none"> • Tricyclic antidepressants • Gabapentin • Pregabalin • NRI Duloxetine • Topical lidocaine in frail and elderly patients 	<ul style="list-style-type: none"> • Tramadol • Capsaicin • Opioid analgesics (third line) Tramadol 	<ul style="list-style-type: none"> • Systemic side effects • Potential drug interactions • Need for dose adjustment in the elderly and in patients with hepatic or renal impairment • Potentially long titration periods • Inconvenient regimens
European Federation of Neurological Societies (EFNS, 2010) ²	<ul style="list-style-type: none"> • Gabapentin • Pregabalin • SNRI Duloxetine • Tricyclic antidepressants • Medical plaster with lidocaine in elderly 	<ul style="list-style-type: none"> • Capsaicin • Opioids 	

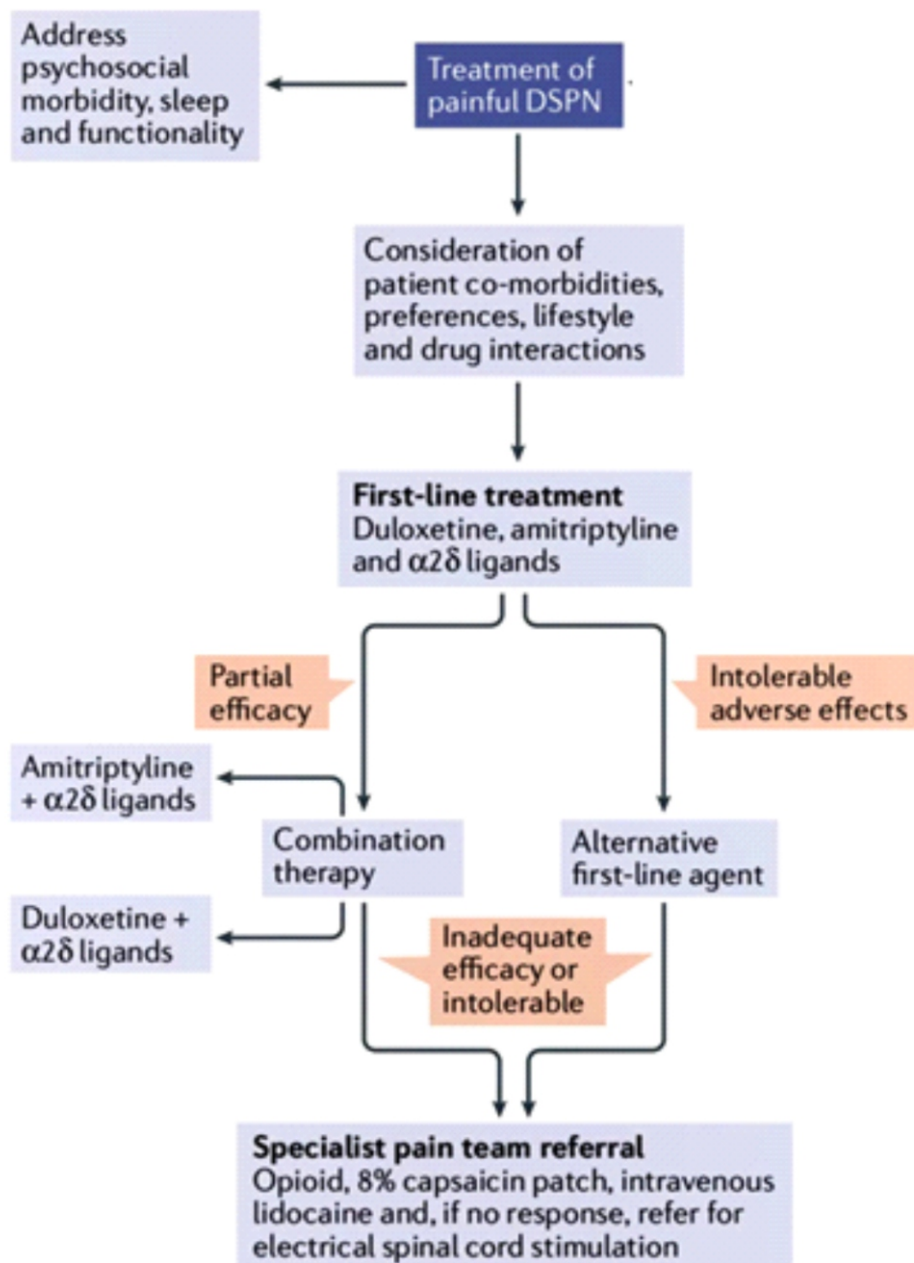
As presented during IDF 2021

According to NICE guidelines (2020 update), a choice of amitriptyline, duloxetine, gabapentin or pregabalin should be offered as an initial treatment for neuropathic pain (including PDN). If the first choice of drug is not effective, the remaining drugs should be tried in turn depending on response and tolerance. Tramadol should be considered if acute rescue therapy is needed and capsaicin should be considered for people with localized neuropathic pain who do not want, or who cannot tolerate, oral treatments.

It should be noted that combination therapy from the mentioned classes often results in situations including

- Systemic adverse events
- Drug interactions
- Need for dose adjustments in elderly/patients with renal or hepatic impairment
- Potentially long period of administration
- Inconvenient or complex administration regimen

Proposed Algorithm for the Management of Painful DPN



Tesfaye S, et al. Nature Reviews Endocrinology. 2021;17:400-420

The concluding talk of the session was from Prof. Kara Mizokami on the non-pharmacological treatment of pain. A summary of key take home messages are listed below:

Nutraceuticals for Neuropathic Pain						
Nutraceutical	Study (ref.)	T1D/T2D n	Daily dose (mg)	Duration	Effects	Adverse events
Benfotiamine	BENDIP	16/117	300/600/placebo	6 weeks	Symptoms+ (PP) Signs--	None
	BEDIP	8/32	400/placebo	3 weeks	Symptoms/signs+ Pain+	None
Vitamin B12	Didangelos et al.	0/90	1/placebo	1 year	Symptoms+, Signs-- Pain+, VPT+ NCS+	None
Vitamin D	Karonova et al.	0/67	40000 IU/5000 IU per week	24 weeks	Pain+ Symptoms+ Signs+	None
Vitamin E	VENUS	300*	400/placebo	1 year	Symptoms-- Lancinating pain (+)	None
Acetyl-L- carnitine	Sima et al.	1257*	3000/placebo	1 year	Pain+ VPT+ NCS--	None
γ -Linolenic acid (GLA)	Keen et al.	57/51	480/placebo	1 year	NCS+ Signs+	None
	Won et al.	0/100	320 GLA/600 ALA	12 weeks	Symptoms, pain non- inferior	None
Magnesium	de Leeuw et al.	110/0	300/no supplement	5 years	DPN stage+ [§] NCS+	GI symptoms

Ziegler et al, J Diab Invest 2021

Non-pharmacological approach includes adoption of healthy behavior interventions including exercise/physical activity and dietary modifications.

Key components of a healthy diet in the setting of DPN

- Calorie restriction
- Processed carbohydrate restrictions
- Emphasis on polyunsaturated fats
- Anti-oxidant foods
- Plant-based diet like the Mediterranean diet (45% carbohydrate, 35–40% fat with less than 10% of saturated fat)

Lifestyle Interventions for DPN – ADA Clinical Compendium Series 2022 (in-press)

Intervention Type	Absolute Intensity	Relative Intensity (Scale of 0–10)	Frequency/Duration	Modes
Aerobic exercise	Moderate (3.0–5.9 METs)/vigorous (>6.0 METs) physical activity*	Moderate: 5 or 6 Vigorous: 7 or 8	<ul style="list-style-type: none"> 3–7 days/week 150 min/week with no more than 2 consecutive days off 	Brisk walking, running, cycling, swimming, or dancing
	High-intensity interval training (maximum effort over short time)	Maximum effort	Unknown	Running or cycling
	Light-intensity physical activity (1.6–2.9 METs)*	<5	<ul style="list-style-type: none"> Daily, multiple times throughout the day Avoid being sedentary for >1 hour at a time except when sleeping 	Slow walking, cooking, or light household chores
Resistance or strengthening exercise	Vigorous	6–8 repetitions of a weight that can be lifted ≤6–8 times	<ul style="list-style-type: none"> 2–3 sessions on nonconsecutive days/week 3–6 exercises of major muscle groups per session 	Weight machines, WBV, free weights, elastic bands, or body weight
	Moderate	15 repetitions of a weight that can be lifted ≤15 times		
Balance exercise			2–3 days/week	Tai Chi, single leg balance, or obstacle course
Anti-sedentary behavior				Wearable devices, coaching, or goal-setting
Diet modification				Calorie restriction, processed carbohydrate restriction, and emphasis on polyunsaturated fats and antioxidant foods

*MET, or metabolic equivalent, refers to the energy expenditure required to carry out a specific activity, with 1 MET equal to the rate of energy expenditure while sitting at rest.

As presented during IDF 2021

Energy or Nerve Stimulation Treatment

Transcranial magnetic stimulation (TMS)

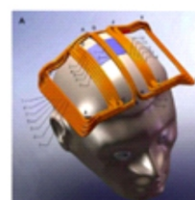
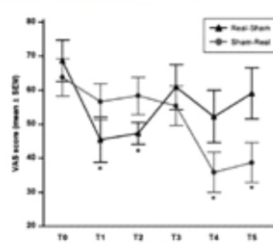
H-coil repetitive transcranial magnetic stimulation for pain relief in patients with diabetic neuropathy

E. Onesti¹, M. Gabriele¹, C. Cambieri¹, M. Ceccanti¹, R. Raccab¹, G. Di Stefano¹, A. Biasiotto¹, A. Truini¹, A. Zangen², M. Inghilleri¹

Eur J Pain 17 (2013) 1347–1356

N=25 DPN patients, cross-over, randomized to assess deep real rTMS for 5 days relieves pain comparing Sham rTMS

Primary end point- Visual Analog Scale (VAS)



As presented during IDF 2021

Transcutaneous electrical nerve stimulation (TENS)

N=22 DPN on micro-TENS vs 19 on placebo over 4 weeks
 Standardized questionnaires (Pain Disability Index [PDI], neuropathic pain score [NPS])

Outcome: defined as 30% reduction in NPS

TENS group



6/21 patients

Placebo group



10/19 patients

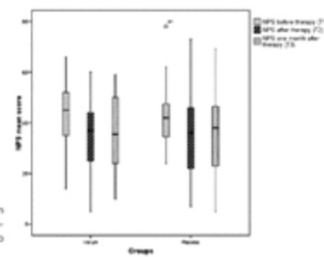


Figure 1 Neuropathic pain score (NPS) score: Development during verum and placebo therapy.

Results: non-superior to a placebo.

Gossrau et al: Pain Medicine 2011; 12: 953-960

Photon Stimulation

Pulsed infrared light or near-infrared laser energy applied transcutaneously

N=121 participants with DPN, randomized, placebo-controlled trial
 Outcomes: Pain intensity, pain relief, and pain qualities

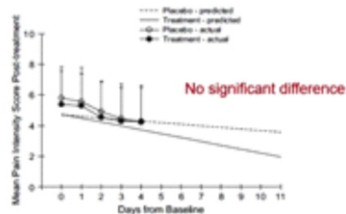


Fig. 2. Predicted and actual changes over time in pain intensity scores immediately post-treatment in the placebo (n=58) and treatment (n=63) groups.

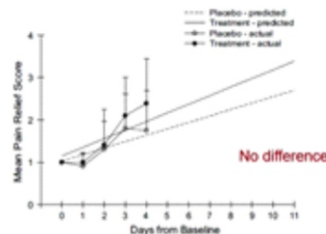


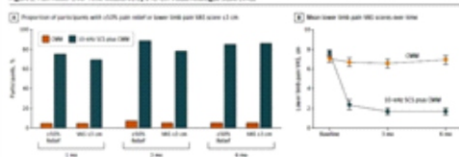
Fig. 3. Predicted and actual changes over time in pain relief scores immediately post-treatment in the placebo (n=58) and treatment (n=63) groups.

As presented during IDF 2021

Spinal cord stimulation (SCS)

Primary end point- percentage of participants with 50% pain relief or more on Visual Analog Scale (VAS)

Figure 2. Pain Relief Over Time Measured by a 10-cm Visual Analog Scale (VAS)

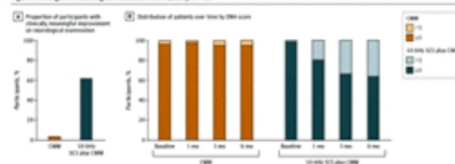


Difference, 73.6%; 95%CI, 64.2-83.0; P < .001

N=216 DPN, prospective, multicenter, randomized, open-label comparing conventional medical management (CMM) with 10-kHz SCS

Secondary end point- Neurological exam

Figure 3. Changes in Neurological Assessment and Quality of Pain



Difference, 58.6%; 95%CI, 47.6-69.6; P < .001

As presented during IDF 2021

Summary

- Health behavior interventions, particularly exercise, are emerging as effective interventions for painful DPN
- SCS may be considered as alternative strategies for neuropathic pain reduction in those individuals with DPN pain refractory to medical therapy
- Other modalities have low quality evidence for pain improvement in neuropathy



GLOBAL OVERVIEW OF THE DIABETIC FOOT

SESSION 5


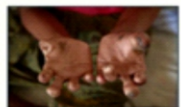



By:
DR. SHARAD PENDSEY
Consultant, Diabetes, India

The session saw various speakers presenting the overview and current status of the diabetic foot complication from different regions of the world. The overview of the South-East Asia (SEA) region was presented by Dr. Sharad Pendsey. Few highlights and key takeaways from his presentation are listed below:

Lacunae in the foot care in SEA region are

- No screening programs
- Podiatry – non-existent
- Orthoses – unheard
- Team approach is lacking
- Patients as well as doctors are ignorant about foot care in diabetes
- Belief in faith healers
- Barefoot walking

Differences between Leprosy & Diabetic Neuropathy			
Characteristics	Leprosy Neuropathy	Diabetic Neuropathy	
Etiology	Infiltration leprabacilli	Metabolic Microangiopathy	
Type	Mononeuritis multiplex	Symmetrical Polyneuropathy	
Nerves	Superficial in hands & feet	Glove & Stockings	
Bilateral feet	Common	Rare	
Bilateral Hands	Very common	Extremely rare	
Charcot foot	Very common	Less common	
Peripheral nerves	Thick & Tender	Non tender	
Malignancy in	Does Occur	Never	
Chronic Ulcer			
Limb Amputation	Rare	Common	

Only indication for limb amputation in Leprosy is squamous cell carcinoma because of long standing neuropathic ulcer

As presented during IDF 2021

Mononeuropathy multiplex of leprosy

- In diabetes, it's mainly symmetrical polyneuropathy, while in leprosy it's mononeuropathy multiplex where individual nerves are destroyed
- However, both these neuropathies lead to sensory motor and autonomic dysfunction
- India continues to be country with highest number of leprosy cases followed by Brazil
- However, in last 20 years, with intensive screening and early treatment, new cases of lepromatous leprosy are no more seen



HOW SHOULD I TREAT INDIVIDUALS WITH DIABETIC KIDNEY DISEASE (DKD)

SESSION 6



By:

DR. DRAZENKA BARLOVIC

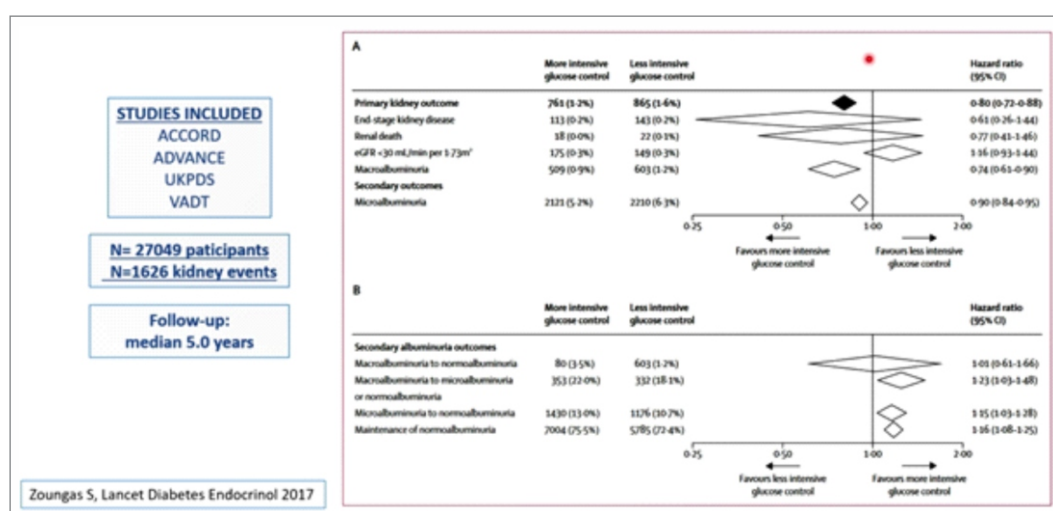
Consultant, Department of Endocrinology, University Medical Centre Ljubljana, Ljubljana, Slovenia

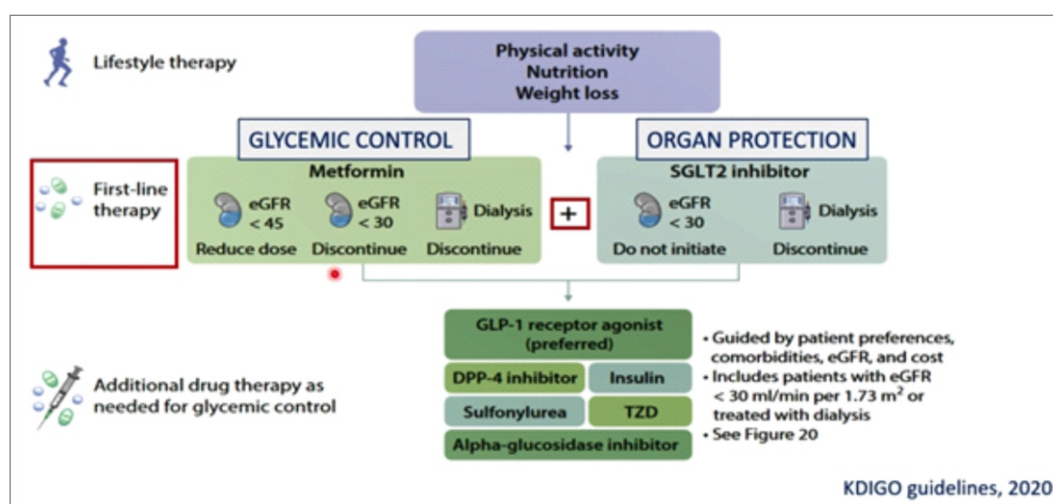
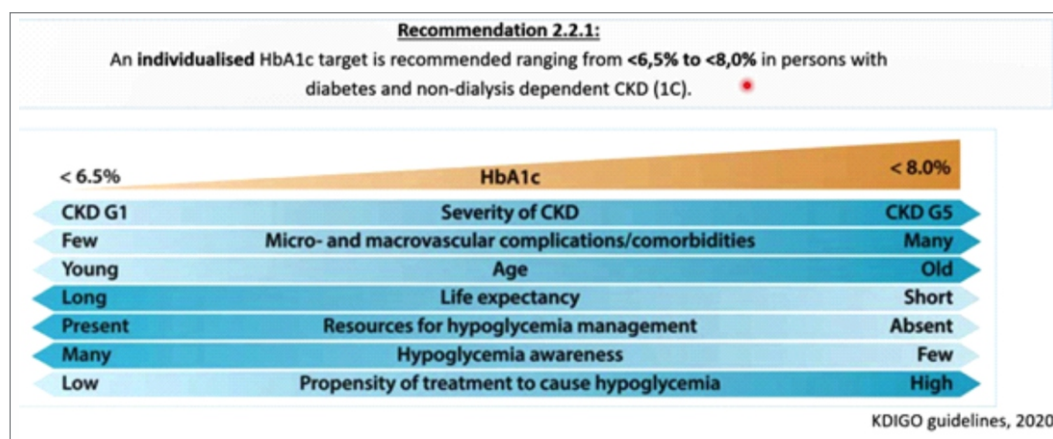
This session covered talks on standard of care and role of different drug classes in the management of DKD. The first talk of the session by Dr. Drazenka Barlovic focused on the standard of care. Excerpts of her talk are summarized below:

Dr. Barlovic shared the “5-Finger Rule” that can be followed for comprehensive standard of care in the management of DKD

- **1st Finger** – Glycemic control
- **2nd Finger** – Blood pressure control
- **3rd Finger** – Lipid control
- **4th Finger** – Obesity and inactivity
- **5th Finger** – Quit smoking

1st Finger – Intensive glycemic control and impact on renal outcomes

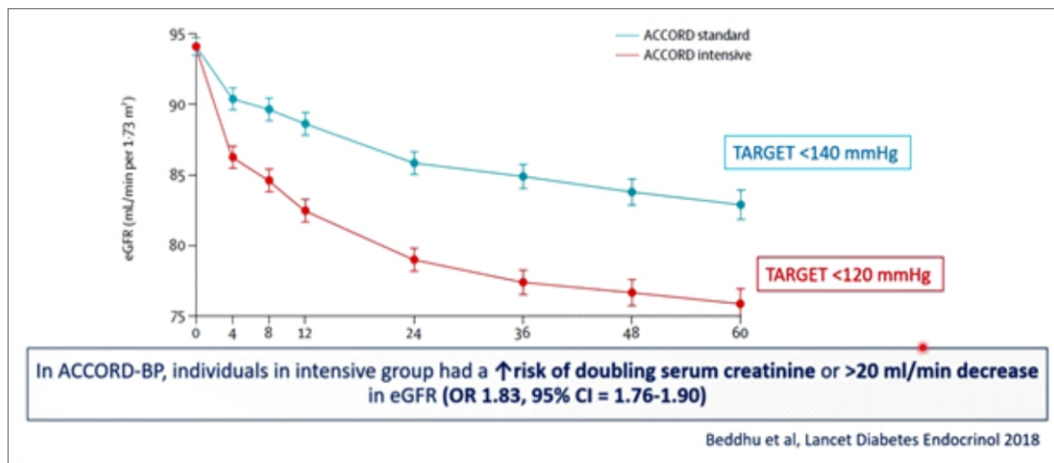




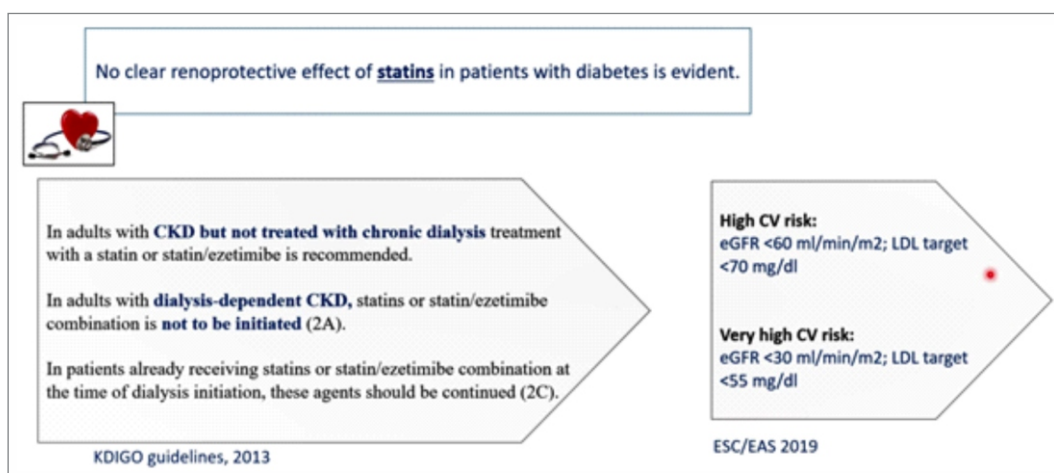
A healthy kidney diet

- Maintain a protein intake of 0.8 gms protein/kg/day for those with diabetes and CKD not treated with dialysis. Patients treated with hemodialysis, and particularly peritoneal dialysis, should consume between 1–1.2 gms protein/kg/day
- Patients with diabetes and CKD should consume an individualized diet high in vegetables, fruits, whole grains, fibers, legumes, plant-based proteins, unsaturated fats, and nuts; and lower in processed meats, refined carbohydrates, and sweetened beverages
- Suggested sodium intake to be <2 g of sodium or <5 g of sodium chloride/d in patients with diabetes and CKD

2nd Finger – Blood pressure control and renal outcomes

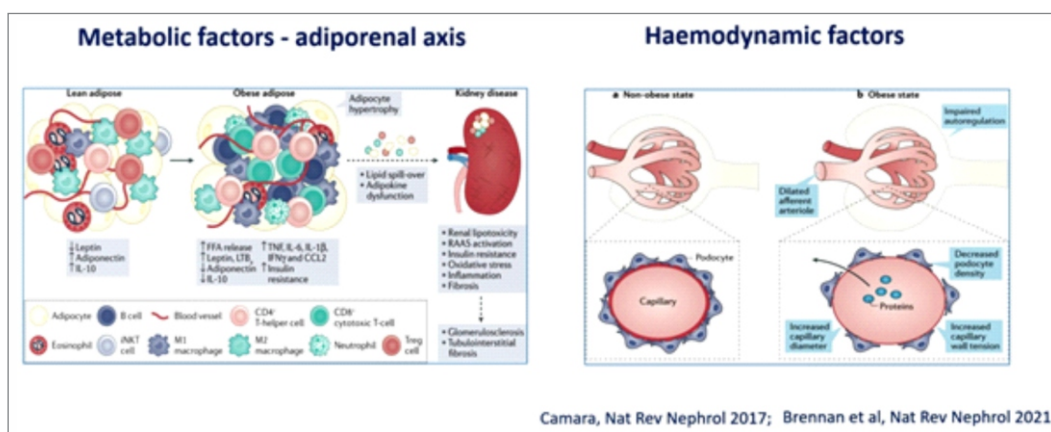
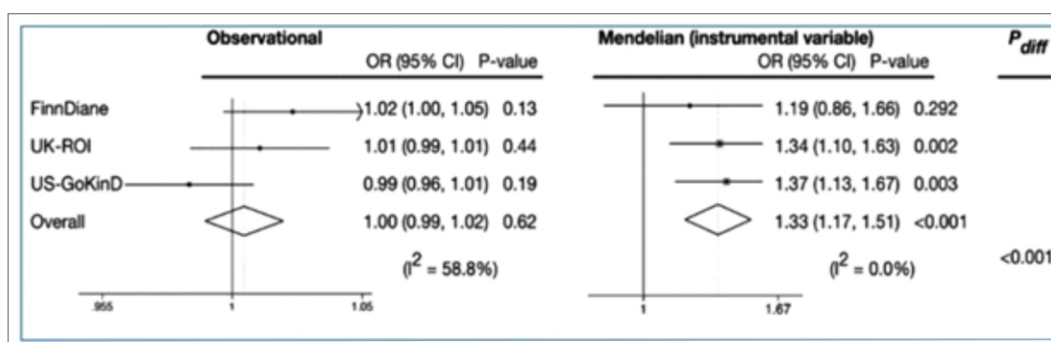


3rd Finger – Lipid control and renal outcomes

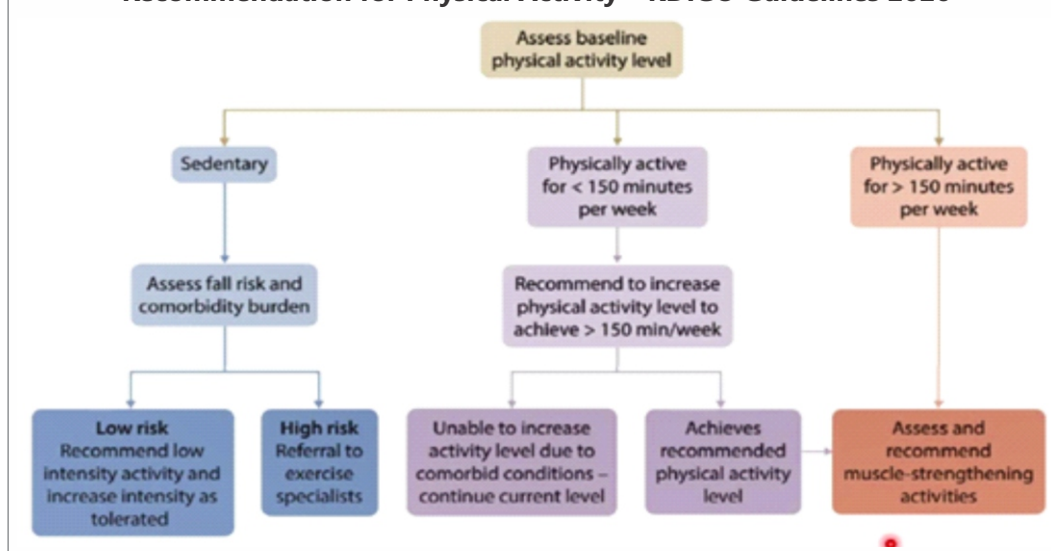


4th Finger – Obesity and physical activity and renal outcomes

- Genetically there is a causal link between BMI and DKD in type 1 diabetes

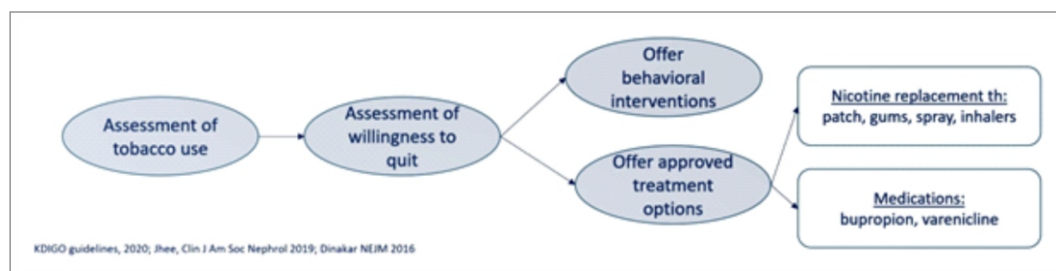


Recommendation for Physical Activity – KDIGO Guidelines 2020



5th Finger – Quit smoking

- Tobacco is a risk factor for development of CKD
- E-cigarettes also increases the risk of CVD and lung disease

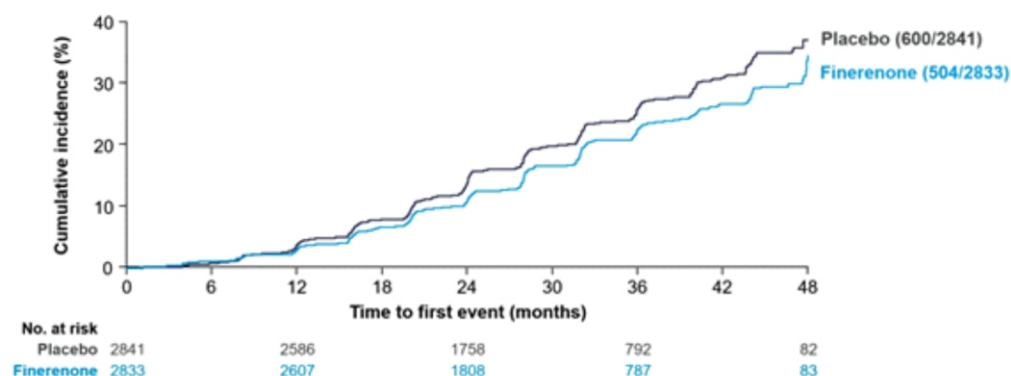


Other speakers shared benefits of pharmacological treatment including incretin-based therapies like GLP-1 RAs and DPP-4i in improving the glycemic control without increasing the risk of hypoglycemia. GLP-1RAs may also have direct effects on slowing the progression of renal disease.

Trials like CREDENCE and DAPA-CKD have shown the benefits of SGLT2i class of drugs in improving the outcomes in patients of DKD. Similarly, FIGARO-DKD and FIDELIO-DKD trials have shown benefits of finerenone therapy across a broad spectrum of eGFR and CKD categories.

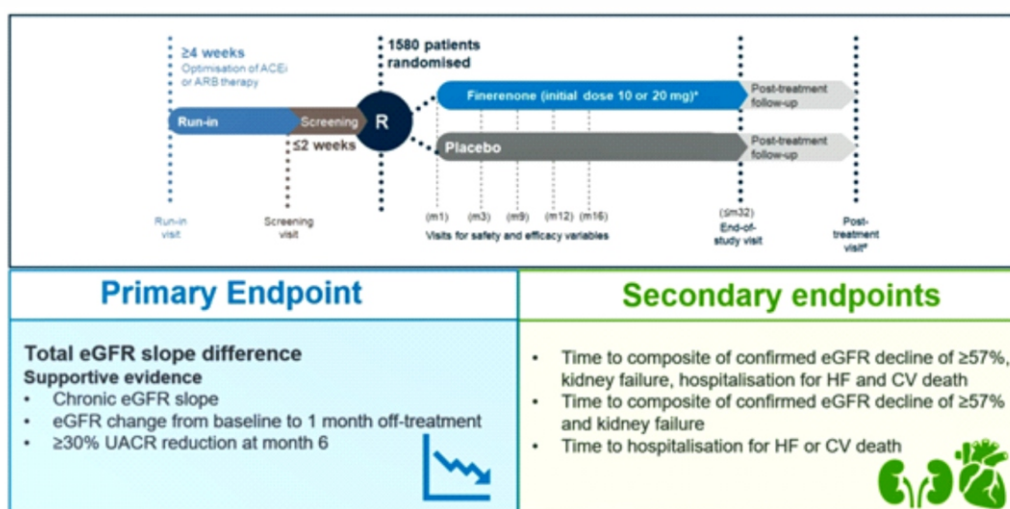
FIDELIO-DKD: Finerenone protects the kidney

Kidney failure*, sustained $\geq 40\%$ decrease in eGFR from baseline, or renal death



*ESKD or an eGFR <15 ml/min/1.73 m²
Bakris GL, et al. *N Engl J Med* 2020. doi: 10.1056/NEJMoa2025645

FIND-CKD: Non-diabetic CKD study design and end-points

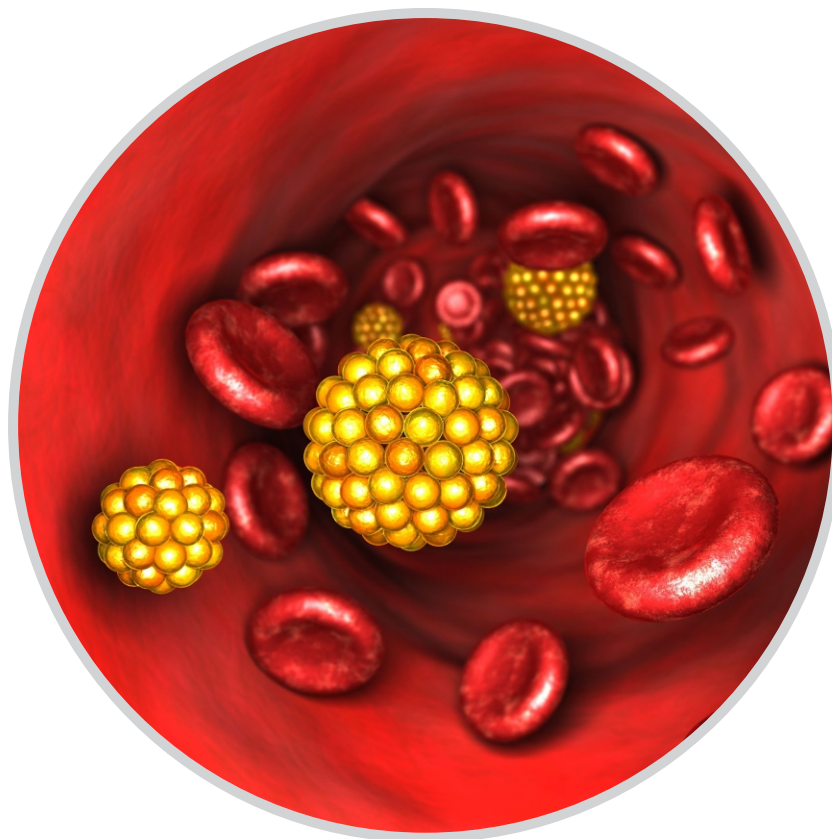


*Starting dose based on eGFR, 10mg <60 ml/min/1.73 m² ml and 20mg ≥ 60 ml/min/1.73 m² Up-titration and down-titration of study drug was encouraged dependent on potassium value and eGFR; *4 weeks Off-treatment phase
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; m, month; R, randomisation; UACR, urine albumin-to-creatinine ratio

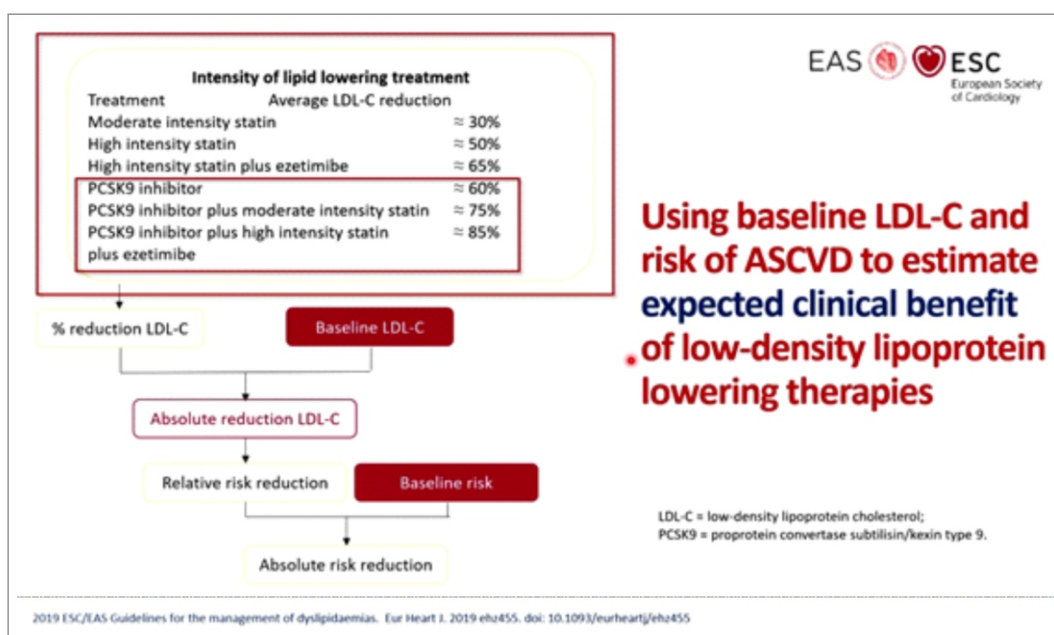


LIPIDS IN DIABETES

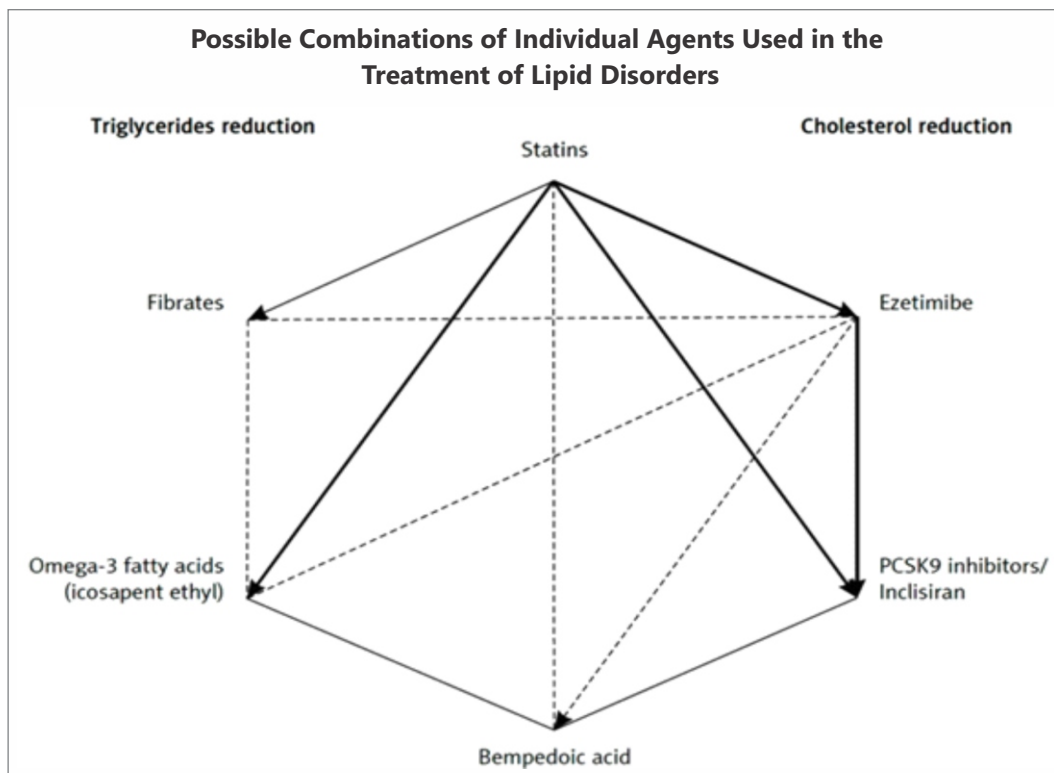
SESSION 7



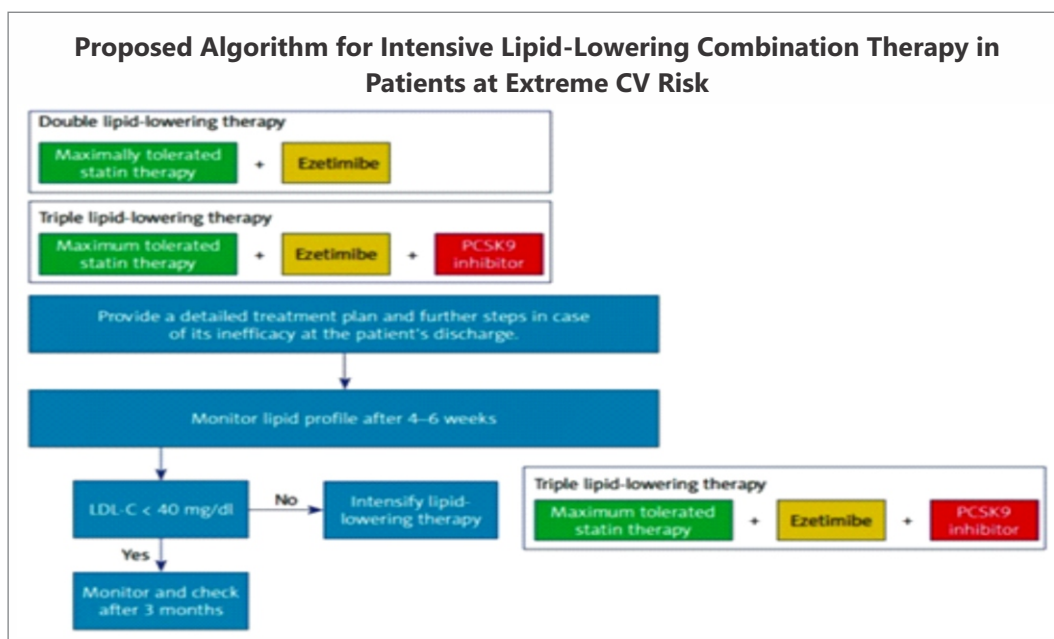
This session covered discussion related to the use of statin in Type 2 diabetes, other options for LDL-C reduction beyond statins and when and how to target high triglycerides in diabetes. Few of the important takeaways of the session are highlighted below:



- Meta-analysis of observational studies has shown the evidence that statins possess diabetogenic properties
- There was found to be increased risk of new-onset diabetes among statin users compared with non-users
- This effect is shown by all the studied molecules and thus suggested a class effect
- The excess risk of cardiovascular events is outweighed by the achievable large reduction in cardiovascular risk. However, the burden of diabetes is difficult to be estimated



As presented during IDF 2021



As presented during IDF 2021

Lowering Triglycerides – The Importance of Apo B

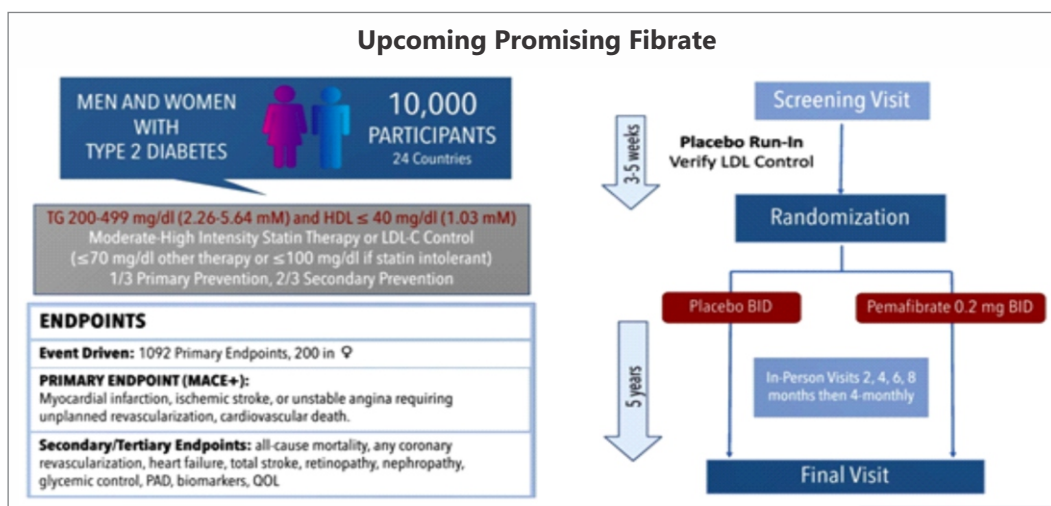
- 654,783 participants including 91,129 cases of coronary disease
- Genetic scores: **lipoprotein lipase pathway (LPL score)** and **LDL receptor pathway (LDLR score)**
- Risk of coronary disease: weighted per per 10mg/dL lower apo B (genetically determined)

Genetic score	Δ trig (mg/dL)	P value	Δ LDL-c (mg/dL)	P value	OR for coronary heart disease	P value
LPL score	-70	7 X 10 ⁻¹³⁶³	0.7	0.04	0.77 (0.74-0.80)	4 X 10 ⁻³⁸
LDLR score	-2	0.04	-14.2	1.4 X 10 ⁻⁴⁶⁵	0.77 (0.75-0.80)	1 X 10 ⁻⁴⁶

As presented during IDF 2021

The clinical benefit of lowering triglycerides or LDL-C or both may be proportional to the absolute change in Apo-B containing lipoproteins, regardless of the observed changes in the triglycerides or LDL-C.

Upcoming Promising Fibrate



As presented during IDF 2021

- In cases of extreme elevation of triglycerides, the priority should be to prevent pancreatitis, and rapidly achieve good glycemic control
- Moderate elevation of triglyceride in type 2 diabetes is common. Priority for lipid modification is preventing CVD and for that statin therapy is usually the best option. Addition of triglyceride lowering agent on top of statin should only be considered if the Apo-B levels are sufficiently high and the chosen therapy reduces Apo-B meaningfully



COVID-19 AND DIABETES: THERAPEUTIC CHALLENGES FOR PEOPLE WITH DIABETES

SESSION 8



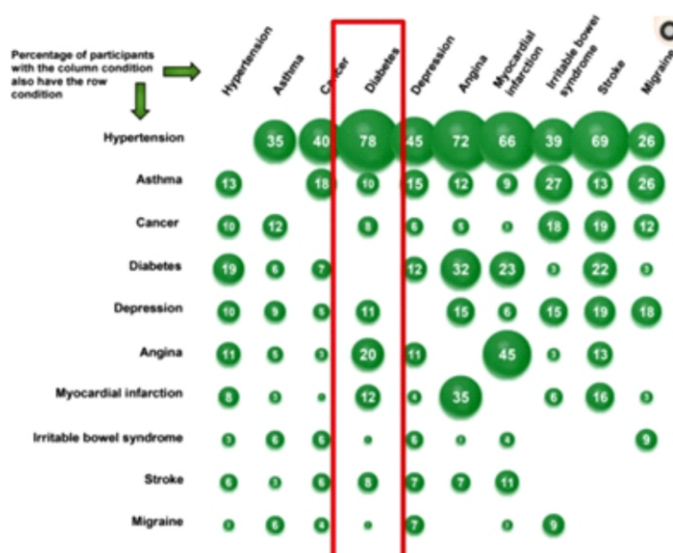
By:

DR. ANOOP MISRA

Executive Chairman, Fortis C-DOC Hospital for Diabetes and Allied Sciences,
Director, National Diabetes Obesity and Cholesterol Foundation (NDOC),
President, Diabetes Foundation, India

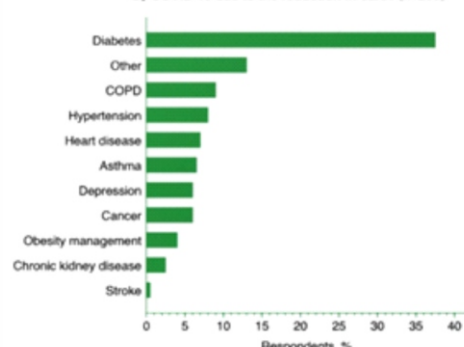
This session covered the current clinical management updates for COVID-19 and diabetes along with the role of non-insulin anti-diabetic agents in patients with Type 2 diabetes and COVID-19. A few excerpts of the session are highlighted below:

The Most Common Co-Occurring Chronic Diseases in Patients Tested Positive with COVID-19

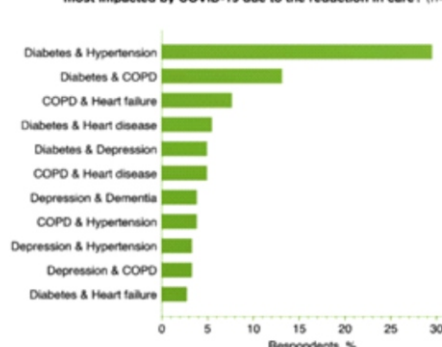


Chudasama YV et al. Diab Met Syndr 2020; 14: 775-776.

Which area of chronic disease has been most impacted by COVID-19 due to the reduction in care? (n=200)



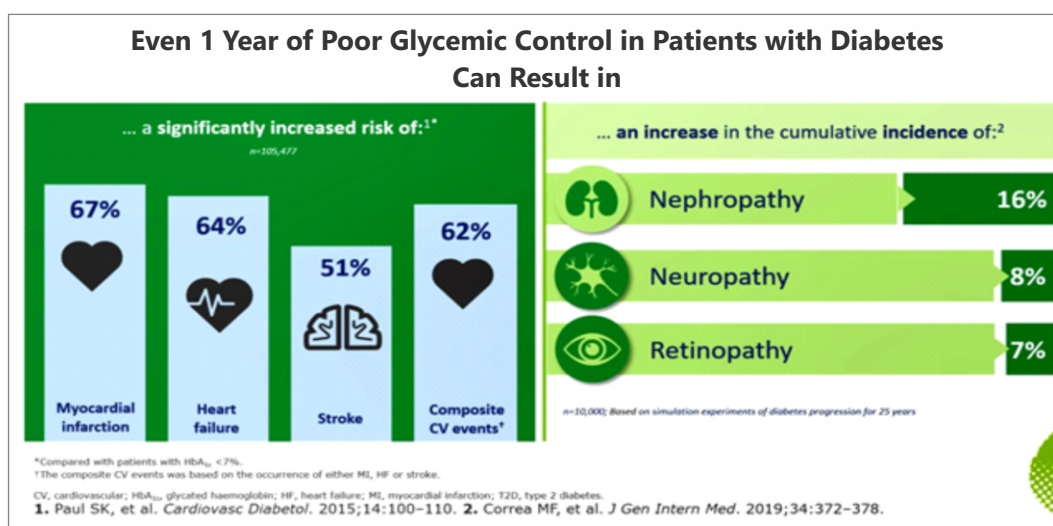
What are the two most common co-occurring chronic diseases (co-morbidity) most impacted by COVID-19 due to the reduction in care? (n=183)



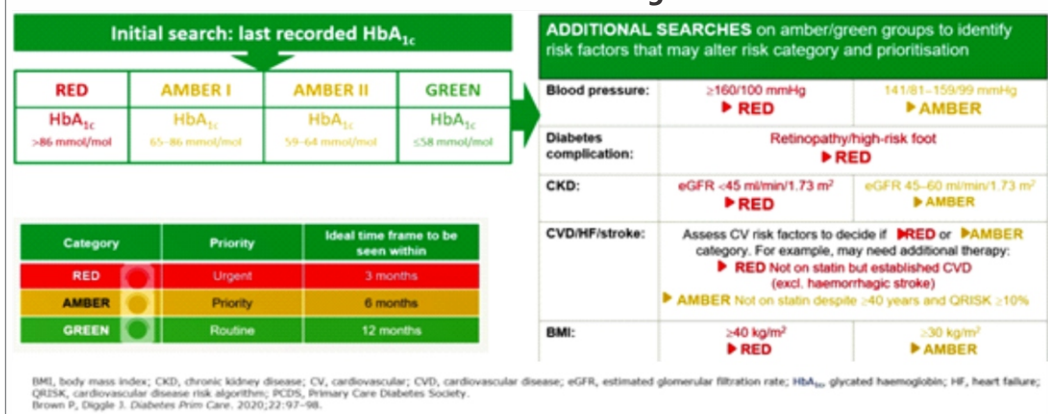
As presented during IDF 2021

Also, our experiences of the past disasters like Marmara earthquake or Katrina hurricane have shown that the glycemic parameters and overall QoL gets adversely impacted post the event and same can be expected in case of COVID-19. As per recent survey (Diabetic Medicine 2021) by Forde and his colleagues, around 85% population reported an increased negative impact on the psychological health. Among the psychological disorders, anxiety, diabetes distress and depression are the top 3 most common clinical problems.

During COVID-19, the screening for diagnosis was down along with the follow-up HbA1c tests and standard of care. The challenge now is to make up for the lost time with significant backlog of patients.

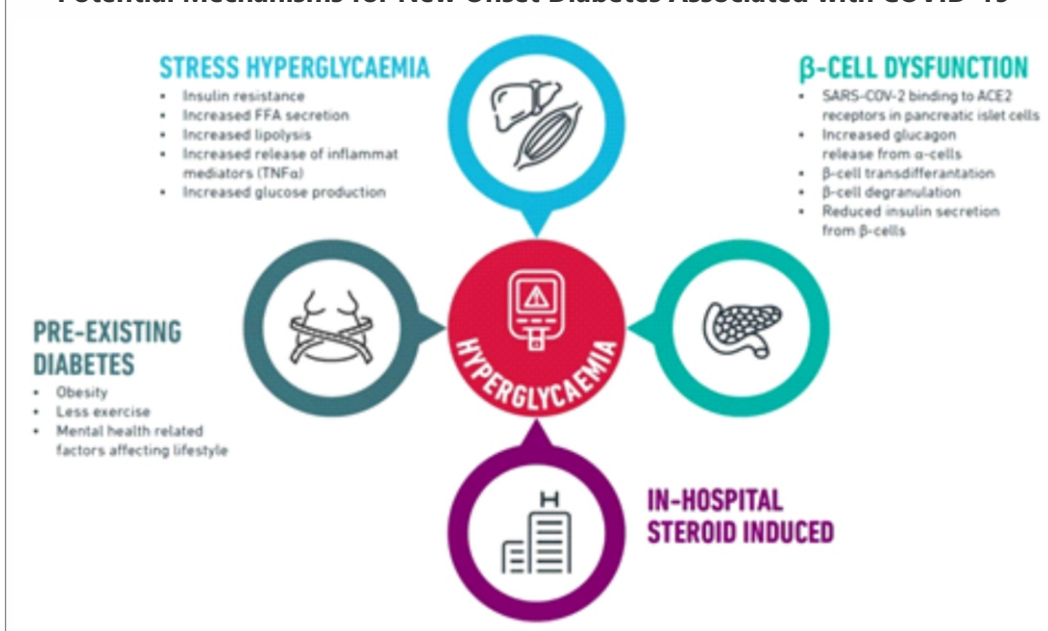


Suggested Approach for Risk Stratification for Prioritizing Patients Monitoring



As presented during IDF 2021

Potential Mechanisms for New Onset Diabetes Associated with COVID-19



As presented during IDF 2021

Dr. Anoop Misra presented his talk on the role of non-insulin anti-diabetic agents in patients with Type 2 diabetes. Few excerpts of his presentation are given below:

- A good glycemic control can reduce the mortality rates in diabetic patients suffering from COVID-19 and at the same time can reduce the complication rates as well
- In fact, a slight increase in blood glucose has shown to be independent predictor of 28-days mortality in patients suffering from COVID-19 even without previous diagnosis of diabetes
- Thus, good glycemic control is very critical. In general, physicians continue the ongoing treatment in mild COVID-19 cases and in severe cases with hospitalization, they switch to insulin. However, very few prospective studies are available to evaluate the effect of anti-diabetic drugs on the mortality and morbidity related to COVID-19
- Effects of various non-insulin drugs were reviewed in the talk

Metformin

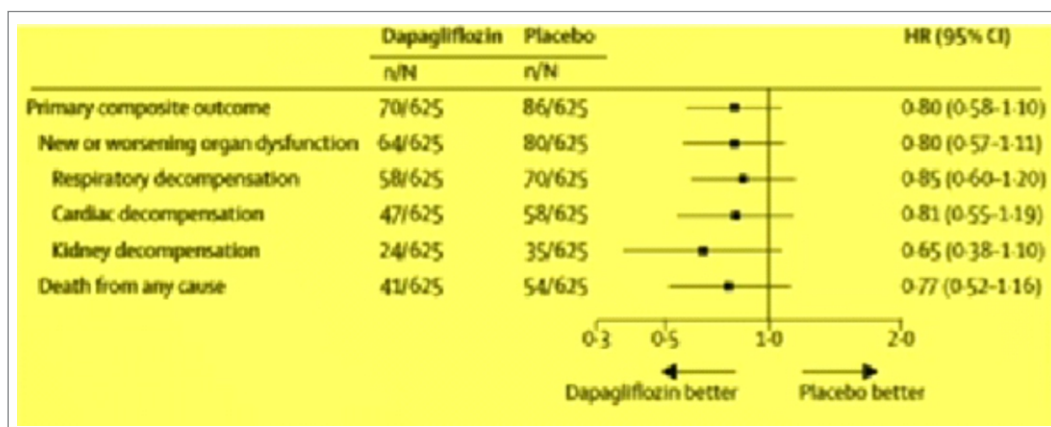
- Most of the data is retrospective and couple of prospective studies have shown beneficial effect of Metformin on COVID-19 outcomes
- A case control study on Metformin has shown decrease in mortality especially in women (maybe due to decrease in TNF-alpha and activation of AMP-K)
- Multiple mechanisms are postulated for the beneficial effect of Metformin in COVID-19 outcomes including its effect on body weight, insulin resistance, TNF-alpha, inhibition of m-TOR pathway, activation of CMPK pathway and others

DPP4i

- DPP-4 is the entry receptor for MERS-CoV infection
- Both ACE-2 and DPP-4 could be involved with the receptor binding domain of SARS-CoV-2
- Few retrospective studies suggested neutral effect of DPP-4i on COVID-19 related outcomes, couple of retrospective/observational studies have shown negative effect whereas a couple of prospective and case control studies have shown beneficial effect of the drug
- Some of the proposed mechanism for benefit of the drug class includes reduction of NOD-like Receptor 3, CRP, TNF-alpha, IL-6, mRNA expression of CD26 and lung fibroblast activation

SGLT2i

- In general, SGLT2i are avoided/discontinued in patients with COVID-19 since they may cause hypotension and euglycemia ketoacidosis
- However, some actions may help alleviate pathogenesis process of COVID-19 including inhibition of glycolysis, reduction in oxidative stress and improved endothelial function and oxygen carrying capacity
- An observational study in UK has shown significant decrease in mortality rates in patients on SGLT2i versus the non-users.
- DARE-19, a RCT on use of Dapagliflozin in hospitalized patients with COVID-19, has shown improvement in primary outcomes



As presented during IDF 2021

GLP1-RA and Pioglitazone

- A retrospective analysis of the results from multicenter healthcare organizations have shown a positive outcome with use of GLP1-RA and Pioglitazone in diabetic patients with COVID-19
- Use of GLP1-RA and/or Pioglitazone was associated with significant reduction in hospital admissions
- Use of GLP1-RA was also associated with reduction in respiratory complications and incidences of mortality
- Data from meta-analysis also suggests that pre-admission use of GLP1-RA was associated with reduction in mortality rate from COVID-19

Other drugs and future trials

- Data regarding use of SU is inconclusive although one study showed lower mortality in SU users versus non-users
- RCTs are in progress with Metformin/DPP4i/GLP1-RA to evaluate their effect on outcomes in diabetic patients with COVID-19

General conclusions on use of drugs in diabetic patients with COVID-19

- Metformin is beneficial and should be continued
- GLP1-RA have shown promising data and should be appropriately used
- SGLT2is do not show any harm and could be continued in selected patients
- DPP-4i should be restarted after discharge from hospital
- We still need further data to conclusively decide on the use of these drugs



PSYCHOLOGICAL MORBIDITY AND DIABETES COMPLICATIONS

SESSION 9

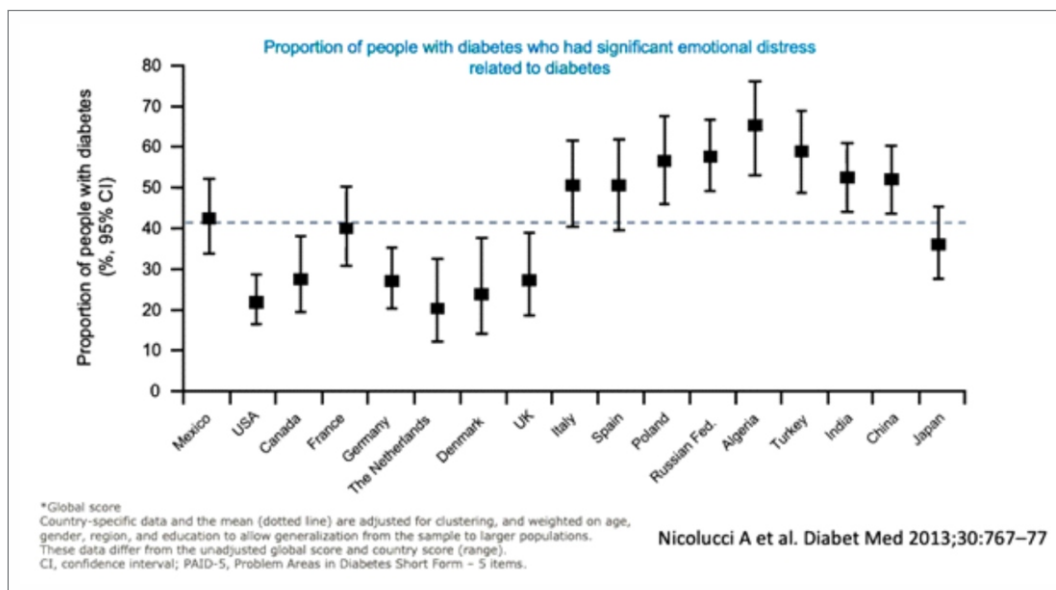


By:
PROF. FRANS POWWER

Researcher, Department of Medical and Clinical Psychology, Tilburg School of Social and Behavioral Sciences, Tilburg University, Netherlands

During this session, Prof. Frans Pouwer highlighted the various psychological problems associated with diabetes and their management. Few excerpts of his talk are highlighted below:

- Diabetes distress or diabetes burnout is the common psychological problem associated with diabetes which indicates a negative emotional or affective experience resulting from the challenge of living with the demands of diabetes
- Studies have shown around 40% of the diabetic population suffers from diabetes distress
- Meta-analysis has also demonstrated that psychoeducational interventions can significantly reduce diabetes distress and improve HbA1c compared to controls



- Among others, worries about hypoglycemia is one of the major causes of distress
- A 6-weeks manualized group for people with impaired hypoglycemia awareness have shown 3 thinking traps that leads to hypoglycemia unawareness –
 - Trap 1 – The belief that one could 'soldier on' through hypoglycemic episodes and delay treatment; “The Soldier” – I will be ok, no worries
 - Trap 2 – The belief that there are no adverse outcomes related to hypoglycemia; “The Ostrich” – Don't make a fuss, get on with it
 - Trap 3 – Overestimation of the risk of intermittent hyperglycemia; “The Smoke Alarm” – Avoid high glucose at any cost
 - Another common distress is related to disordered eating and insulin omission
- Latest Danish registry (Diabetes Res Clin Pract 2021) – DanDiabKids, has shown that youth with Clinical Binge Eating symptoms scores lowest on generic and diabetes specific QoL, highest on anxiety and depression symptoms, and had a higher HbA1c
- Poor sleep quality is also attributed to diabetes distress and studies have shown that Obstructive Sleep Apnea remained an independent predictor of progression to pre-proliferative/proliferative diabetic retinopathy
- Depression is commonly observed in diabetes patients with as many as 2 in 10 patients suffering from it. Depression has been marked as an independent risk factor for adverse outcomes in diabetes including all-cause mortality

- Some of the mechanisms causing increased complications in depression include –
 - Depression is associated with poor glycemic control
 - Associated with less optimal self-care behavior
- Psychotherapeutic interventions combined with diabetes self-management interventions are found to be most effective in managing depression
- Studies have also shown reduced cost of overall diabetes management after effective depression treatment
- Web-based CBT (Cognitive-Behavior Therapy) reduces depression and distress in people with diabetes
- CBT can also improve symptoms of anxiety, QoL, and fasting plasma glucose
- Latest study (2020) DiaMind has shown that Mindfulness-therapy can be effective against stress and depression in people with diabetes

Conclusion

- Psychological problems are common in people with diabetes
- Depression is a risk factor for complications and higher mortality in diabetes
- Effective management of depression can improve the outcomes in patients



DIABETES TREATMENT ALGORITHMS AND CURRENT GUIDELINES

SESSION 10



By:
PROF. MILES FISHER
Honorary Professor, University of Glasgow, Scotland

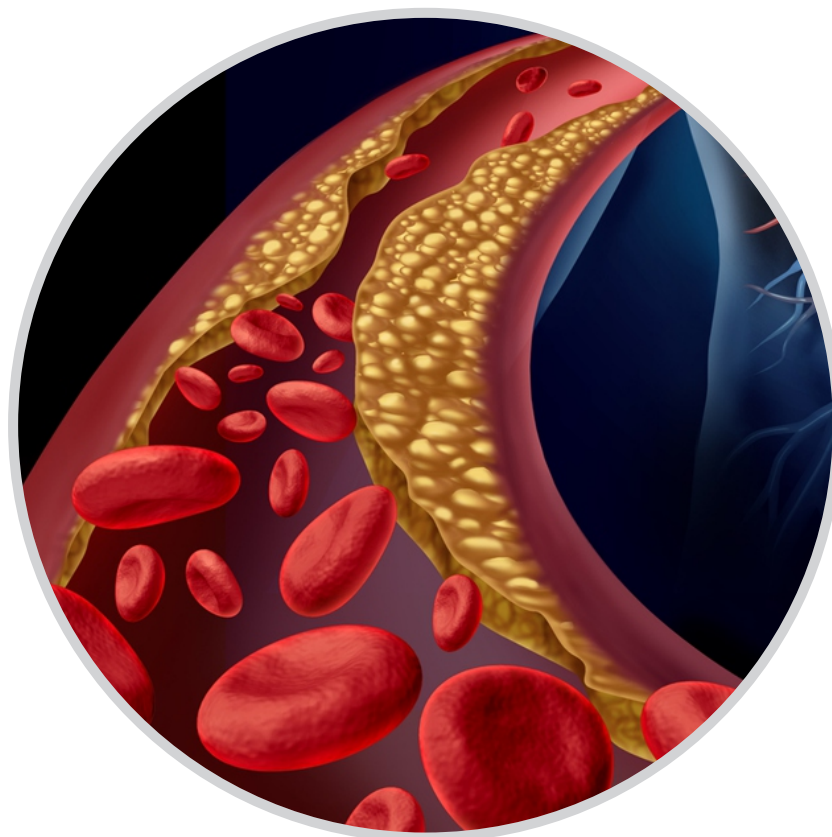
Prof. Miles Fisher presented a novel view from diabetes perspective on the newer guidelines. Few highlighting points of his talk are summarized below:

- Guidelines are good directive to bring uniformity in standard of care however certain shortcomings include –
 - Absence of multidisciplinary team or patients in the team
 - Preference to Metformin over all other drugs
 - Still based on step-wise approach
 - GLP1-RA features before SGLT2i
 - At least 4 criteria to weight up
- We need to evaluate
 - Should guidelines be based on level of cardiorenal risk rather than HbA1c?
 - Should Metformin be reordered in the hierarchy?
 - Should SGLT2i get preference over GLP1-RA based on the available data?



CORONARY ARTERY DISEASE (CAD) IN DIABETES

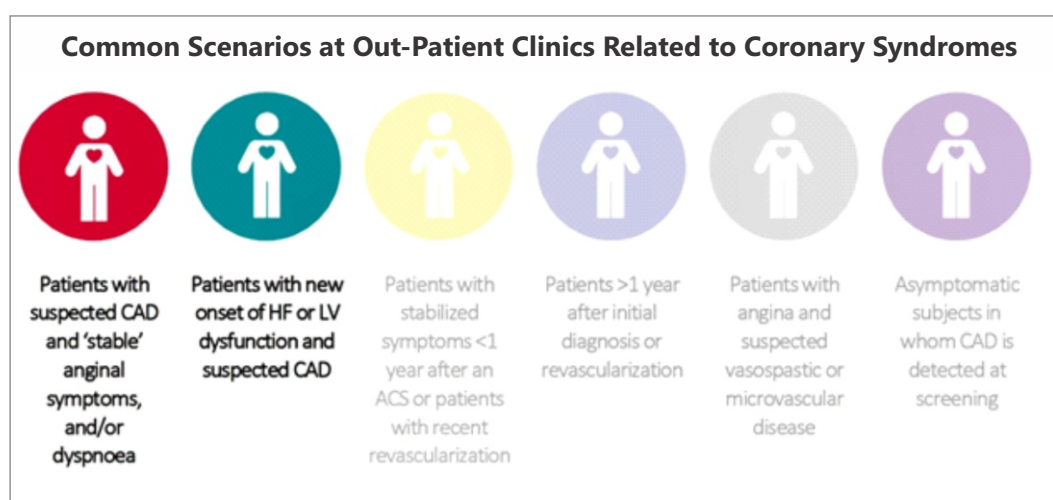
SESSION 11



By:
DR. CRISTINA GAVINA

Director, Medicine and Cardiology Department, Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos,
Assistant Professor, Medicine, University of Porto, Portugal

During this session Dr. Cristina Gavina highlighted the importance of diagnosis and regular follow-up for CAD in diabetes. Few excerpts from her presentations are noted below:



As presented during IDF 2021

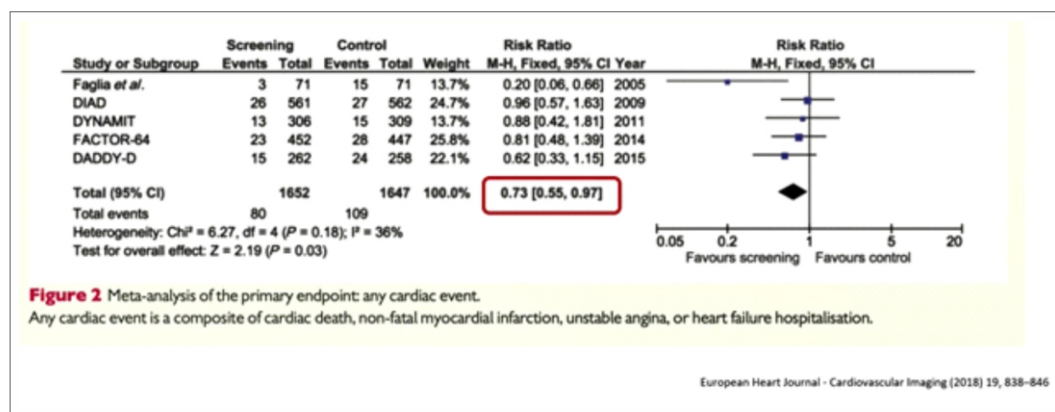
3 important steps to improve CV outcome trends in diabetes

- Early diagnosis
- Aggressive treatment to ambitious targets
- Regular follow-up

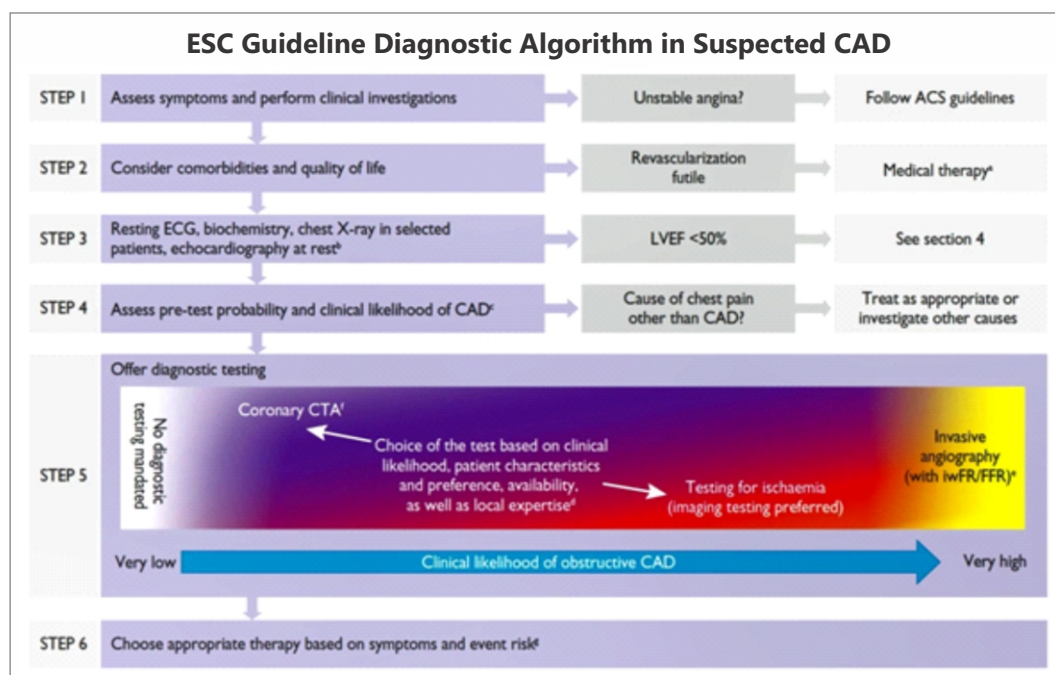
Early diagnosis to include

- CV risk assessment
- Screening in asymptomatic individuals
- Clinically suspected CAD

Non-invasive screening for CAD in asymptomatic diabetic patients have shown to improve the risk ratio

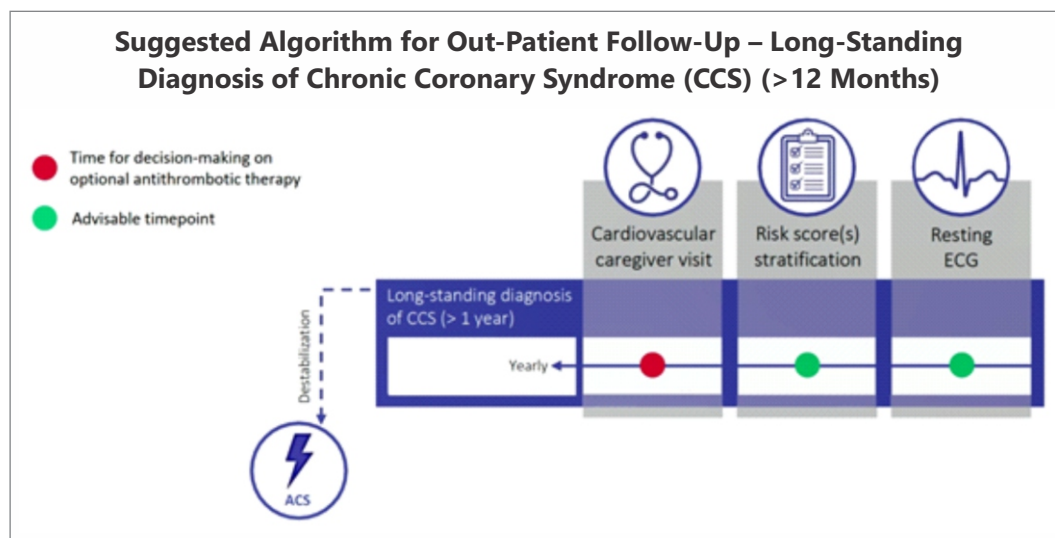


Aggressive treatment to ambitious targets



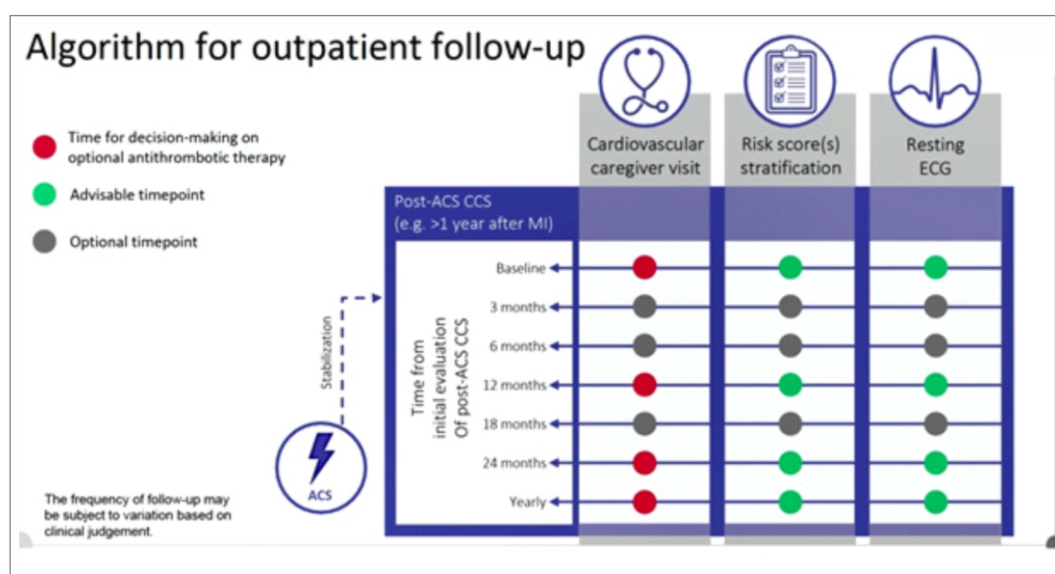
As presented during IDF 2021

Regular follow-up



As presented during IDF 2021

Follow-Up of CCS Post-ACS (>12 Months)



As presented during IDF 2021

Key Messages

Very high risk

Patients with DM **and** established CVD
or other target organ damage^b
or three or more major risk factors^c
or early onset T1DM of long duration (>20 years)

Protection

Aggressive targets
Use protective drugs irrespective
of HbA1c (iSGLT2 / GLP1 RA)
Intensify antithrombotic
treatment (if bleeding risk not high)

As presented during IDF 2021

ATHEROSCLEROTIC
DISEASE

New targets



Risk factor	Target
Blood Pressure	<ul style="list-style-type: none"> Target SBP 130 mmHg for most adults, <130 mmHg if tolerated, but not <120 mmHg Less-stringent targets, SBP 130-139 in older patients (aged >65 years) HbA1c target for most adults is <7.0% (<53 mmol/mol) More-stringent HbA1c goals of <6.5% (48 mmol/mol) may be suggested on a personalized basis if this can be achieved without significant hypoglycaemia or other adverse effects of treatment Less-stringent HbA1c goals of <8% (64 mmol/mol) or <9% (75 mmol/mol) may be adequate for elderly patients (see section 6.2.7)
HbA1c	
C-LDL	<ul style="list-style-type: none"> In patients with DM at very high CV risk* target LDL-C to <1.4 mmol/L (<55 mg/dL) In patients with DM at high risk* target LDL-C to <1.8 mmol/L (<70 mg/dL) In patients with DM at moderate CV risk* aim for an LDL-C target of <2.5 mmol/L (<100 mg/dL)

As presented during IDF 2021

New drugs



The sodium-glucose co-transporter 2 inhibitors empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with diabetes and CVD.

A glucagon-like peptide-1 receptor agonist (liraglutide or semaglutide) is recommended in patients with diabetes and CVD.

I	A
I	A

ATHEROSCLEROTIC
DISEASE

Recommendations	Class	Level	
Treatment with a P2Y ₁₂ receptor blocker, ticagrelor or prasugrel, is recommended in patients with DM and ACS for 1 year with aspirin, and in those who undergo PCI or CABG.	I	A	PLATO (ticagrelor vs clopidogrel) TITON (prasugrel vs clopidogrel)
Prolongation of DAPT beyond 12 months should be considered, for up to 3 years, in patients with DM who have tolerated DAPT without major bleeding complications.	IIa	A	PEGASUS (reduced dose ticagrelor) DAPT (clopidogrel)
The addition of a second antithrombotic drug on top of aspirin for long-term secondary prevention should be considered in patients without high bleeding risk.	IIa	A	ATLAS-ACS (low dose riv, ACS) COMPASS (low dose riv, stable)

As presented during IDF 2021

Follow-up: diagnostic testing



Echocardiography
at rest

Early (e.g. 1-3 months) after revascularization to set as a reference and/or periodically (e.g. at 1 year if previously abnormal and/or every 3-5 years) to evaluate LV function, valvular status and haemodynamic status.



Stress test for
inducible ischaemia

As necessary, to investigate changes in symptoms level, and/or early (e.g. 1-3 months) after revascularization to set as a reference and/or periodically (e.g. every 3-5 years) to reassess ischaemia.



Invasive coronary
angiography

As necessary, for patients at high risk based on noninvasive ischaemia testing, or severe angina symptoms (e.g. CCS class 3-4). Not recommended solely for risk stratification.

As presented during IDF 2021

Summary

- Chronic CAD is challenging in diabetes
- Imaging for risk stratification in asymptomatic individuals may be useful for therapy intensification (CAC score, Carotid US)
- Screening of CAD in asymptomatic Type 2 diabetes is not routinely recommended since invasive stratification does not lead to more revascularization
- To set secondary prevention goals in very high-risk patients
- Yearly follow-up is advisable



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