NATIONAL MEDICINES SYMPOSIUM 2025

Complications of Diabetes

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NGURANG DALI MANA BURUDI

A PLACE TO GET BETTER

Acknowledgement of Country

Artwork

Ngurang Dali Mana Burudi — a place to get better

The map was created by our Aboriginal Health staff telling the story of a cultural pathway for our community to gain better access to healthcare.

Artwork by Aboriginal artist Lee Hampton utilising our story.

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The Agenda

- Rationale for use of medicines in people with diabetes
- Rational use of medicines in people with diabetes
- Consumer advice in use of such medicines
- Risk-benefit in medication use in diabetes complications
- Practical adherence issues in medication use in diabetes

Why (Rationale) Manage Blood Glucose in People with Diabetes?

- To prevent ‘end-organ’ chronic diabetes complications
- To prevent acute diabetes complications and death
- To prevent and manage symptomatic hyperglycaemia

Development of the Diabetes Mellitus Syndrome and its Complications

Initial insult(s)

↓

Insulin resistance and deficiency

↓

Elevated blood glucose levels

↓

Cell and tissue injury

↓

Diabetes organ complications

blood pressure, cholesterol, smoking

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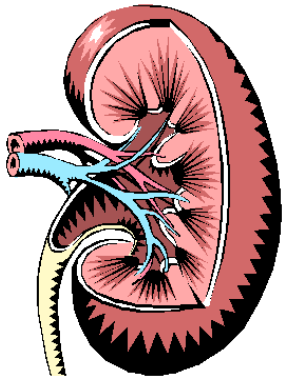
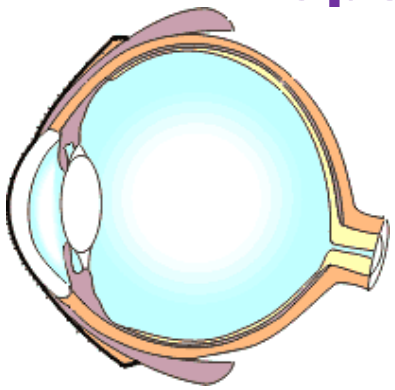
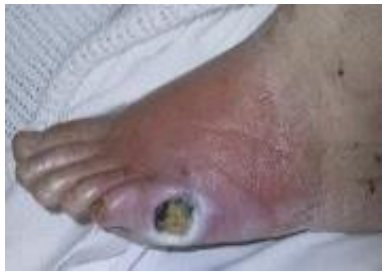
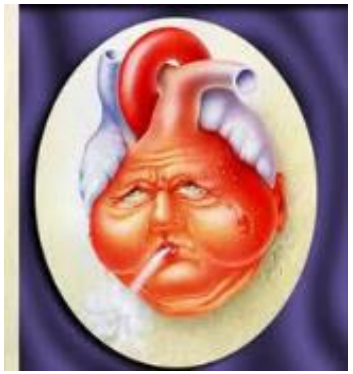
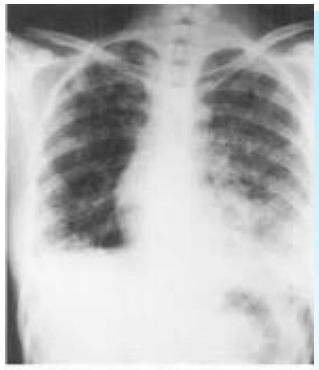
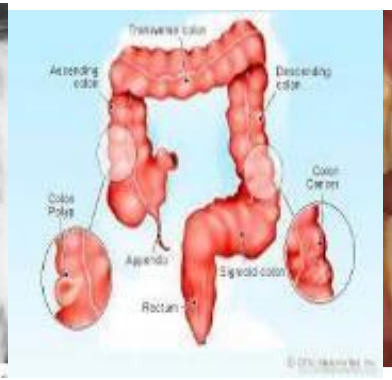
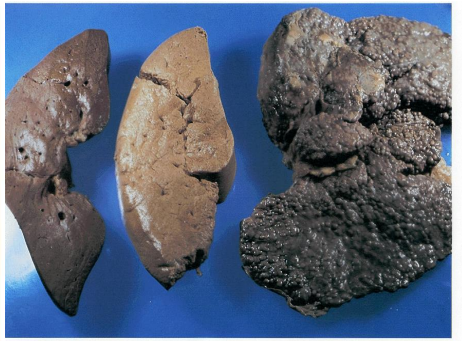
The Spectrum of Diabetes-Related Complications: Biopsychosocial



Normal Liver, Fatty Liver, and Cirrhosis

<u>The imperative to prevent diabetes complications: a broadening spectrum and an increasing burden despite improved outcomes.</u>

Twigg SM, **Wong J.**

Med J Aust. 2015;202(6):300-4.

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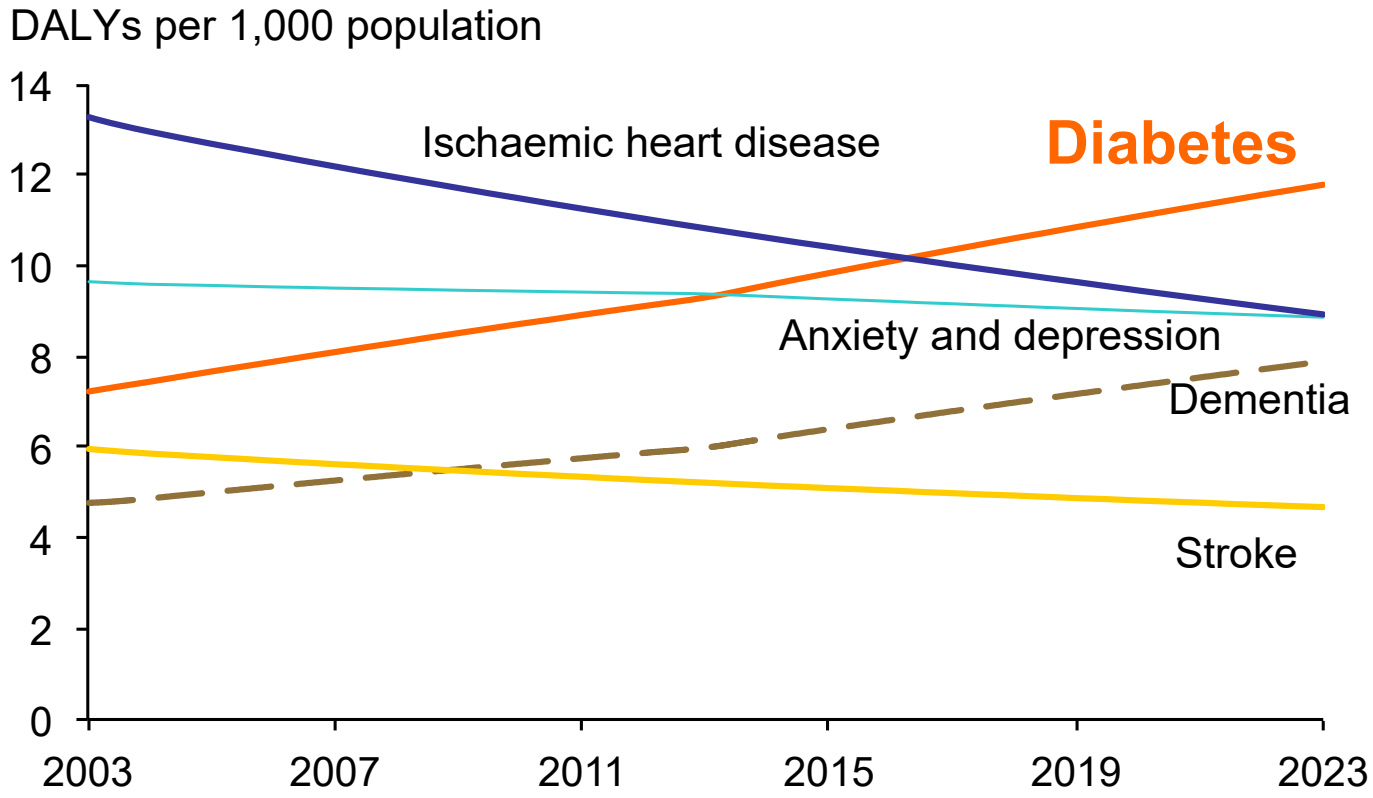
The Burden of Diabetes (by Disability)



Source: AIHW Burden of disease database

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Management Methods to Aid Patient Outcomes in Diabetes - Combined Processes and Many Medicines!


‘Lifestyle’

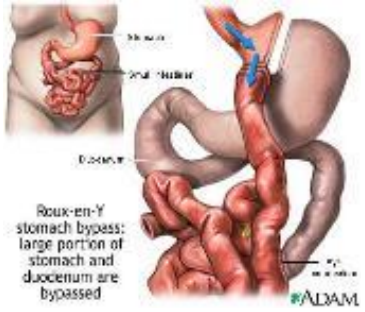


Building rapport



‘Medication’


‘The knife’



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A Broad Overview Approach to Diabetes Complications

- Individualise glycaemic targets
- Screen for key diabetes complications
- Use medicines with lifestyle care that help particularly to prevent severe organ complications such as CVD, CHF, CKD, DFD and MASH with liver fibrosis
- Manage BP and lipids esp. LDL-C, and minimise adverse effects of medicines
- Be aware of specific care needs in diabetes complications: feet, eyes, kidneys, heart, autonomic neuropathy

Preventing end-organ diabetes complications through chronic glycaemic care

- Targeting glucose helps to prevent micro-vascular complications of diabetes in time
  - Retinopathy
  - Chronic kidney disease
  - Less clear in forms of neuropathy
  - No data in foot ulcer healing
- Preventing macrovascular complications by targeting chronic hyperglycaemia is more controversial; BP and lipid care are key
- Know the evidence base, and individualise glycaemic targets and care

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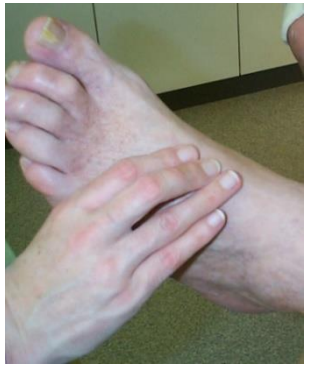
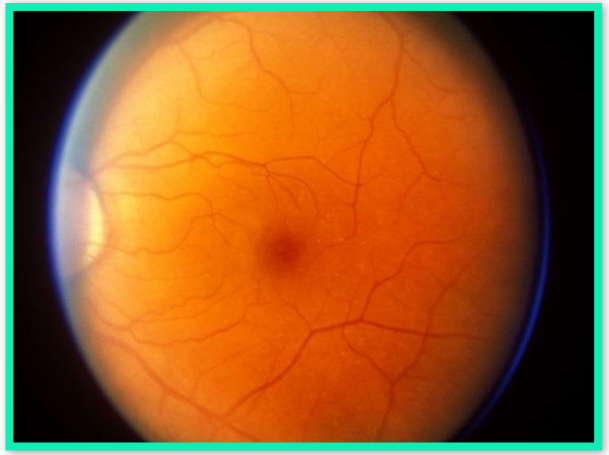
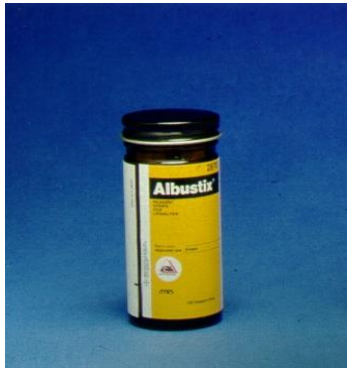
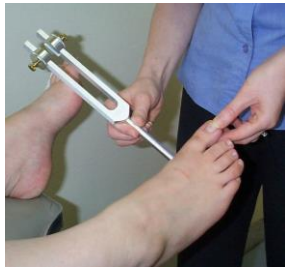
Diabetes Complications Screening Can Detect Complications Early and Help to Prevent Complications Worsening

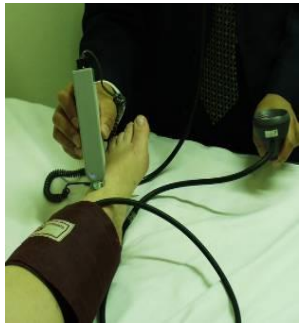


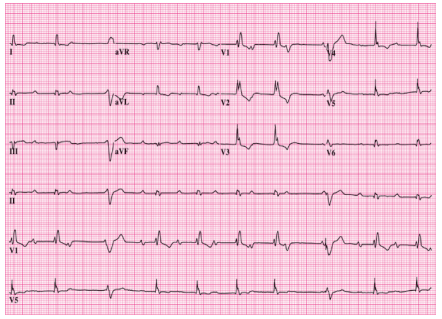
albuminuria



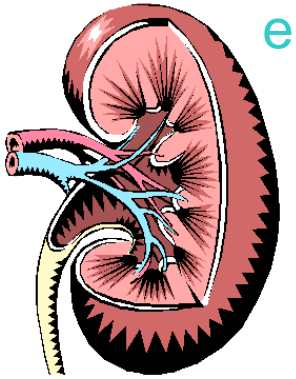


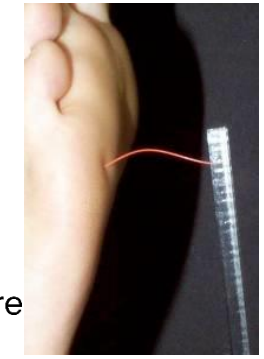






eGFR





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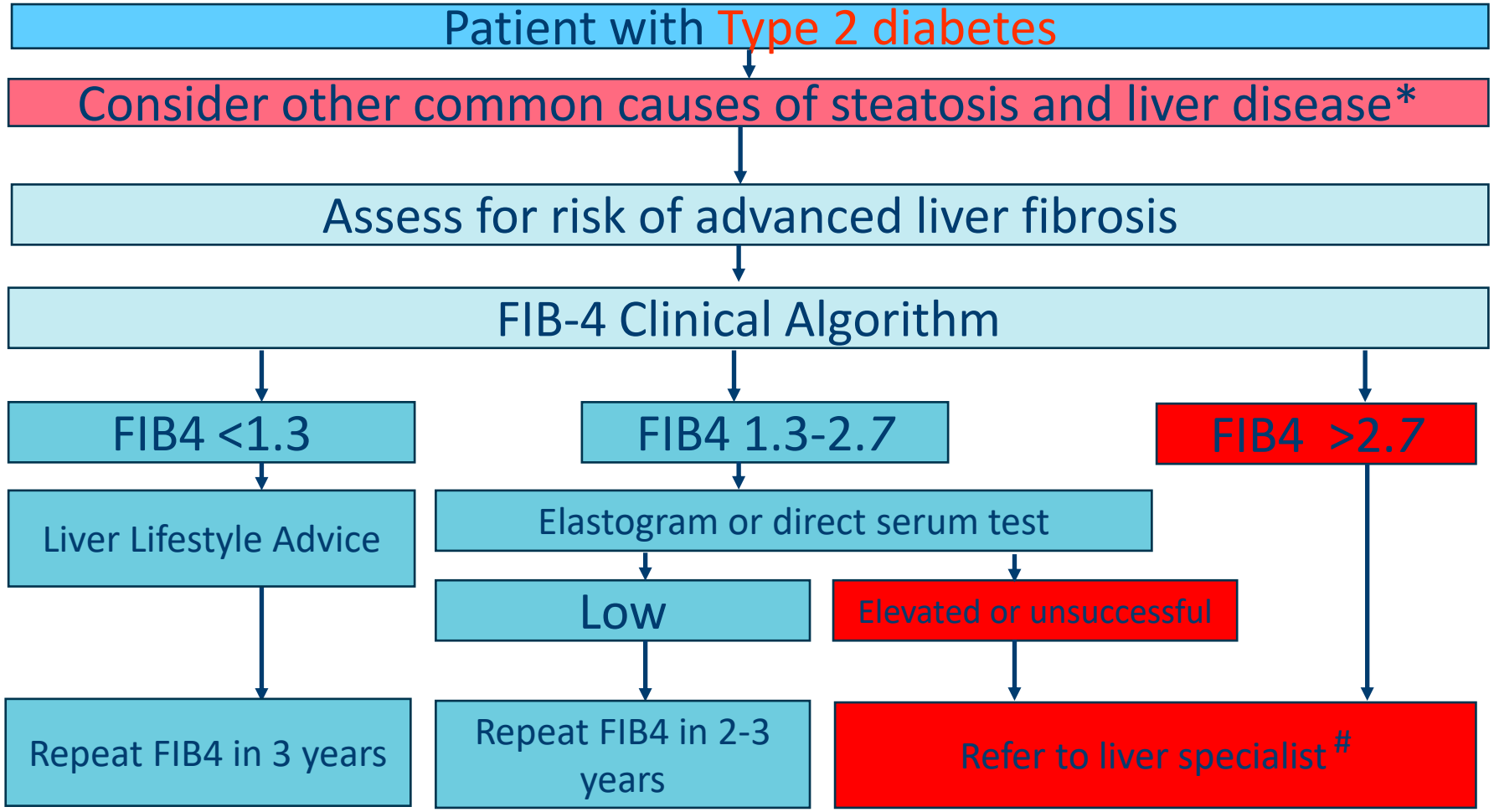
ADS have Aligned with the GESA MAFLD screening guidelines for Specialists to be utilised in People with Type 2 Diabetes

Adapted from https://www.gesa.org.au/resources/clinical-practice-resources/



** Evaluate alcohol intake, medications, risk factors for viral hepatitis, iron overload*

[#] refer all high FIB4 and LSM ≥12.0 kPa to liver specialist, and in cases of indeterminant FIB4, or LSM 8.0 to 12.0 kPa refer as services allow

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FIB-4, fibrosis-4; MAFLD, metabolic-dysfunction-associated steatohepatitis

Adapted from Figure 2. Assessment algorithm for a patient presenting with MAFLD from GESA "Recommendations for the assessment of metabolic dysfunction-associated fatty liver disease (MAFLD) in primary care: a consensus statement" Manuscript for consultation

GESA MAFLD guidelines available at: https://www.gesa.org.au/public/13/files/Education%20%26%20Resources/Clinical%20Practice%20Resources/MAFLD/MAFLD%20Consensus%20Manuscript%20Draft%20for%20Consultation.pdf Accessed August 2024

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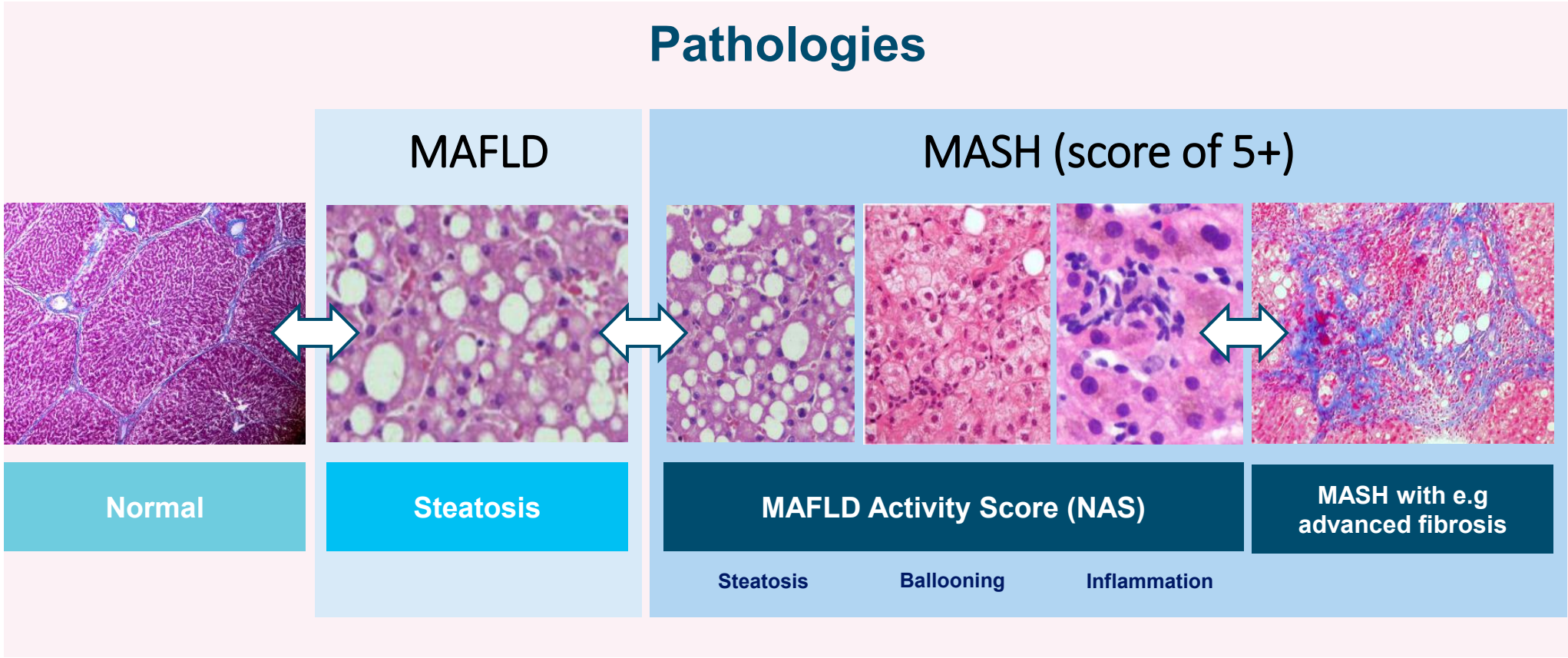
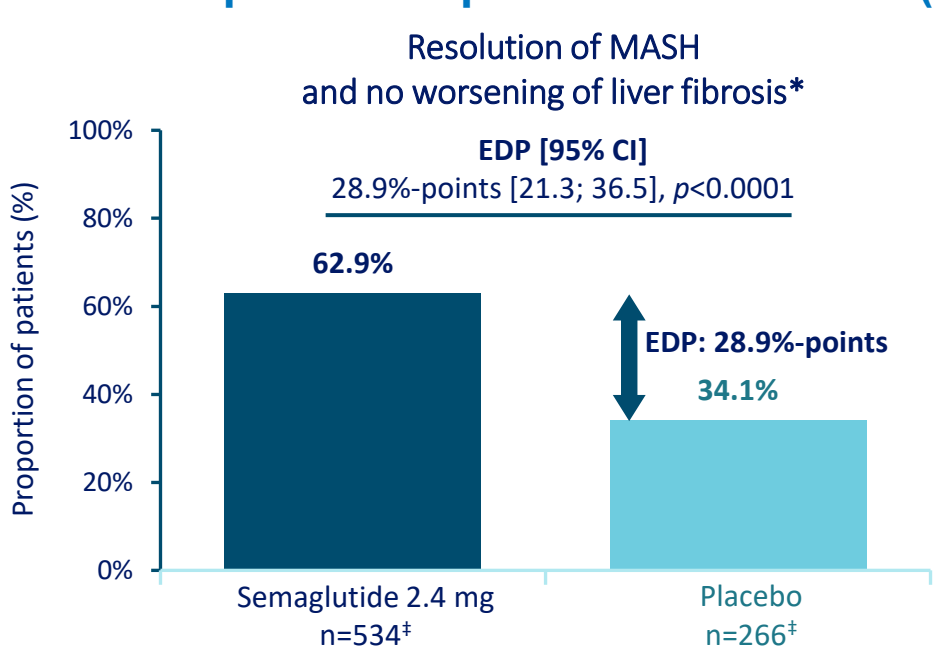
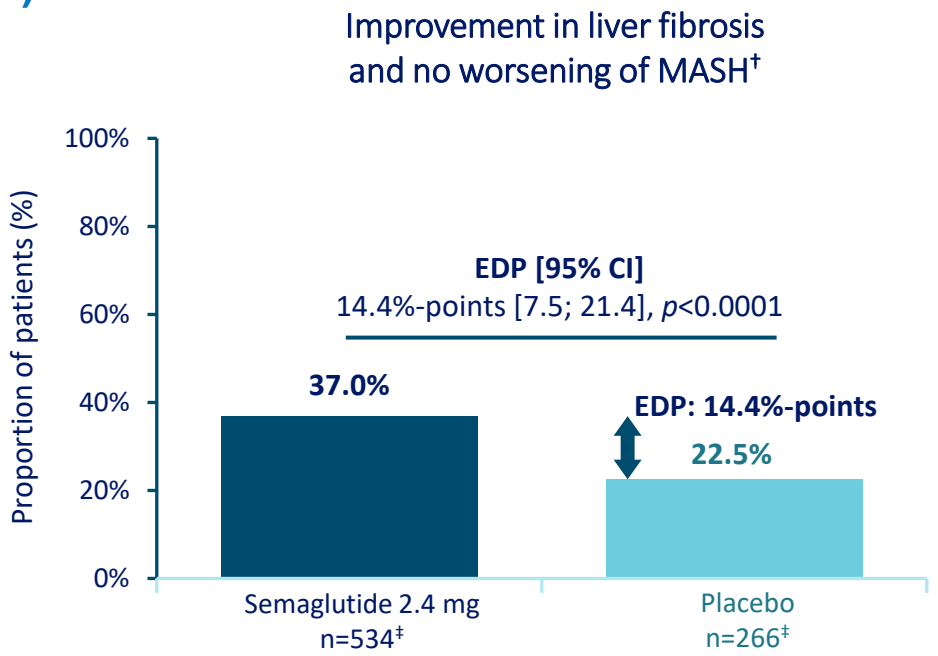
MAFLD has a Diversity of Pathologies



Steatohepatitis resolution and improvement in liver fibrosis

Proportion of patients at Week 72 (full analysis set)





Significantly more patients with MASH F2–F3 treated with semaglutide 2.4 mg achieved **both primary endpoints of MASH resolution (62.9%) and improvement in liver fibrosis (37.0%)** than those treated with placebo **(34.1%, 22.5% respectively)**

*Analysis set: FAS (interim), first 800 randomised subjects. EDP: Estimated difference in responder proportions with 95% confidence interval and two-sided p-value. *Resolution of steatohepatitis is defined as a NAS of 0-1 for inflammation, 0 for ballooning and any value for steatosis according to NASH CRN. No worsening of liver fibrosis is defined as no increase in fibrosis score. Fibrosis is graded on the NASH CRN fibrosis scale from 0-4. †Improvement in fibrosis is defined as >= 1 grade improvement on the NASH CRN fibrosis scale. No worsening of steatohepatitis is defined as no increase from baseline in NAS score for ballooning, inflammation or steatosis. The absolute difference between responder proportions, 95% confidence interval, P value was generated with the use of Cochran-Mantel-Haenszel (CMH) test stratified by baseline diabetes status (medical history) and fibrosis stage (eligibility read). ‡Missing data were handled by reference-based multiple imputation and Rubin's rule based on the Mantel-Haenszel estimator and Sato's estimate of the standard error (reference) were used to aggregate results. CI, confidence interval; EDP, estimated difference in responder proportions; F, fibrosis stage; MASH, metabolic dysfunction associated steatohepatitis; NASH CRN, Non-Alcoholic Steatohepatitis Clinical Research Network. Newsome PN et al. Oral Presentation at American Association for the Study of the Liver The Liver Meeting; Late Breaker 5018; November 19 2024; San Diego, USA.*

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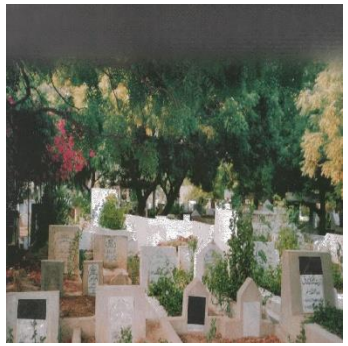
EMPA-REG All-cause mortality

Empagliflozin 10 mg
HR 0.70
(95% CI 0.56, 0.87)
p=0.0013

Empagliflozin 25 mg
HR 0.67
(95% CI 0.54, 0.83)
p=0.0003



No. of patients									
Empagliflozin 10 mg	2345	2327	2305	2274	2055	1542	1303	847	201
Empagliflozin 25 mg	2342	2324	2303	2282	2073	1537	1314	875	213
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

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Kaplan-Meier estimate. HR, hazard ratio

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Number needed to treat (NNT) to prevent one death across landmark trials in patients with high CV risk

Simvastatin[1] for 5.4 years

30

High CV risk
5% diabetes, 26% hypertension

Ramipril[2] for 5 years

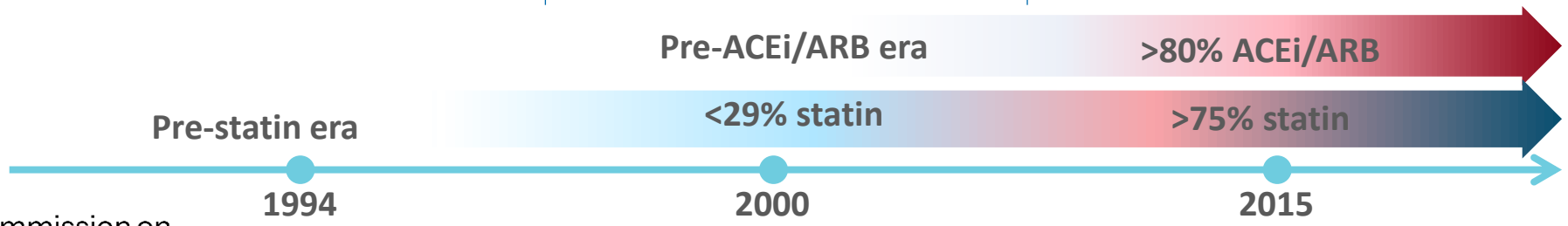
56

High CV risk
38% diabetes, 46% hypertension

Empagliflozin for 3 years

39

T2DM with high CV risk
92% hypertension



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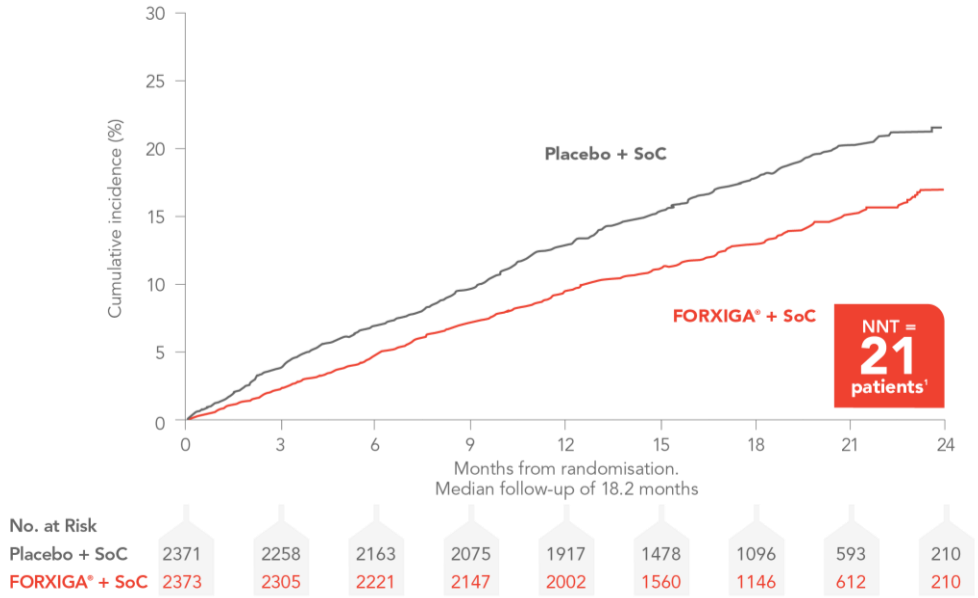
1. 4S investigator. Lancet 1994; 344: 1383-89, http://www.trialresultscenter.org/study2590-4S.htm;
2. HOPE investigator N Engl J Med 2000;342:145-53, http://www.trialresultscenter.org/study2606-HOPE.htm

DAPA-HF primary composite endpoint: CV death and worsening HF[1,2†]



26% RRR

(4.9% ARR)

(HR 0.74; 95% CI: 0.65, 0.85; *P*<0.0001)

Adapted from McMurray *et al.* 2019.[1]

*HFrEF defined as NYHA class II–IV HF and ejection fraction of ≤40%.[1] †Worsening HF is defined as hHF or urgent HF visit requiring initiation or intensification of treatment specifically for HF.[3]
ARR=absolute risk reduction, CV=cardiovascular, HFrEF=heart failure with reduced ejection fraction, NNT=number needed to treat, NYHA=New York Heart Association, RRR=relative risk reduction, SoC=standard of care, T2D=type 2 diabetes.

References: 1. McMurray JJV *et al. N Engl J Med.* 2019; 381(21):1995–2008. **2.** FORXIGA® Approved Product Information. **3.** Protocol for: McMurray JJV *et al. N Engl J Med.* 2019; 381:1995–2008. NEJM website. https://www.nejm.org/doi/ suppl/10.1056/NEJMoa1911303/suppl_file/nejmoa1911303_protocol.pdf. Last accessed August 2021.

Dapagliflozin (FORXIGA®) significantly reduced the risk of CV death and worsening HF vs placebo[1,2†]

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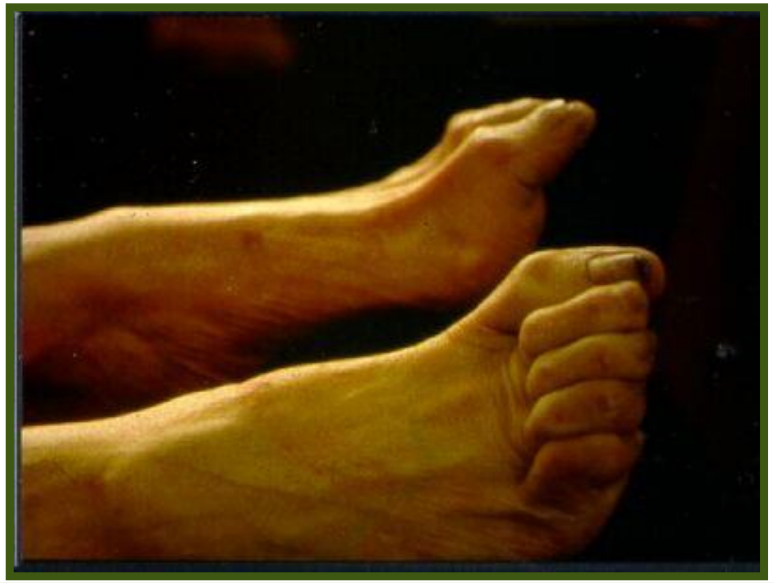
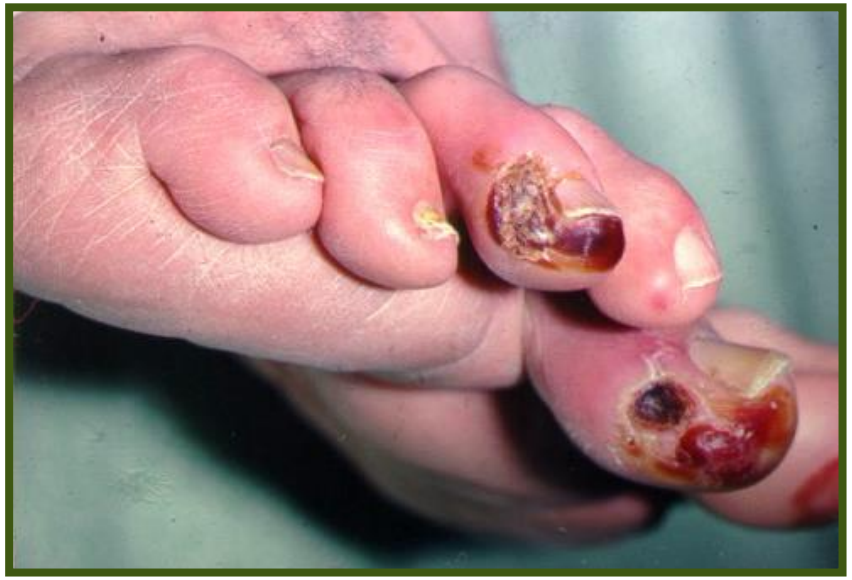
Individualised Treatment of Diabetes Foot Disease

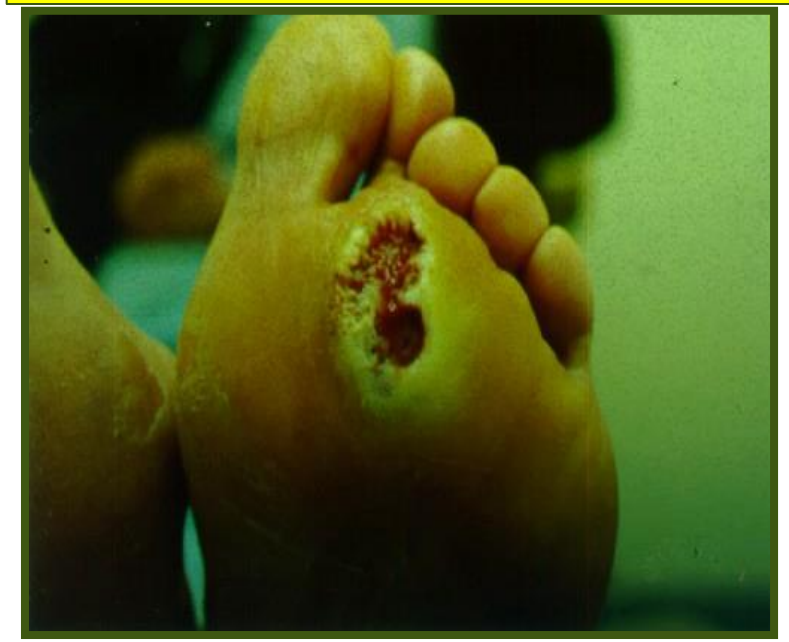
Assess the feet and determine risk of foot ulceration

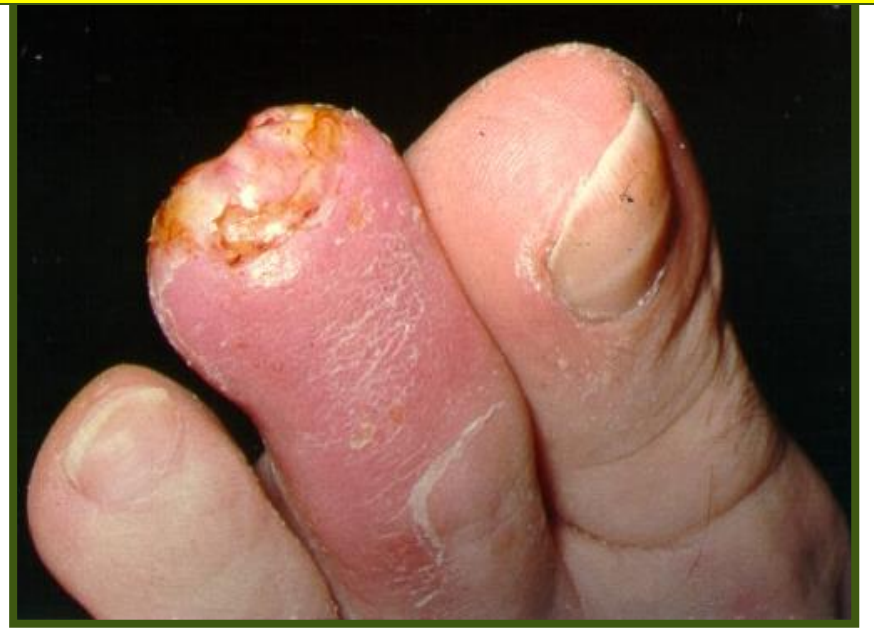
Prevent ulcers and Amputations with an individualised approach

Treat any foot ulcers in an Interdisciplinary High-Risk Foot Service, as able









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The Agenda

- Rationale for use of medicines in people with diabetes
- Rational use of medicines in people with diabetes

What Class Effect Evidence Exist for Lowering Glucose with Diabetes?

- Metformin may reduce cardiovascular events
- SGLT2i's reduce cardiovascular and renal complications
- GLP-1 mimetics reduce cardiovascular and renal and liver complications
- Less so glucose lowering by sulphonylureas, DPP-4i's, insulin, or acarbose
- The enigma of pioglitazone!

Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes

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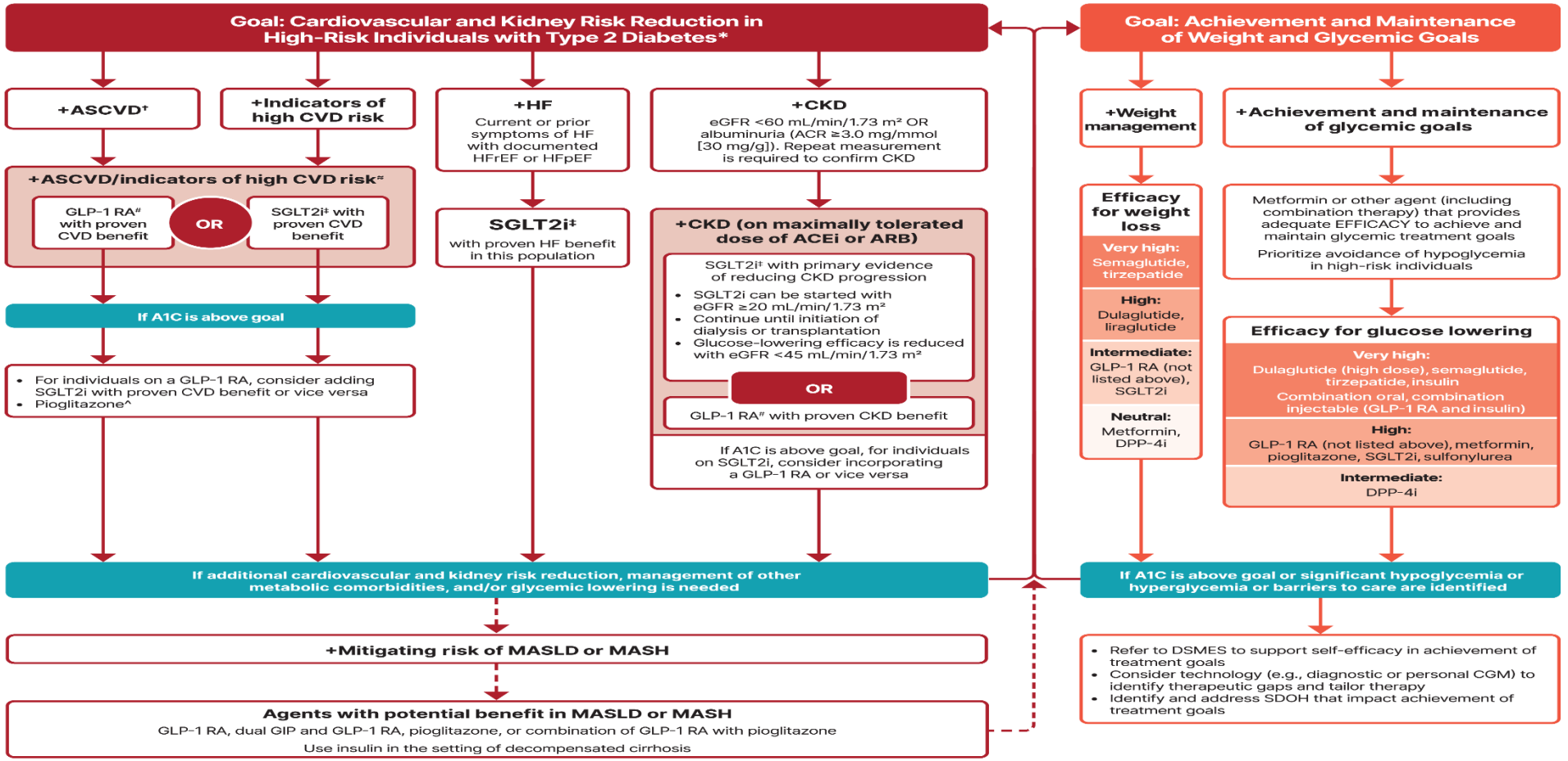
American Diabetes Association. 2025

HEALTHY LIFESTYLE BEHAVIORS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT; SOCIAL DETERMINANTS OF HEALTH

To avoid therapeutic inertia, reassess and modify treatment regularly (3–6 months)



* In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be made irrespective of background use of metformin or A1C.

† ASCVD: Defined differently across CVOTs but all included individuals with established CVD (e.g., MI, stroke, and arterial revascularization procedure) and variably included conditions such as transient ischemic attack, unstable angina, amputation, and symptomatic or asymptomatic coronary artery disease. Indicators of high risk: While definitions vary, most comprise ≥55 years of age with two or more additional risk factors (including obesity, hypertension, smoking, dyslipidemia, or albuminuria).

≈ A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high-risk CVD. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details.

For GLP-1 RAs, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke, and kidney end points in individuals with T2D with established or high risk of CVD. One kidney outcome trial demonstrated benefit in reducing persistent eGFR reduction and CV death for a GLP-1 RA in individuals with CKD and T2D.

‡ For SGLT2is, CV and kidney outcomes trials demonstrate their efficacy in reducing the risks of composite MACE, CV death, all-cause mortality, MI, HHF, and kidney outcomes in individuals with T2D and established or high risk of CVD.

^ Low-dose pioglitazone may be better tolerated and similarly effective as higher doses.

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The Agenda

- Rationale for use of medicines in people with diabetes
- Rationale for use of medicines in people with diabetes
- Consumer advice in use of such medicines

What Priorities Do Consumers Emphasise in Their Diabetes Complications Care?

- Body weight vs complications
- Hypoglycaemia minimisation
- Avoiding chronic complications such as blindness, dialysis, heart failure, amputation, and dementia!
- Financial cost and equity of access

The Agenda

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The Management Challenge: To Optimise Care



‘One-size fits all’ can work to some degree in most cases

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The Management Challenge: To Optimise Care



‘One-size fits all’ can work to some degree in most cases

All elements can be personalised and rationally individualised, especially with TEAM based care!

The Agenda

- Rationale for use of medicines in people with diabetes
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- Practical adherence issues in medication use in diabetes

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Medication Adherence in Diabetes Medicines and Complications

- Newer and older agents demonstrate frustratingly low adherence levels
- Treating clinical depression alone will not aid adherence
- Adherence to medicines can be very selective
- Medication ‘discrepancies’ rates reflect suboptimal stewardship

The Agenda - Summarised

- Rationale for use of medicines in people with diabetes
- Rationale for use of medicines in people with diabetes regarding complications
- Consumer advice in use of such medicines
- Risk-benefit in medication use in diabetes
- Practical adherence issues in medication use in diabetes complications
- Medications in diabetes have come a long way! Flora and Fauna have helped
- Further progress is expected
  - Route of administration/convenience/safety in dosing e.g. insulin
  - Combinations to minimise polypharmacy and further reduce complications
  - Targeting medicines to aid personalised care: use of ‘omics’

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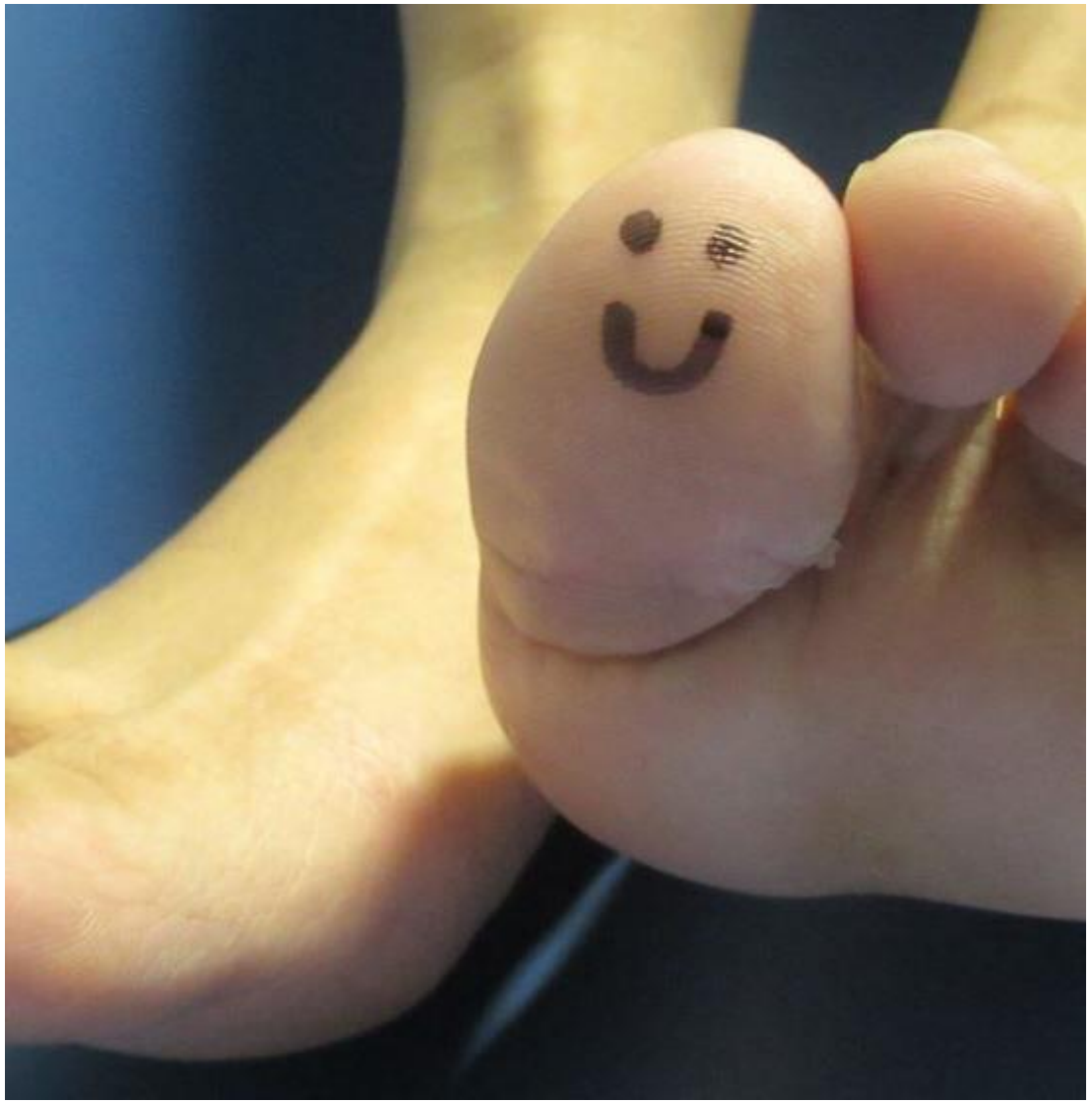

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Thank you

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