Joint ADA/EASD—Management of Hyperglycaemia in Type 2 Diabetes

Friday, September 23, 2022

12:15 – 13:45 CEST

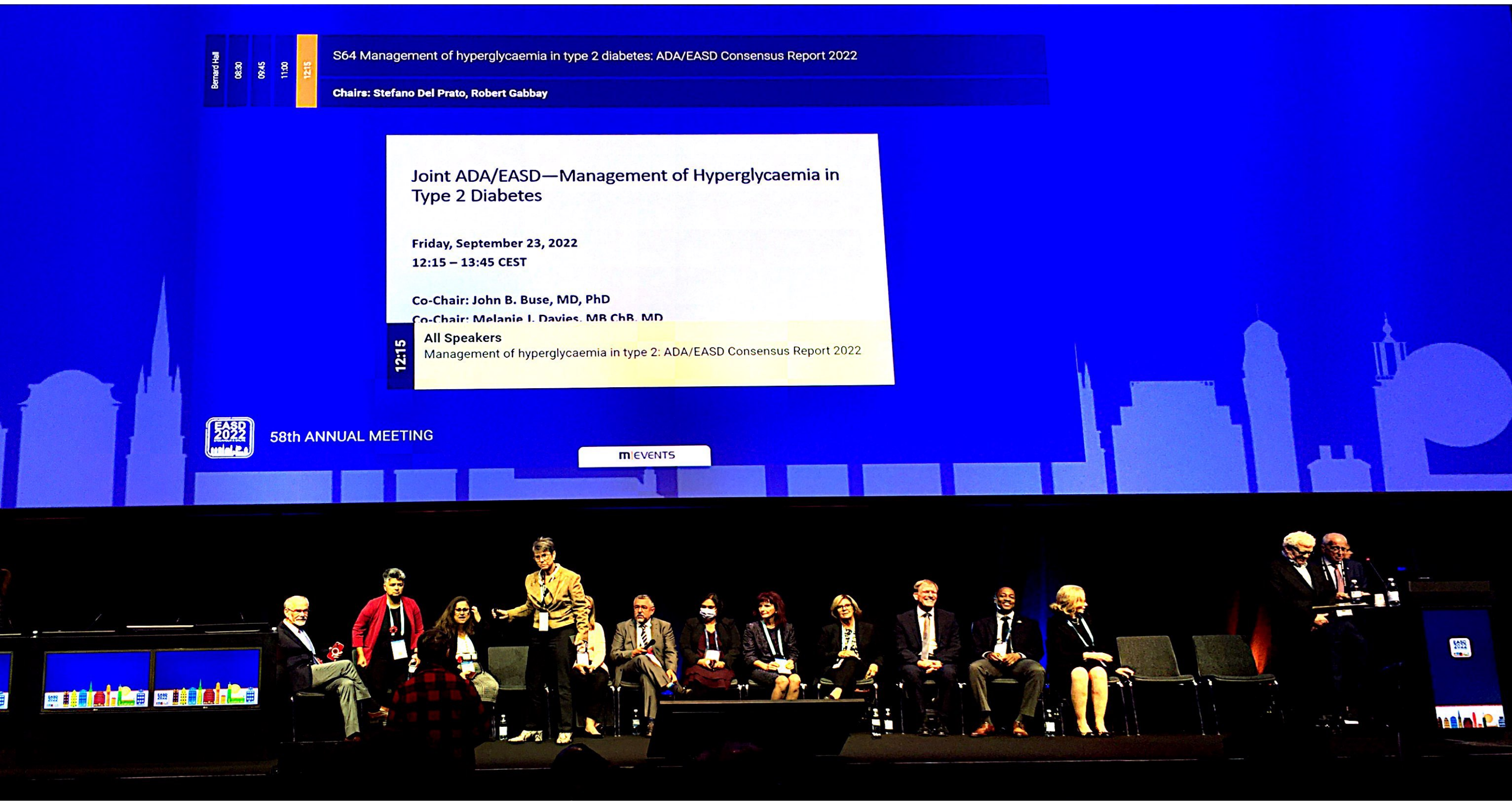
Co-Chair: John B. Buse, MD, PhD

Co-Chair: Melanie J. Davies, MB ChB, MD

12:15

All Speakers

Management of hyperglycaemia in type 2: ADA/EASD Consensus Report 2022


S64 Management of hyperglycaemia in type 2 diabetes: ADA/EASD Consensus Report 2022
Chairs: Stefano Del Prato, Robert Gabbay
Joint ADA/EASD—Management of Hyperglycaemia in Type 2 Diabetes
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Management of hyperglycaemia in type 2: ADA/EASD Consensus Report 2022
EASD 2022
58th ANNUAL MEETING
m|EVENTS

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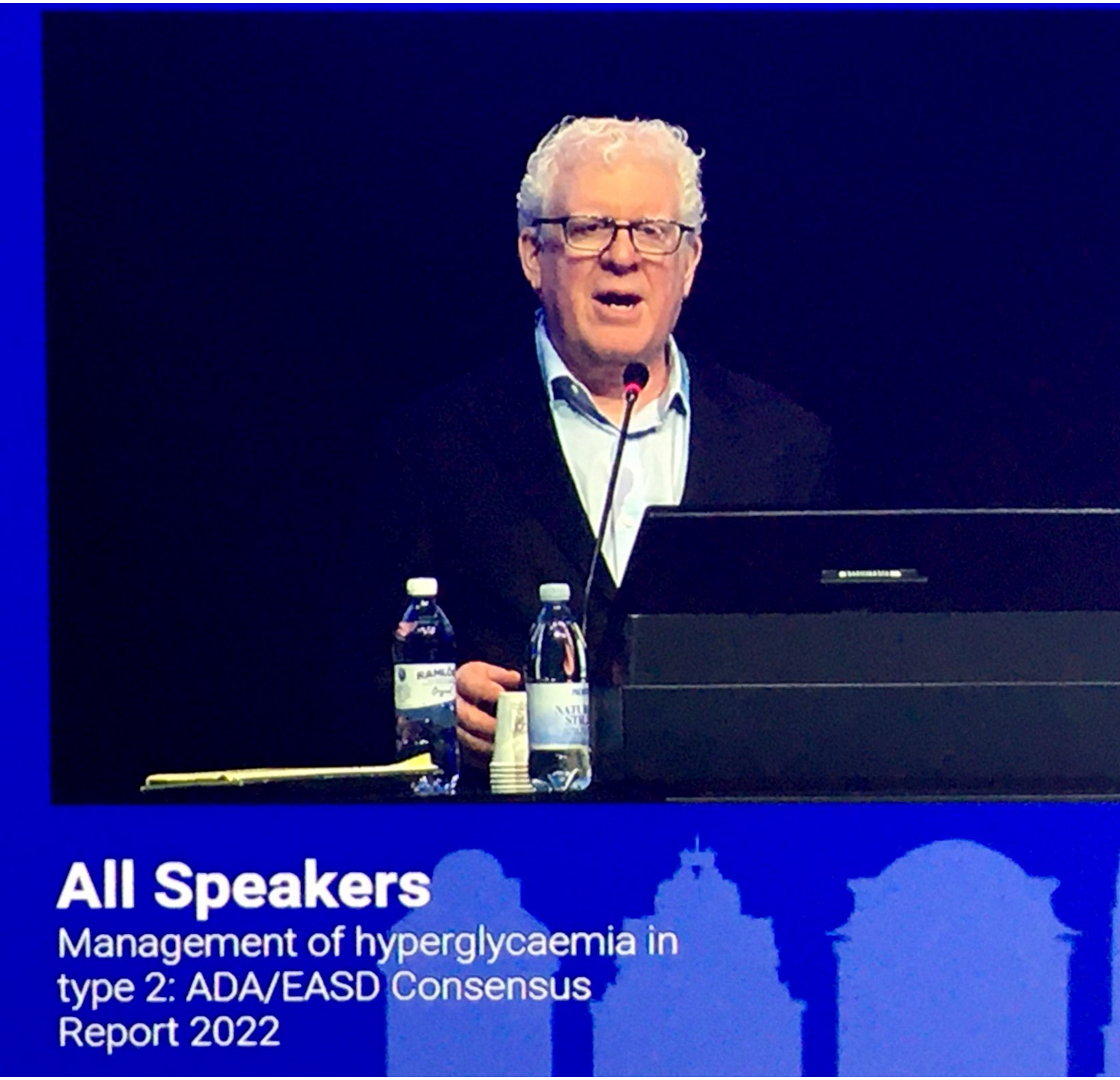
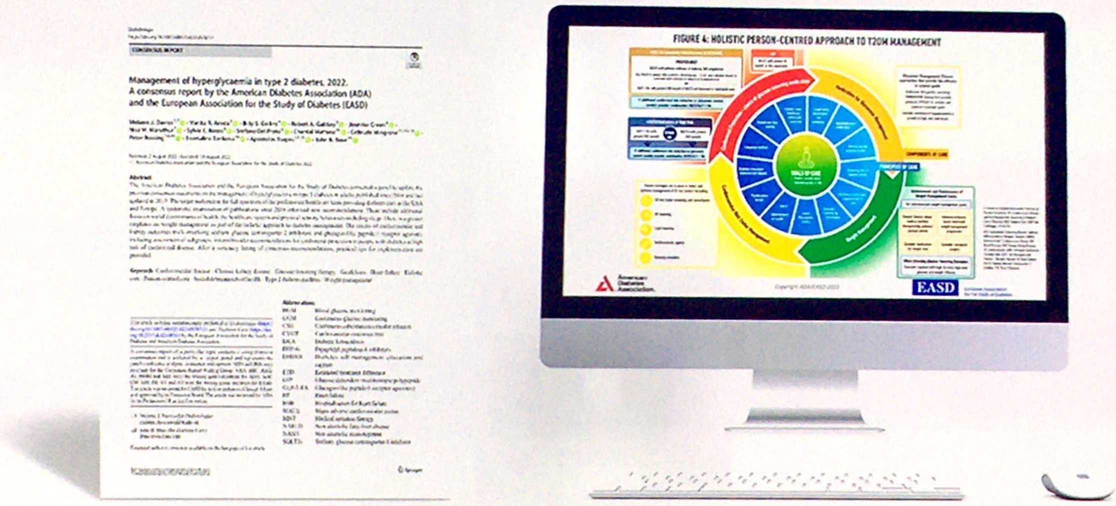

All Speakers
Management of hyperglycaemia in type 2: ADA/EASD Consensus Report 2022

Papers will be simultaneously published and slide set will be available to download



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Co-Chair: John B. Buse, MD, PhD
UNC School of Medicine, USA
Project Oversight & Integration with SOC Mindy Saraco & Malaika Hill
ADA
The Rationale
Peter Rossing, MD
Steno Diabetes Center Copenhagen, Denmark
Billy Collins, DHSc, PA-C
U.S. Public Health Service, USA
Therapeutic Options
Vanita Aroda, MD
Brigham & Women's Hospital, Boston, USA
Geltrude Mingrone, MD, PhD
Catholic University of the Sacred heart, Rome, Italy
Tsvetalina Tankova, MD, DSC
Medical University, Sofia, Bulgaria
Personalised Approach
Apostolos Tsapas, MD, PhD, MSc
Aristotle University Thessaloniki, Greece
Jennifer Green, MD
Duke University, Durham, USA
Strategies for Implementation
Chantal Mathieu, MD, PhD
KU Leuven, Leuven, Belgium
Nisa Maruthur, MD, MHS
Johns Hopkins Medicine, Baltimore, USA
Sylvia Rosas, MD, MSCE
Joslin Diabetes Center, Boston, USA
Support Across Groups
Robert Gabbay, MD, PhD
ADA
Stefano Del Prato, MD
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Methods

Three-day meeting in January 2022, via teleconference

Two-day in-person meeting in April, Amsterdam

Teleconferences every 1-4 weeks, September 2021 to present

Co-chairs and 4 sets of section authors

Evidence review informed the content

Teleconference Jan 2022

Amsterdam April 2022

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Overview

The Rationale, Importance, and Context of Glucose-Lowering Treatment
Billy Collins, DHSc, PA-C & Peter Rossing, MD

Therapeutic Options: Lifestyle and Healthy Behaviour, Weight Management, and Pharmacotherapy for the Treatment of Type 2 Diabetes
Vanita Aroda, MD, Geltrude Mingrone, MD, PhD, & Tsvetalina Tankova, MD, PhD

Personalised Approach to Treatment Based on Individual Characteristics and Comorbidities
Jennifer Green, MD & Apostolos Tsapas, MD, PhD, MSc

Putting it All Together: Strategies for Implementation
Nisa Maruthur, MD, MHS, Sylvia Rosas, MD, MSCE, & Chantal Mathieu, MD, PhD

Key Knowledge Gaps and A Call to Action
John B. Buse, MD, PhD

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Methods

The writing group accepted the 2018 edition and 2019 update of this consensus report as a starting point for the evidence search.

To identify newer evidence, a search was conducted on PubMed for randomized clinical trials (RCTs), systematic reviews, and meta-analyses published in English between January 28, 2018, and December 12, 2021.

Eligible publications examined the effectiveness or safety of pharmacologic or non-pharmacologic interventions in adults with type 2 diabetes mellitus.

Reference lists were scanned in eligible reports to identify additional articles relevant to the subject.

Details on the keywords and the search strategy are accessed via a link in the papers.

Papers were grouped according to subject; the authors reviewed this new evidence to inform the consensus recommendations.

We updated the search to June 13th 2022.

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Key points to emphasise

Informed by evidence generated in the past 3 years

Greater focus on social determinants of health and systems and equality of care

Emphasis on holistic person-centred care

Greater focus on weight goals as an essential component of comprehensive care

Consolidation of evidence from CVOTs

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This is a consensus report

The 346 references included in the manuscript are not listed here in the data presented today.

Though evidence based, the recommendations presented reflect the values and preferences of the authors.

Not everyone agreed with every point. As a point of process, we agreed in advance that we would vote on areas of disagreement and proceed on basis of super-majority (60%), though that never came to pass.

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Review Process

The draft Consensus was presented at the ADA in June 2022

Feedback after the ADA presentation (>450 comments)

Diabetes Care and *Diabetologia* editors invited reviewers as well as;

ADA's Professional Practice Committee

EASD's Committee of Clinical Affairs

All comments were evaluated by the writing team and informed the papers simultaneously published and presented today in *Diabetes Care* and *Diabetologia*

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Acknowledgements

ADA
Nuha El Sayed
Malaika Hill
Raveendhara R. Bannuru, MD, FAGE
Nuha El Sayed, MD, MMSc

EASD
Petra Niemann
Natasha Buckley-Muehge

Invited Reviewers
CCA of the EASD
PPC of the ADA

From Leicester Diabetes Centre, the University of Leicester and the NHS Hospital Trust (UHL University of Leicester NHS Trust):
Michael Bonar
Charlie Franklin
Shehnaz Jamal
Francesco Zaccardi
Joe Henson
Tom Yates

From Aristotle University Thessaloniki
Thomas Karagiannis

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The Rationale, Importance, and Context of Glucose-Lowering Treatment

Peter Rossing, MD, DMSc* and Billy Collins, DHSc, PA-C#
for the ADA-EASD Management of Hyperglycaemia in Type 2 Diabetes Working Group

*Professor University of Copenhagen, Head of Complications Research, Steno Diabetes Center Copenhagen, Denmark
#Associate Investigator, Director of Clinical Services, Social Determinants of Obesity and Cardiovascular Risk Laboratory, National Heart, Lung & Blood Institute, NIH

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Goals of Diabetes Care

Prevent complications

Optimise quality of life

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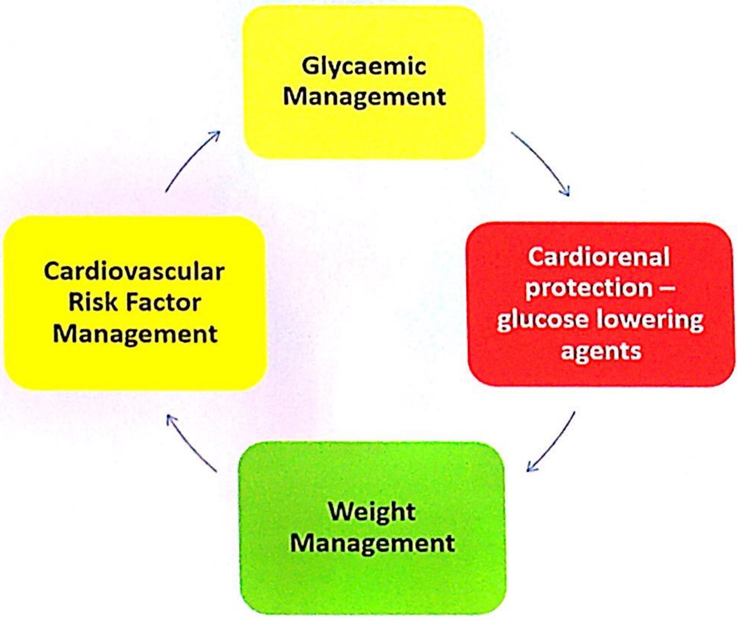
Preventing Complications



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Language matters

- Communication between people living with type 2 diabetes and health care team members is at the core of integrated care
- Clinicians must recognise how language matters
- Language in diabetes care should be neutral, free of stigma, and based on facts; be strengths-based (focus on what is working), respectful, and inclusive; encourage collaboration; and be person-centred
- People living with diabetes should not be referred to as “diabetics,” or described as “noncompliant,” or blamed for their health condition.

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Social Determinants of Health

- SDOH must be addressed to improve health outcomes
- Five SDOH areas have been identified:
    - socioeconomic status (education, income, and occupation),
    - living and working conditions,
    - multisector domains (e.g., housing, education, criminal justice system),
    - sociocultural context (e.g., shared cultural values, practices, experiences), and
    - sociopolitical context (e.g., societal and political norms that are root-cause ideologies and policies underlying health disparities)
- Environmental, social, behavioural, and emotional factors, known as psychosocial factors, influence living with diabetes, and achieving satisfactory medical outcomes and psychological well-being
- Individuals' heterogeneity, SDOH, and psychosocial factors challenge individuals with diabetes, their families, and their providers when attempting to integrate diabetes care into daily life

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Importance of Glycaemic Control

Averting symptomatic hyperglycaemia

Substantial and enduring reduction in microvascular complications

- 50-76% reduction DCCT with HbA1c 7% vs 9%
- 25% reduction UKPDS with HbA1c 7% vs 7.9%
- Greatest benefit with reduction from higher levels of HbA1c

Uncertainty regarding macrovascular benefit of BG control in T2D

Benefits emerge slowly while harms of glucose control medications can be more immediate

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Glucose Control: Monitoring

HbA1c test

- Excellent performance in certified labs
- Limitations in conditions that alter red blood cell turnover and in certain racial and ethnic groups
- Consider reliability of HbA1c assay with discrepancies between measured HbA1c and glucose levels

Blood glucose monitoring

- Useful for self-management in people with type 2 diabetes particularly when taking insulin
- Limited benefit outside insulin Rx and adds burden and cost
- Continuous glucose monitoring (CGM) provide more information and may be useful for people with type 2 diabetes, particularly those using insulin

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Improving Glycaemic Management

Focus on treatments for glycaemic management

- Behavioural approaches
- Medications
- Metabolic surgery

Addresses increasing complexity of person-centred therapeutic decisions in the context of expanding therapeutic options and new information on benefits and risks

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Weight Reduction as a Targeted Intervention

- Weight reduction has mostly been seen as a strategy to improve glycaemic management and reduce the risk for weight-related complications.
- It was recently suggested that weight loss of 5-15% should be a primary target in management for many people living with type 2 diabetes.
- A higher magnitude of weight loss confers better outcomes, and a 5-10% loss confers metabolic improvement, and a loss of 10-15% or more of body weight can have a disease-modifying effect, and lead to remission of diabetes.
- Weight loss may exert benefits that extend beyond glycaemic management to improve risk factors for cardiometabolic disease and quality of life.

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Putting the Person with Diabetes at the Centre of Care

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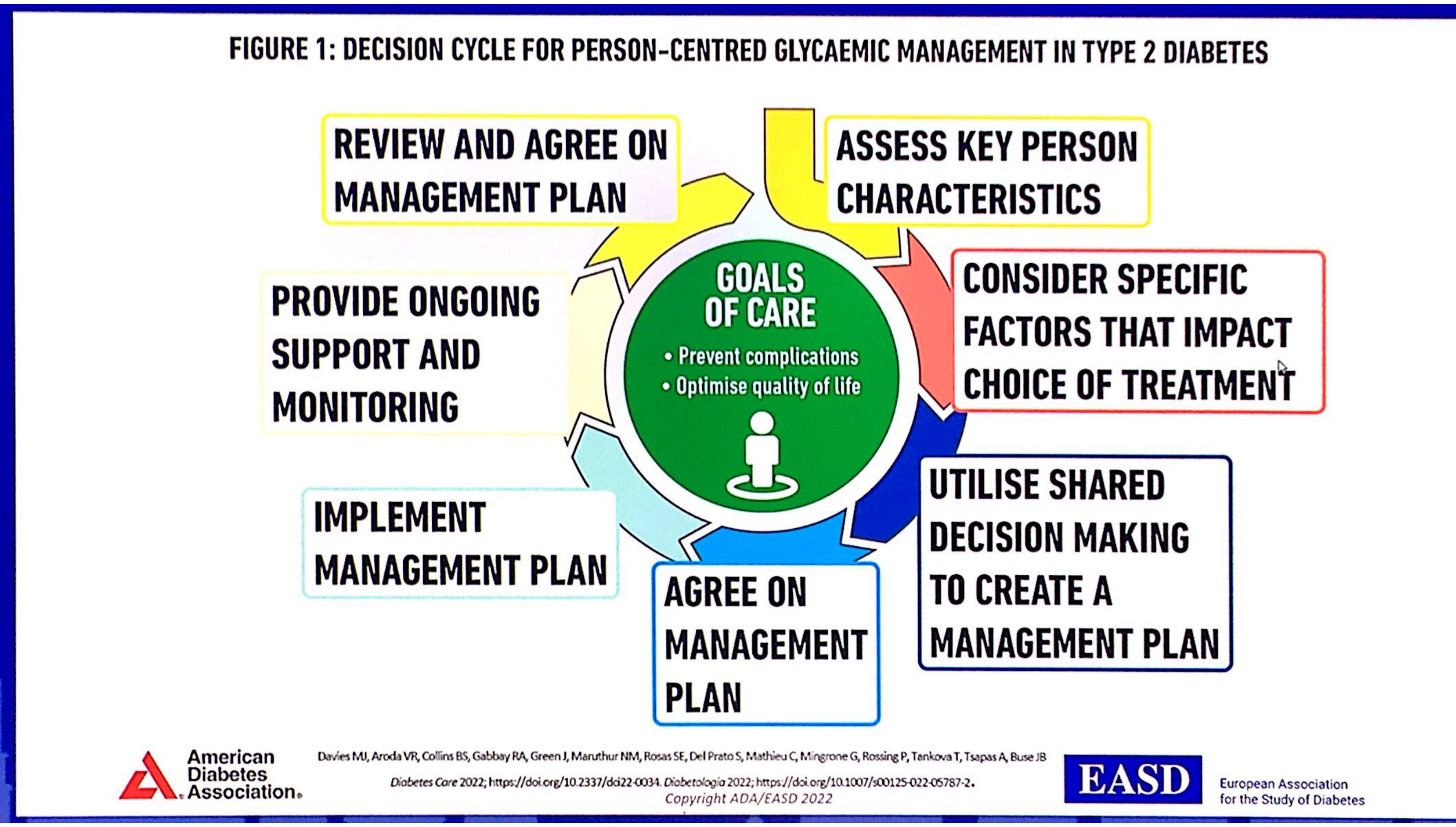
FIGURE 1: DECISION CYCLE FOR PERSON-CENTRED GLYCAEMIC MANAGEMENT IN TYPE 2 DIABETES
ASSESS KEY PERSON CHARACTERISTICS
CONSIDER SPECIFIC FACTORS THAT IMPACT CHOICE OF TREATMENT
UTILISE SHARED DECISION MAKING TO CREATE A MANAGEMENT PLAN
AGREE ON MANAGEMENT PLAN
IMPLEMENT MANAGEMENT PLAN
PROVIDE ONGOING SUPPORT AND MONITORING
REVIEW AND AGREE ON MANAGEMENT PLAN
GOALS OF CARE
• Prevent complications
• Optimise quality of life
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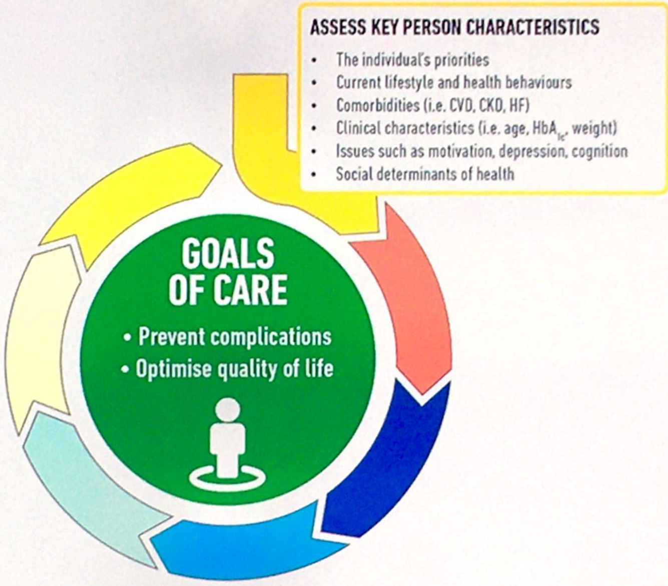

BGM, Blood Glucose Monitoring; BP, Blood Pressure; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; CVD, Atherosclerotic Cardiovascular Disease; DSMES, Diabetes Self-Management Education and Support; HF, Heart Failure.

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Shared Decision-Making in Type 2 Diabetes

Shared decision-making can improve

- decision quality
- knowledge about risks, safety, and benefits
- incorporation of individual preferences and values when formulating a management plan

Ethical imperative for support of person's autonomy

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Diabetes Self-Management Education and Support (DSMES)

Face-to-face contact in group or individual sessions with trained educators

Promote healthy eating, physical activity, good medication-taking behavior, and increase self-efficacy

Theory based DSMES, with structured curriculum and contact time > 10 hrs

- decrease HbA_{1c}
- reduce hospital admissions
- improve person with diabetes knowledge
- improve clinical and psychological outcomes
- cost-effective
- potentially reduce the risk of all-cause mortality

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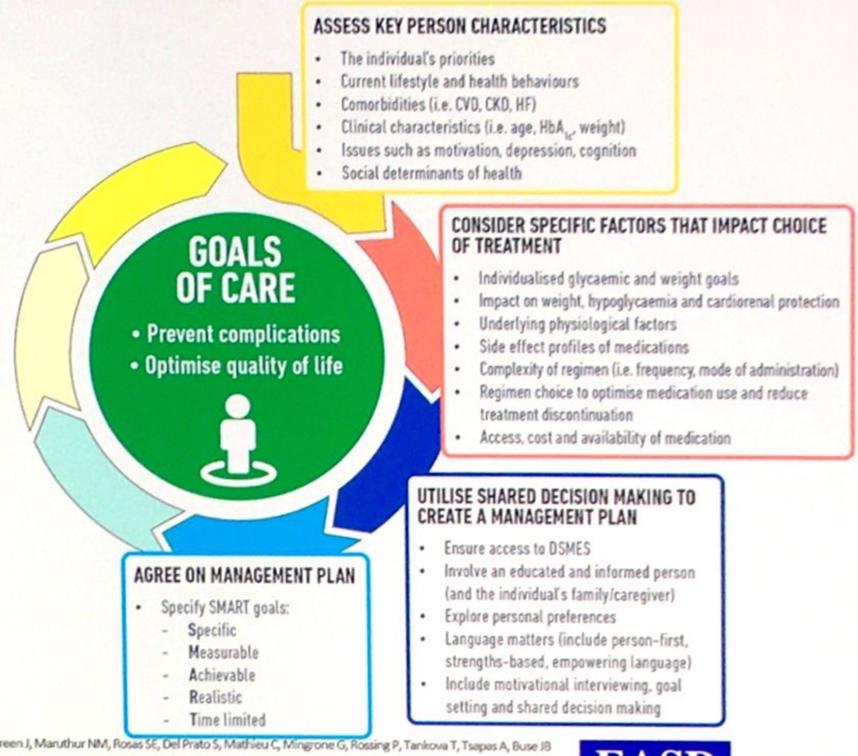

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Clinical Inertia

Clinical inertia: failure of healthcare providers to initiate or intensify therapy when indicated, due to:

- overestimation of care provided
- use of “soft” reasons to avoid intensification of therapy
- lack of education, training, and practice organisation aimed at achieving therapeutic goals

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Therapeutic Options: Lifestyle and Healthy Behaviour, Weight Management, and Pharmacotherapy for the Treatment of Type 2 Diabetes

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Medical University, Sofia, Bulgaria

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Director, Diabetes Clinical Research, Brigham and Women's Hospital;
Associate Professor of Medicine, Harvard Medical School

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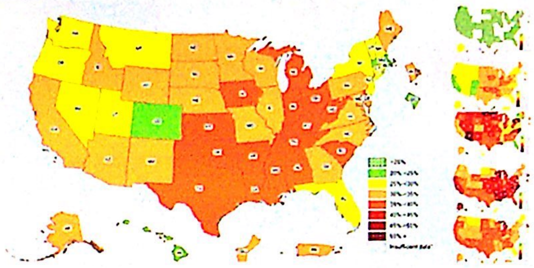

The NEW ENGLAND JOURNAL *of* MEDICINE

SPECIAL ARTICLE

Projected U.S. State-Level Prevalence of Adult Obesity and Severe Obesity

Zachary J. Ward, M.P.H., Sara N. Bleich, Ph.D., Angie L. Cradock, Sc.D., Jessica L. Barrett, M.P.H., Catherine M. Giles, M.P.H., Chasmine Flax, M.P.H., Michael W. Long, Sc.D., and Steven L. Gortmaker, Ph.D.

By 2030 **~50% obesity** **~25% morbid obesity**

One Billion People Globally Estimated to be Living with Obesity by 2030

Call for Global Action Plan on Obesity at World Health Assembly in May 2022

- The World Obesity Atlas 2022, published by the World Obesity Federation, predicts that one billion people globally, including 1 in 5 women and 1 in 7 men, will be living with obesity by 2030.
- The findings highlight that countries will not only miss the 2025 WHO target to halt the rise in obesity at 2010 levels, but that the number of people with obesity is on course to double across the globe.
- The greatest number of people living with obesity are in low- and middle-income countries (LMICs), with numbers more than doubling across all LMICs, and tripling in low income countries, compared to 2010.

Ward ZJ *et al*; *NEJM* 2019; 381: 2440-2450
https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2022, Accessed 04 June,
https://www.cdc.gov/obesity/data/prevalence-maps.html, Accessed 04 June, 2022

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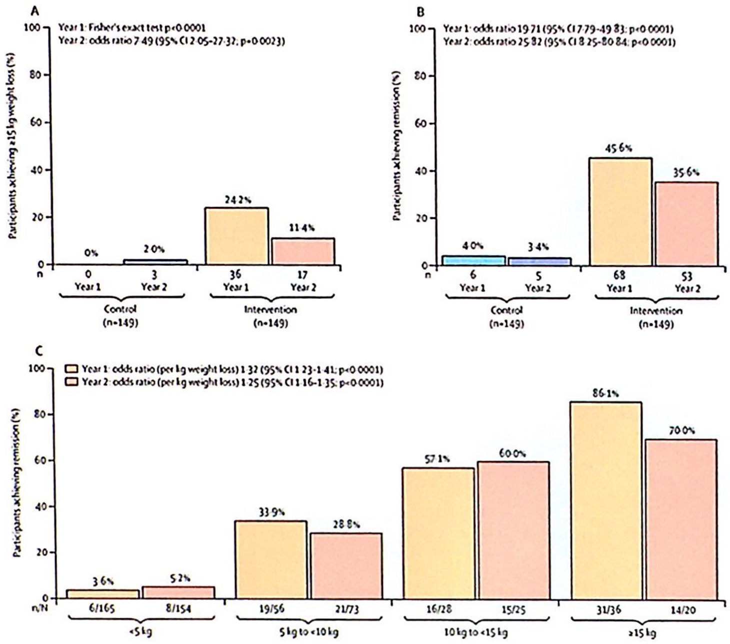
Intensive Structured Weight Management: the DiRect RCT



- 10 kg at 2 year follow-up = 64% diabetes remission

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Lean et al. *The Lancet Diabetes & Endocrinology* 2019;7:344-355.

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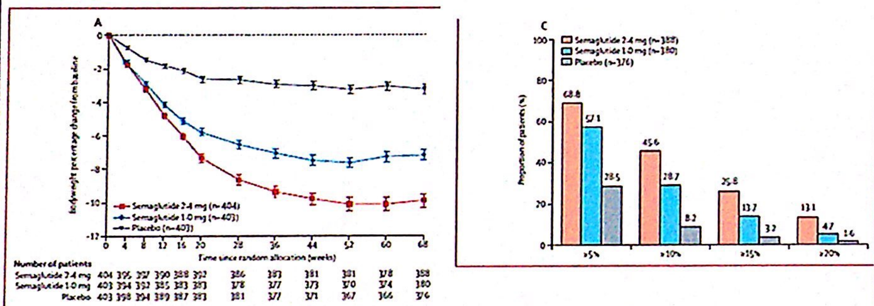
Weight Management in Type 2 Diabetes

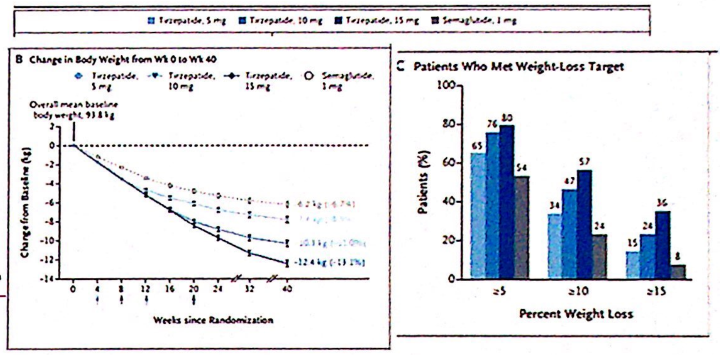
Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial

*Melanie Davies, Louise Færch, Ole K Jeppesen, Arash Pakseresht, Sue D Pedersen, Leigh Perreault, Julio Rosenstock, Iichiro Shimomura, Adie Viljoen, Thomas A Wadden, Ildiko Lingvay, for the STEP 2 Study Group**



Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes

Juan P. Frías, M.D., Melanie J. Davies, M.D., Julio Rosenstock, M.D., Federico C. Pérez Manghi, M.D., Laura Fernández Landó, M.D., Brandon K. Bergman, Pharm.D., Bing Liu, Ph.D., Xuewei Cui, Ph.D., and Katelyn Brown, Pharm.D., for the SURPASS-2 Investigators*



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Davies M *et al; Lancet* 2021; 397: 971-84
Frías JP *et al. N Engl J Med* 2021;385:503-515

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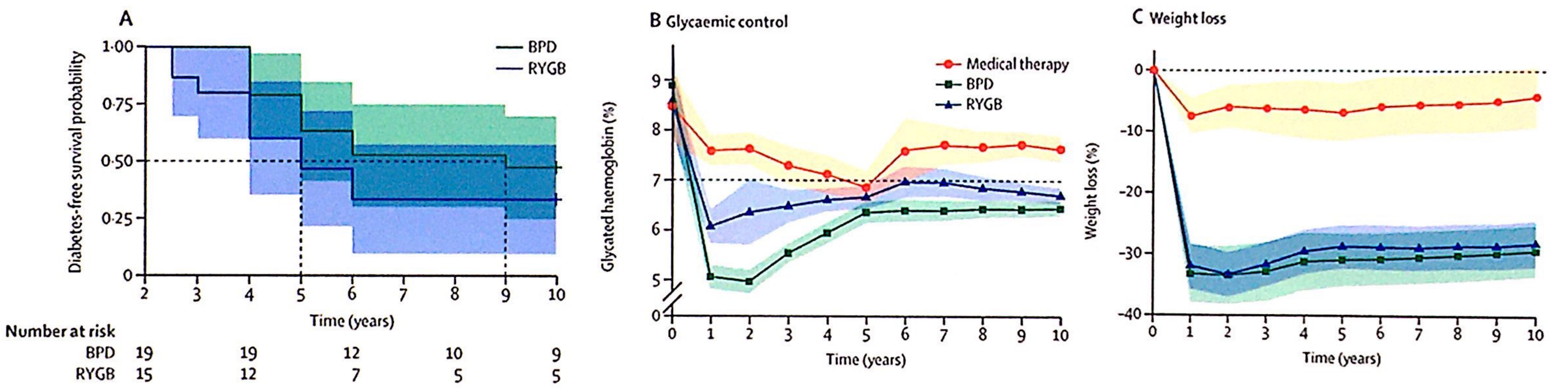
Weight Management: Metabolic Surgery



Mingrone et al. *The Lancet.* 2021 23;397:293-304

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Achievement and Maintenance of Weight Management Goals:

Set individualised weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity	Intensive evidence-based structured weight management programme
Consider medication for weight loss	Consider metabolic surgery

When choosing glucose-lowering therapies:

Consider regimen with high-to-very-high dual glucose and weight efficacy

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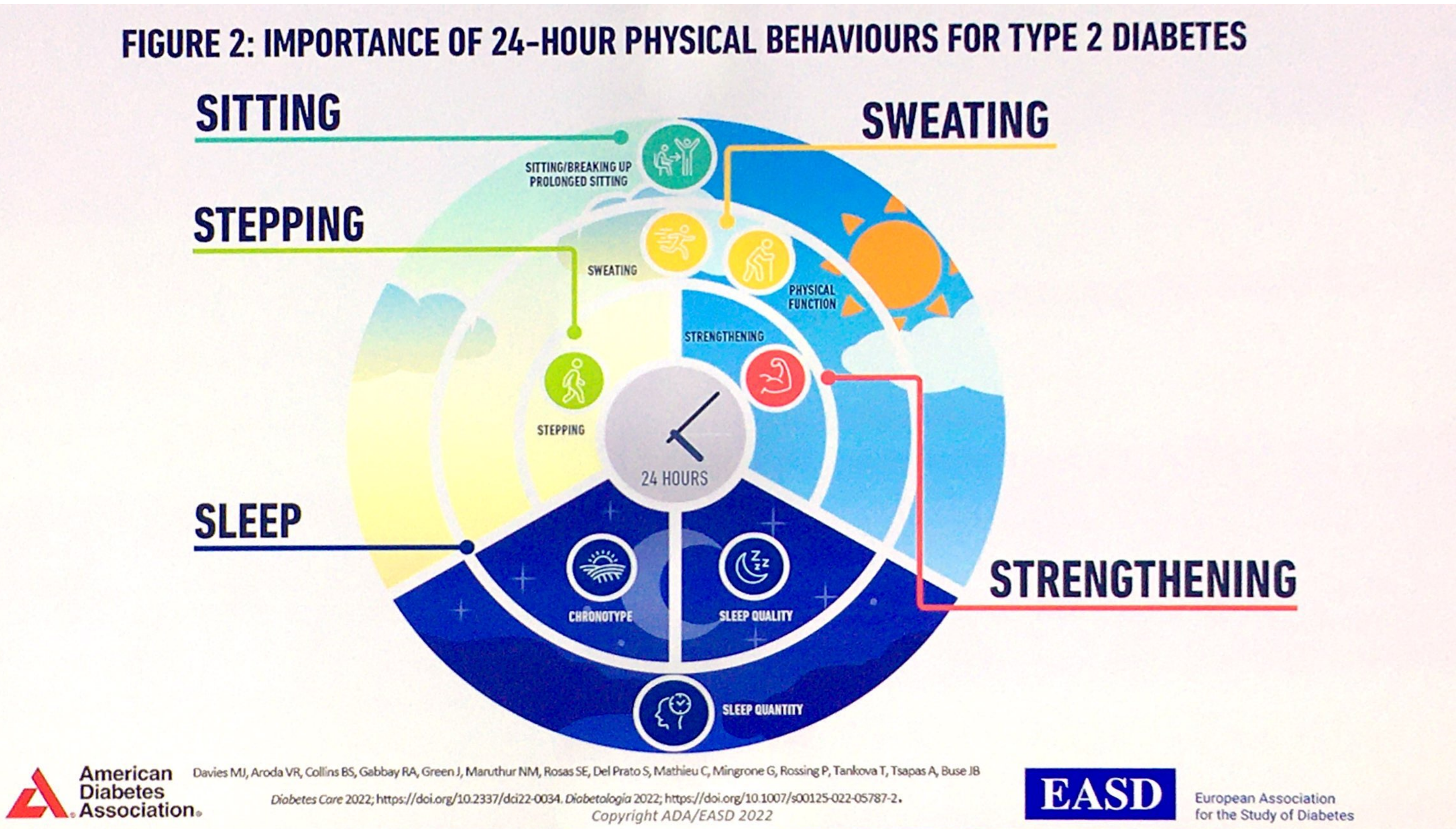
FIGURE 2: IMPORTANCE OF 24-HOUR PHYSICAL BEHAVIOURS FOR TYPE 2 DIABETES
SITTING
SWEATING
STEPPING
SITTING/BREAKING UP PROLONGED SITTING
SWEATING
PHYSICAL FUNCTION
STRENGTHENING
STEPPING
24 HOURS
SLEEP
CHRONOTYPE
SLEEP QUALITY
SLEEP QUANTITY
STRENGTHENING
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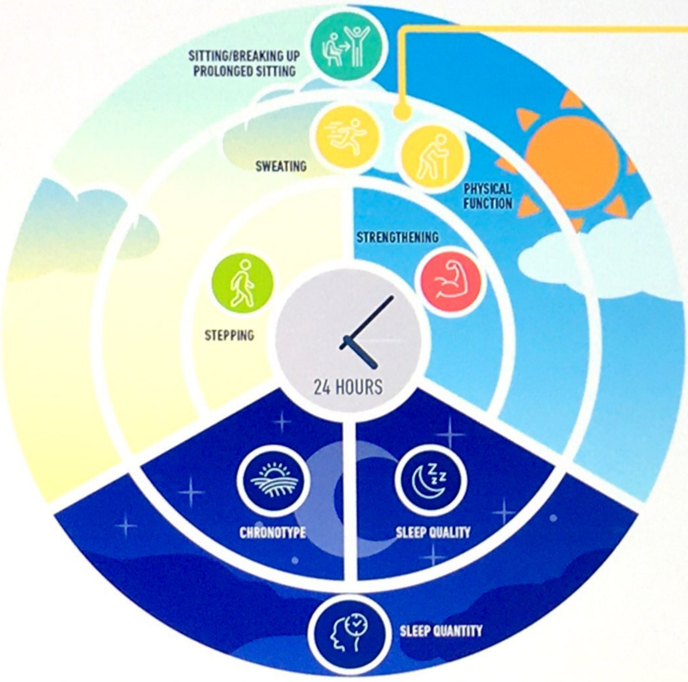

SWEATING (MODERATE-TO-VIGOROUS ACTIVITY)

- Encourage ≥150 min/week of moderate-intensity physical activity (i.e. uses large muscle groups, rhythmic in nature) OR ≥75 min/week vigorous-intensity activity spread over ≥3 days/week, with no more than 2 consecutive days of inactivity. Supplement with two to three resistance, flexibility and/or balance sessions.
- As little as 30 min/week of moderate-intensity physical activity improves metabolic profiles.

Physical function/frailty/sarcopenia

- The frailty phenotype in type 2 diabetes is unique, often encompassing obesity alongside physical frailty, at an earlier age. The ability of people with type 2 diabetes to undertake simple functional exercises in middle-age is similar to that in those over a decade older.

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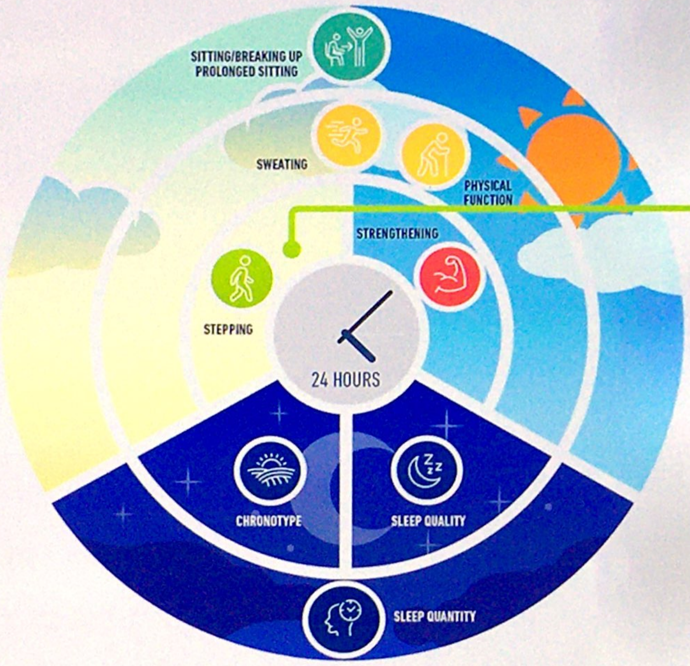

STEPPING

- An increase of only 500 steps/day is associated with 2–9% decreased risk of cardiovascular morbidity and all-cause mortality.
- A 5 to 6 min brisk intensity walk per day equates to ~4 years' greater life expectancy.

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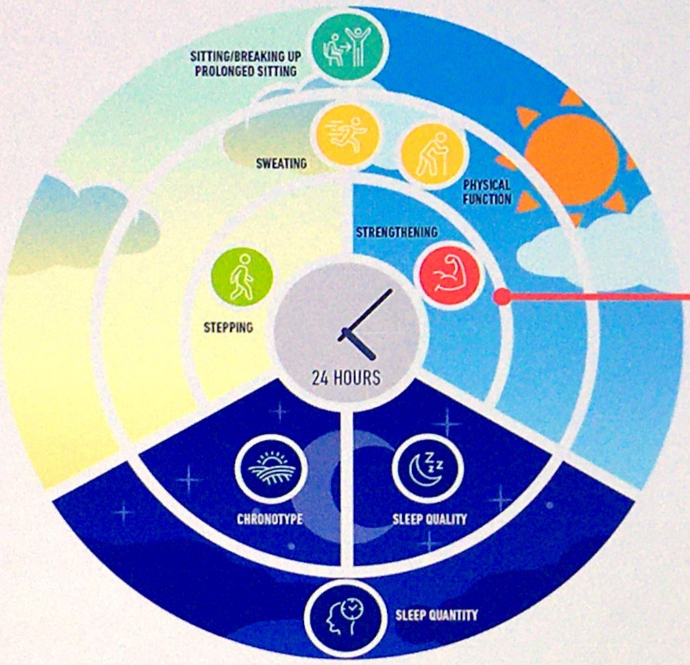

STRENGTHENING

Resistance exercise (i.e. any activity that uses the person's own body weight or works against a resistance) also improves insulin sensitivity and glucose levels; activities like tai chi and yoga also encompass elements of flexibility and balance.

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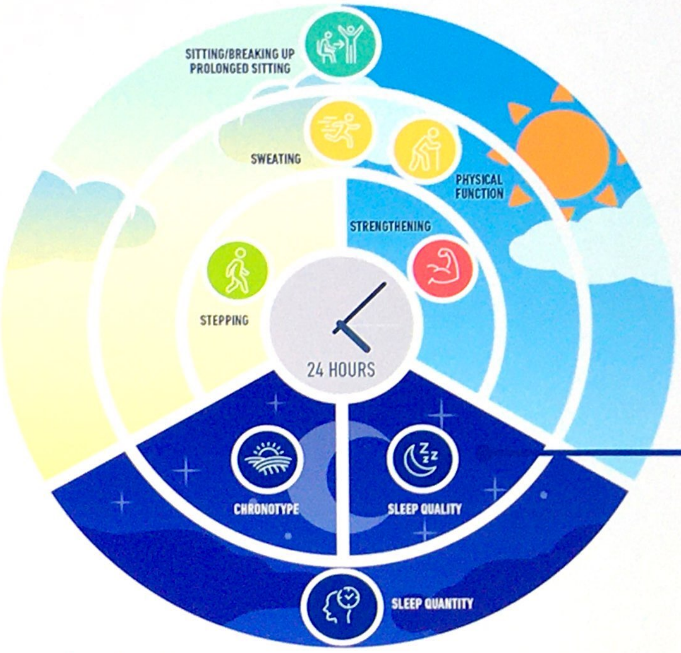

SLEEP

Aim for consistent, uninterrupted sleep, even on weekends.

Quantity – Long (>8h) and short (<6h) sleep durations negatively impact HbA1c.

Quality – Irregular sleep results in poorer glycaemic levels, likely influenced by the increased prevalence of insomnia, obstructive sleep apnoea and restless leg syndrome in people with type 2 diabetes.

Chronotype – Evening chronotypes (i.e. night owl: go to bed late and get up late) may be more susceptible to inactivity and poorer glycaemic levels vs morning chronotypes (i.e. early bird: go to bed early and get up early).

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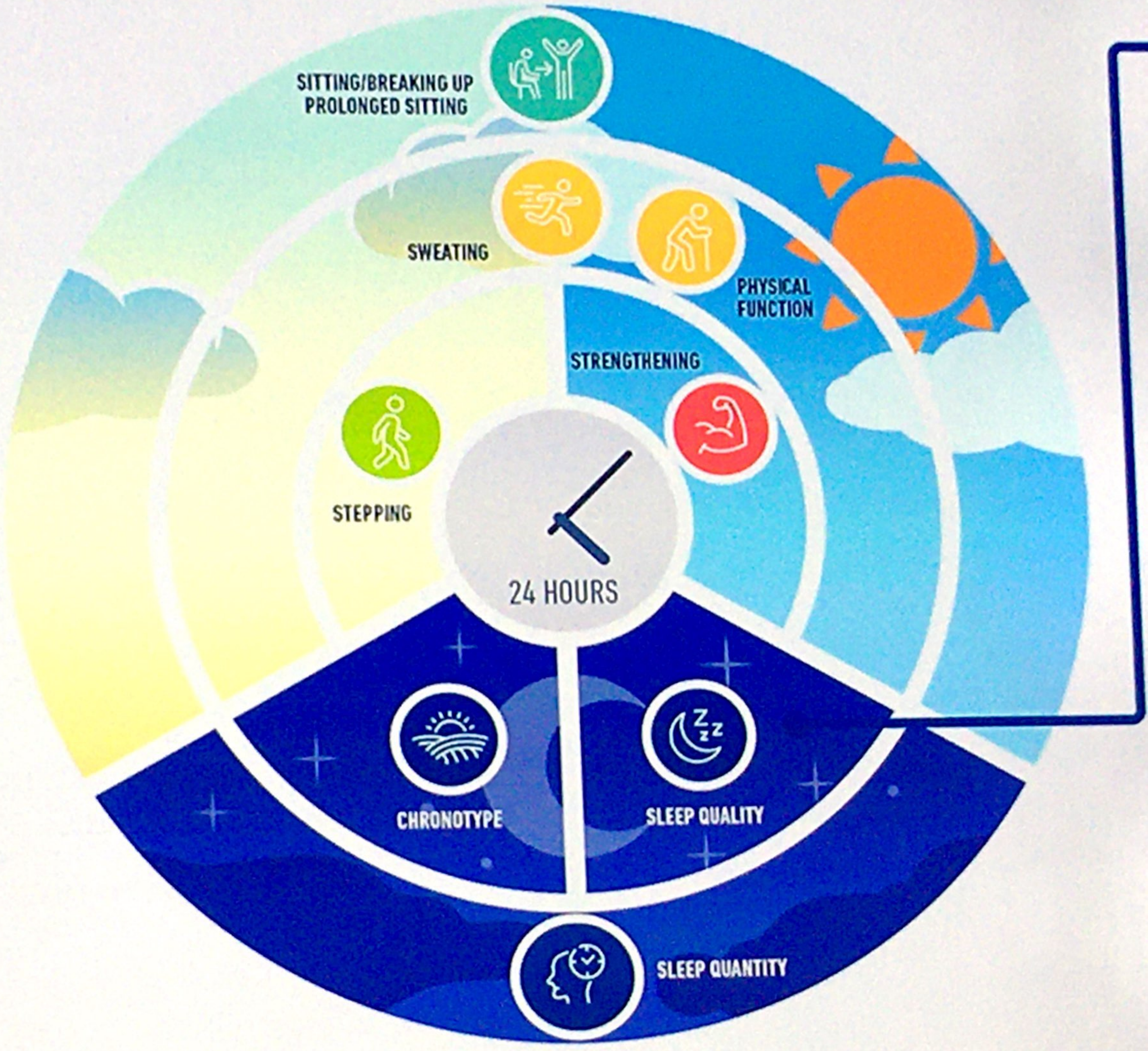
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24 HOURS
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SLEEP QUALITY
SLEEP QUANTITY

Metformin

	Efficacy[1]	Hypogly-caemia	Weight change[2]	CV effects		Renal effects		Oral/SQ	Cost
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*		
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	• Contraindicated with eGFR <30 ml/min per 1.73 m^2	Oral	Low

Traditionally recommended as first-line glucose-lowering therapy for type 2 diabetes, because of its high efficacy in lowering HbA_{1c}, minimal hypoglycaemia risk when used as monotherapy, potential for some modest weight loss, good safety profile, low cost

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Sulfonylureas

	Efficacy[1]	Hypogly-caemia	Weight change[2]	CV effects		Renal effects		Oral/SQ	Cost
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*		
Sulfonylureas (2nd Generation)	High	Yes	Gain	Neutral	Neutral	Neutral	• Glyburide: generally not recommended in chronic kidney disease • Glipizide and glimepiride: initiate conservatively to avoid hypoglycaemia	Oral	Low

- High glucose-lowering efficacy, inexpensive and accessible
- A heterogenous group - sulfonylureas with lower risk of hypoglycaemia to be selected when considered for therapy
- No difference in the incidence of MACE in patients at high CV risk treated with glimepiride or linagliptin

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Thiazolidinediones

	Efficacy[1]	Hypoglycaemia	Weight change[2]	CV effects		Renal effects		Oral/SQ	Cost
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*		
Thiazolidinediones	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Neutral	• No dose adjustment required • Generally not recommended in renal impairment due to potential for fluid retention	Oral	Low

- High glucose-lowering efficacy, durability of glycaemic effect
- Beneficial effects in NASH seen with pioglitazone
- Side effects (e.g. weight gain, fluid retention) can be mitigated by optimising dosing strategies (e.g. using lower doses) and combining therapy with other medications (SGLT2 inhibitors, GLP-1 RA) that promote weight loss and sodium excretion

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DPP-4 Inhibitors

	Efficacy[1]	Hypogly-caemia	Weight change[2]	CV effects		Renal effects		Oral/SQ	Cost
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*		
DPP-4 Inhibitors	Intermediate	No	Neutral	Neutral	Neutral (potential risk, saxagliptin)	Neutral	• Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment • No dose adjustment required for linagliptin	Oral	High

- Intermediate glucose-lowering efficacy, neutral effect on weight, generally well tolerated, minimal risk of hypoglycaemia
- Early combination treatment with metformin and a DPP-4i (vildagliptin) increased glycaemic durability compared to stepwise approach to therapy
- Cardiovascular safety demonstrated

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SGLT2 Inhibitors

	Efficacy[1]	Hypoglycaemia	Weight change[2]	CV effects		Renal effects		Oral/SQ	Cost
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*		
SGLT2 Inhibitors	Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin	• See labels for renal dose considerations of individual agents • Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR	Oral	High

- *Glucose-lowering mechanism of action:* Reduce renal tubular glucose reabsorption
- *Clinical Efficacy Profile:* Intermediate to high glucose-lowering efficacy, lower at lower eGFR; low inherent risk of hypoglycaemia; intermediate weight loss
- *Cardiorenal Effects:* Demonstrated protective effects in studied trial populations:
  - Reduction in major adverse cardiovascular events
  - Reduction in overall CV death (with heterogeneity across the class)
  - Reduction in risk of hospitalisation for heart failure
  - Reduction in risk of kidney outcomes
- Increased confidence surrounding safety issues of interest

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GLP-1 Receptor Agonists

	Efficacy[1]	Hypogly-caemia	Weight change[2]	CV effects		Renal effects		Oral/SQ	Cost
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations*		
GLP-1 RAs	High to very high	No	Loss (intermediate to very high)	Benefit: dulaglutide, liraglutide, semaglutide (SQ) Neutral: exenatide once weekly, lixisenatide	Neutral	Benefit for renal endpoints in CVOTs, driven by albuminuria outcomes: dulaglutide, liraglutide, semaglutide (SQ)	• See labels for renal dose considerations of individual agents • No dose adjustment for dulaglutide, liraglutide, semaglutide • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions	SQ; oral (semaglutide)	High

- *Glucose-lowering mechanism of action:* Augment glucose-dependent insulin secretion & glucagon suppression, decelerate gastric emptying, curb post-meal glycaemic increments, reduce appetite, calorie intake and body weight
- *Clinical Efficacy Profile:* High to Very High glucose-lowering efficacy, low inherent risk of hypoglycaemia; intermediate to high weight loss
- *Cardiorenal Effects:* cardioprotective, with evidence of reduction in major adverse cardiovascular events, CV death, fatal or non-fatal MI, fatal or non-fatal stroke, all-cause mortality, composite kidney outcome driven by macroalbuminuria
- Increased confidence surrounding safety areas of interest

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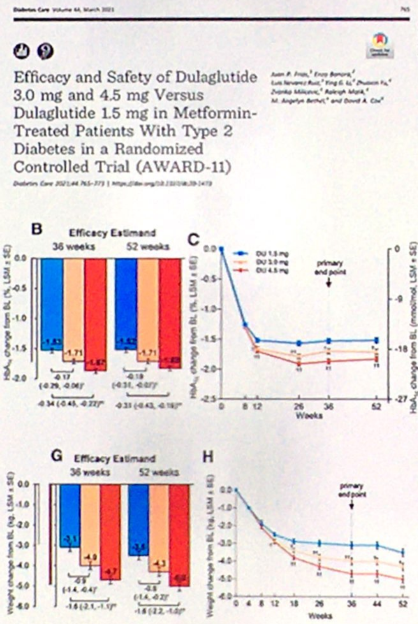
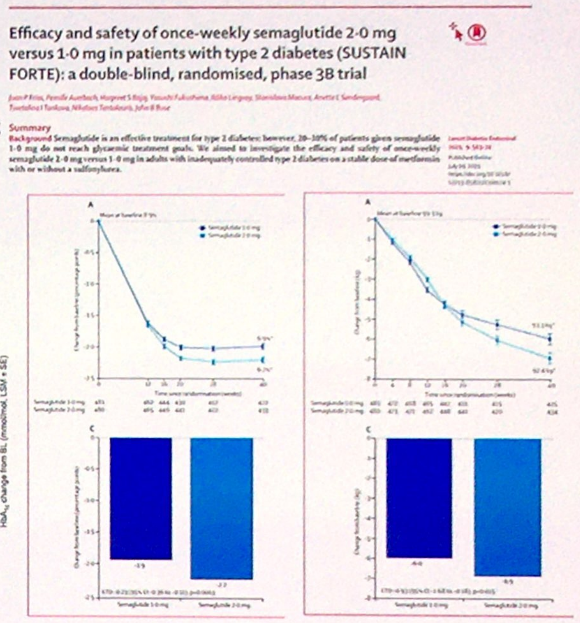
GLP-1 RA Therapeutic Updates

- First oral GLP-1 RA (oral semaglutide) developed and available
- Higher dose GLP-1 RAs (dulaglutide, semaglutide) with incremental benefits in glucose weight efficacy





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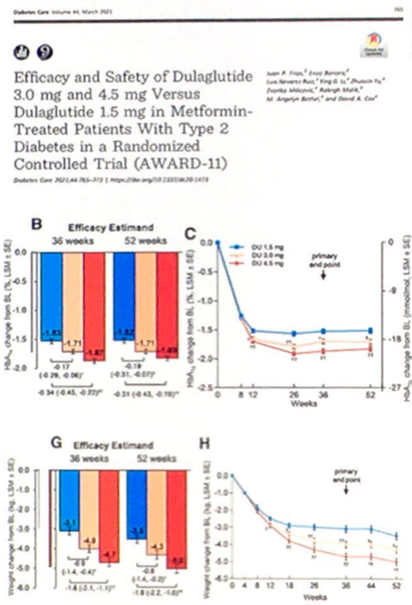
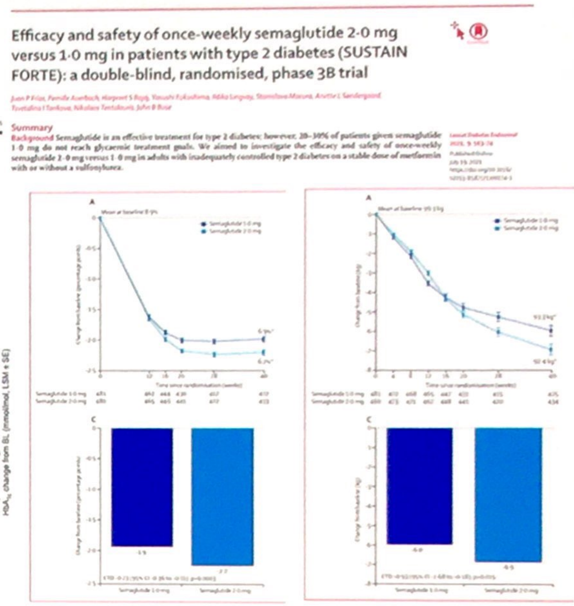
GLP-1 RA Therapeutic Updates

- First oral GLP-1 RA (oral semaglutide) developed and available
- Higher dose GLP-1 RAs (dulaglutide, semaglutide) with incremental benefits in glucose weight efficacy
- Greater clinical expertise in anticipating and addressing GI effects





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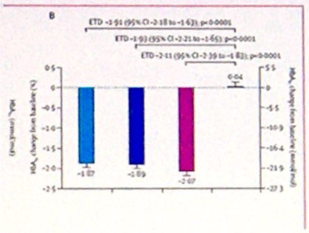
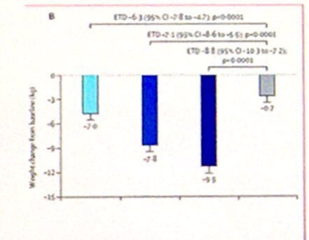
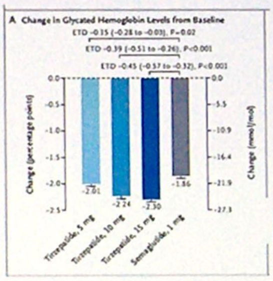
Glucose-dependent insulinotropic polypeptide (GIP) receptor and GLP-1 receptor agonist (tirzepatide)

SURPASS-1

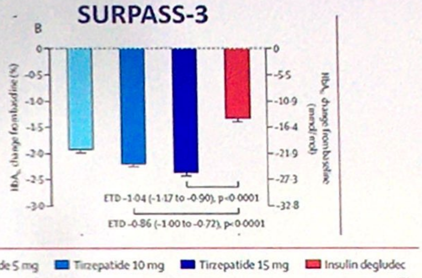




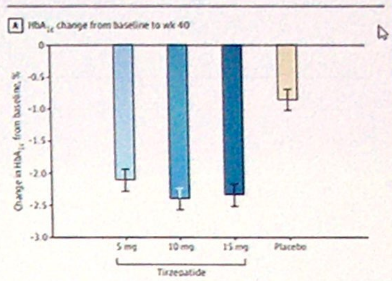
SURPASS-2



SURPASS-3



SURPASS-5



	Tirzepatide 5 mg (n=326)	Tirzepatide 10 mg (n=321)	Tirzepatide 15 mg (n=334)	Insulin glargine (n=978)
HbA_{1c}, %				
Baseline	8·52 (0·049)	8·60 (0·049)	8·52 (0·048)	8·51 (0·028)
At week 52	6·29 (0·054)	6·09 (0·054)	5·95 (0·054)	7·09 (0·031)
Change from baseline at week 52*†	−2·24 (0·053)	−2·43 (0·053)	−2·58 (0·053)	−1·44 (0·030)
ETD vs insulin glargine	−0·80 (−0·92 to −0·68), p<0·0001‡	−0·99 (−1·11 to −0·87), p<0·0001‡	−1·14 (−1·26 to −1·02), p<0·0001‡	..

SURPASS-4

Rosenstock J et al; *Lancet* 2021; 398: 143-55
Frias JP et al; NEJM 2021;385:503-
Ludvik B et al; *Lancet* 2021; 398: 583–98
Del Prato S Kahn SE et al; *Lancet* 2021; 398:1811-1824
Dahl D et al; JAMA. 2022;327(6):534-545

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Glucose-dependent insulinotropic polypeptide (GIP) receptor and GLP-1 receptor agonist (tirzepatide)

	Efficacy[1]	Hypoglycaemia	Weight change[2]	CV effects: Effect on MACE	CV effects: HF	Renal effects: Progression of DKD	Renal effects: Dosing/use considerations*	Oral/SQ	Cost
GIP and GLP-1 RA	Very high	No	Loss (very high)	Under investigation	Under investigation	Under investigation	• See label for renal dose considerations • No dose adjustment • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions	SQ	High

- *Glucose-lowering mechanism of action:* GIP receptor and GLP-1 receptor agonist; enhances first and second-phase insulin secretion, and reduces glucagon levels, both in a glucose-dependent manner
- *Clinical Efficacy profile:* Very high glycaemic efficacy; low inherent risk of hypoglycaemia; weight loss (high); cardiorenal effects unknown (trials in progress)

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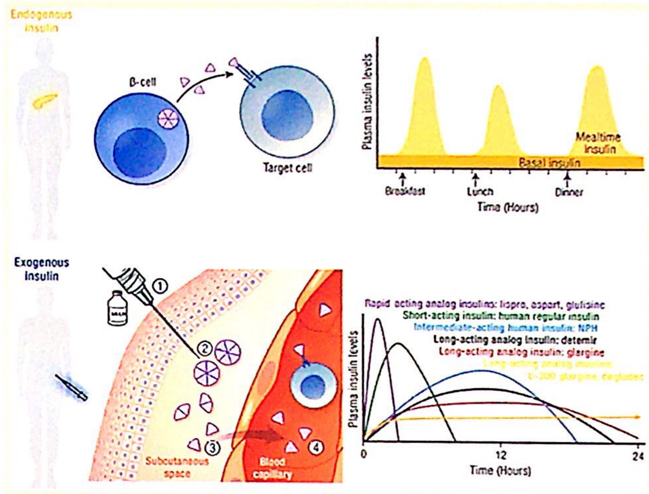
Insulin

- Advantage of lowering glucose in dose-dependent manner, able to address any level of glycaemia
- *Clinical Profile:* High to very high glycaemic efficacy, increased risk of hypoglycaemia and weight gain; neutral cardiorenal profile
- Efficacy and safety are largely dependent on education and support to facilitate self-management
- Importance of matching insulin to physiologic need

The Evolution of Insulin and How it Informs Therapy and Treatment Choices

Irl B. Hirsch,[1] Rattan Juneja,[2] John M. Beals,[3] Caryl J. Antalis,[2] and Eugene E. Wright, Jr.[4]



Adapted from Hirsch I *et al; Endocr Rev* 2020; 41: 733-755

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Combination Therapy

Increasing evidence and rationale:

(1) Increased durability of glycaemic effect, potential to address therapeutic inertia

(2) Simultaneous targeting of multiple pathophysiologic processes characterised by type 2 diabetes

(3) Potential impact on medication burden, adherence, and treatment persistence

(4) Complementary clinical benefits (glycaemia, weight, cardiovascular risk profile)

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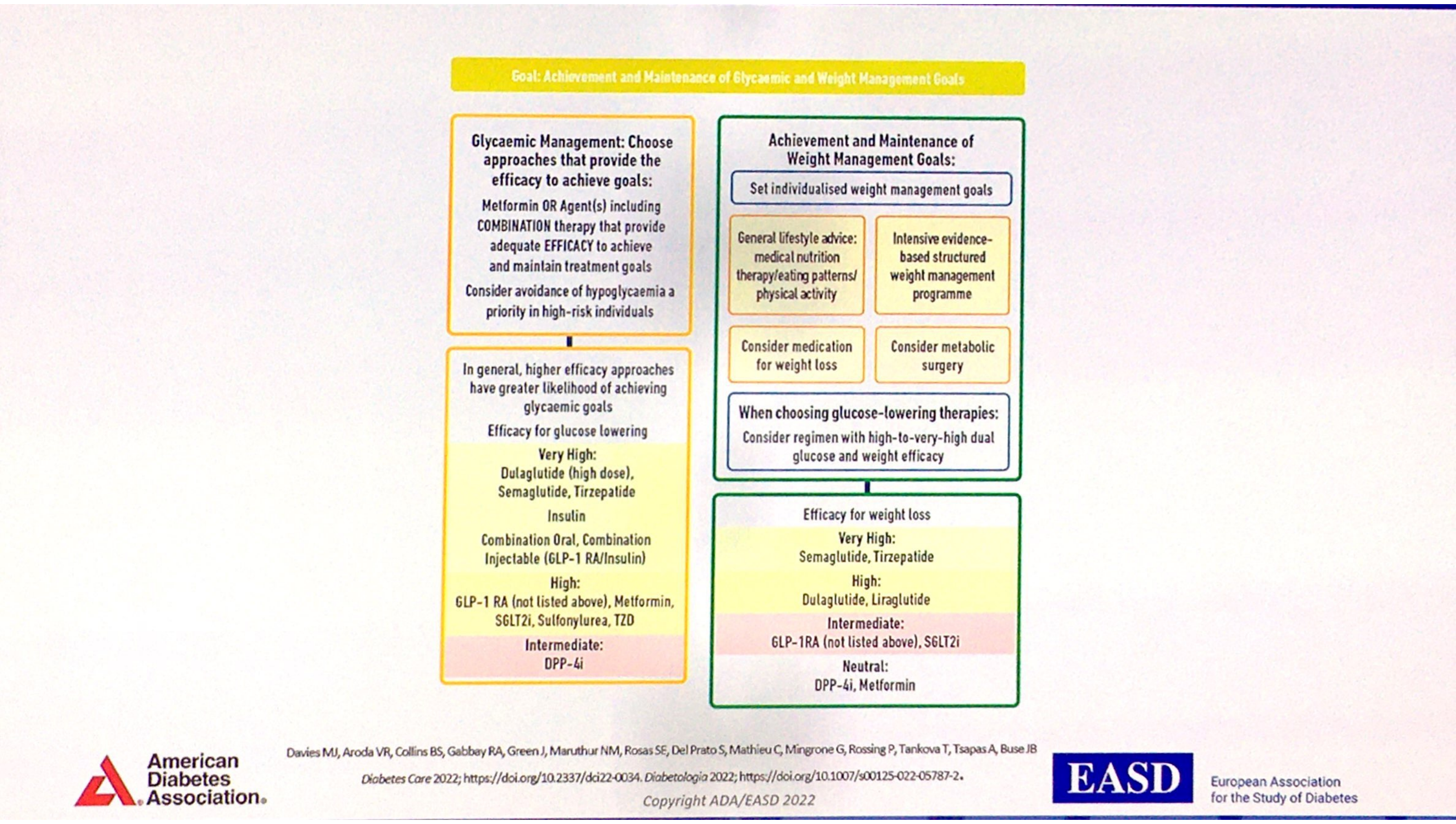

Goal: Achievement and Maintenance of Glycaemic and Weight Management Goals
Glycaemic Management: Choose approaches that provide the efficacy to achieve goals:
Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals
Consider avoidance of hypoglycaemia a priority in high-risk individuals
In general, higher efficacy approaches have greater likelihood of achieving glycaemic goals
Efficacy for glucose lowering
Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide
Insulin
Combination Oral, Combination Injectable (GLP-1 RA/Insulin)
High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD
Intermediate:
DPP-4i
Achievement and Maintenance of Weight Management Goals:
Set individualised weight management goals
General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity
Intensive evidence-based structured weight management programme
Consider medication for weight loss
Consider metabolic surgery
When choosing glucose-lowering therapies:
Consider regimen with high-to-very-high dual glucose and weight efficacy
Efficacy for weight loss
Very High:
Semaglutide, Tirzepatide
High:
Dulaglutide, Liraglutide
Intermediate:
GLP-1RA (not listed above), SGLT2i
Neutral:
DPP-4i, Metformin
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Diabetes Care 2022; https://doi.org/10.2337/dci22-0034. Diabetologia 2022; https://doi.org/10.1007/s00125-022-05787-2.
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Personalised Approach to Treatment Based on Individual Characteristics and Comorbidities

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FIGURE 1: DECISION CYCLE FOR PERSON-CENTRED GLYCAEMIC MANAGEMENT IN TYPE 2 DIABETES

BGM, Blood Glucose Monitoring; BP, Blood Pressure; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; CVD, Atherosclerotic Cardiovascular Disease; DSMES, Diabetes Self-Management Education and Support; HF, Heart Failure.

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New evidence accrued after the last consensus update

- Primary evidence
  - Cardiovascular outcomes trials (AMPLITUDE-O, VERTIS CV, FREEDOM CVO)
  - Heart failure trials (DAPA HF, SOLOIST-WHF, EMPEROR-Reduced, EMPEROR-Preserved)
  - Renal outcomes trials (DAPA CKD, SCORED)

- Secondary evidence
  - Pairwise meta-analyses & syntheses of subgroup analyses (McGuire 2020, Sattar 2021, Neuen 2019, Neuen 2020, Tsapas 2021)
  - Comparative effectiveness network meta-analyses (Tsapas 2020, Palmer 2021)

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Interpretation of syntheses of subgroup analyses

Clinical Review & Education

Users' Guides to the Medical Literature

How to Use a Subgroup Analysis
Users' Guides to the Medical Literature

Xin Sun, PhD; John P. A. Ioannidis, MD, DSc; Thomas Agoritsas, MD; Ana C. Alba, MD; Gordon Guyatt, MD, MSc

Clinicians, when trying to apply trial results to patient care, need to individualize patient care and, potentially, manage patients based on results of subgroup analyses. Apparently compelling subgroup effects often prove spurious, and guidance is needed to differentiate credible from less credible subgroup claims. We therefore provide 5 criteria to use when assessing the validity of subgroup analyses: (1) Can chance explain the apparent subgroup effect; (2) Is the effect consistent across studies; (3) Was the subgroup hypothesis one of a small number of hypotheses developed a priori with direction specified; (4) Is there strong preexisting biological support; and (5) Is the evidence supporting the effect based on within- or between-study comparisons. The first 4 criteria are applicable to individual studies or systematic reviews, the last only to systematic reviews of multiple studies. These criteria will help clinicians deciding whether to use subgroup analyses to guide their patient care.

JAMA. 2014;311(4):405-411. doi:10.1001/jama.2013.285063

Supplemental content at jama.com

Author Affiliations: Author affiliations are listed at the end of this article.

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Development of the Instrument to assess the Credibility of Effect Modification Analyse (ICEMAN) in randomized controlled trials and meta-analyses

Stefan Schandelmaier MD PhD, Matthias Briel MD PhD, Ravi Varadhan PhD, Christopher H. Schmid PhD, Niveditha Devasenapathy MBBS MSc, Rodney A. Hayward MD, Joel Gagnier MD PhD, Michael Borenstein PhD, Geert J.M.G. van der Heijden PhD, Issa J. Dahabreh MD PhD, Xin Sun PhD, Willi Sauerbrei PhD, Michael Walsh MD PhD, John P.A. Ioannidis MD DSc, Lehana Thabane PhD, Gordon H. Guyatt MD MSc

Core question	Randomized controlled trials	Meta-analyses
Is the analysis of effect modification based on comparison within rather than between trials?	-	1
For within-trial comparisons, is the effect modification similar from trial to trial?	-	2
For between-trial comparisons, is the number of trials large?	-	3
Was the direction of effect modification correctly hypothesized a priori?	1	4
Was the effect modification supported by prior evidence?	2	-
Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification?	3	5
Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?	4	6
Did the authors use a random-effects model?	-	7
If the effect modifier is a continuous variable, were arbitrary cut points avoided?	5	8

NA = not applicable.
*Numbers reflect order of appearance within the full instrument (see Appendices 5 and 6).

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JAMA 2014;311(4):405-11
CMAJ 2020;192(32):E901-E906

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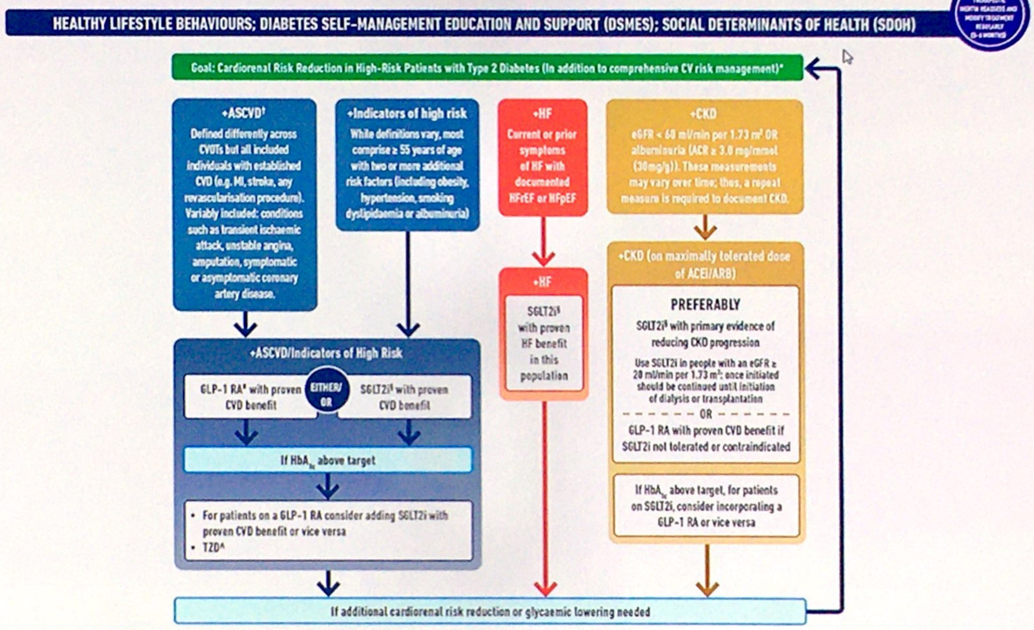
FIGURE 3: USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



ACEI, Angiotensin-Converting Enzyme Inhibitor; ACR, Albumin/Creatinine Ratio; ARB, Angiotensin Receptor Blocker; ASCVD, Atherosclerotic Cardiovascular Disease; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; CV, Cardiovascular; CVD, Cardiovascular Disease; CVOT, Cardiovascular Outcomes Trial; DPP-4i, Dipeptidyl Peptidase-4 Inhibitor; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; HFpEF, Heart Failure with preserved Ejection Fraction; HFrEF, Heart Failure with reduced Ejection Fraction; HHF, Hospitalisation for Heart Failure; MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; SDOH, Social Determinants of Health; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes; TZD, Thiazolidinedione.

* 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 independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. 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; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke and renal endpoints in individuals with T2D with established/high risk of CVD.

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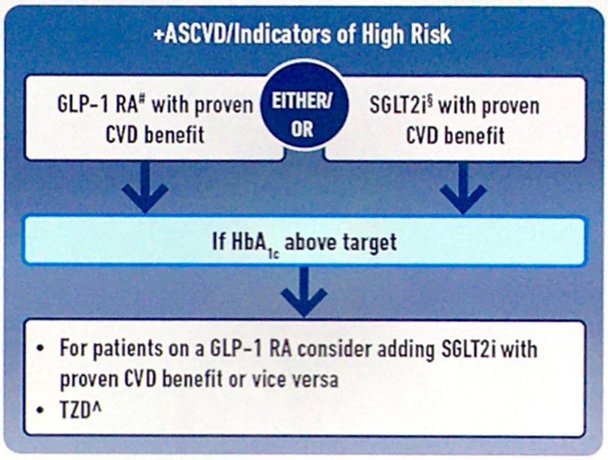
Choosing glucose-lowering medication in people with CVD



ASCVD = atherosclerotic cardiovascular disease

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

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Consensus recommendations

- In people with established CVD, a GLP-1RA with proven benefit should be used to reduce MACE or an SGLT2i with proven benefit should be used to reduce MACE and HF and improve kidney outcomes.

MACE = major adverse cardiovascular events

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB
Diabetes Care 2022; https://doi.org/10.2337/dci22-0034. *Diabetologia* 2022; https://doi.org/10.1007/s00125-022-05787-2.

Consensus recommendations

- In people with established CVD, a GLP-1RA with proven benefit should be used to reduce MACE or an SGLT2i with proven benefit should be used to reduce MACE and HF and improve kidney outcomes.
- In people without established CVD but with multiple cardiovascular risk factors (such as age ≥55, obesity, hypertension, smoking, dyslipidaemia, or albuminuria), a GLP-1RA with proven benefit could be used to reduce MACE or an SGLT2i with proven benefit could be used to reduce MACE and heart failure and improve kidney outcomes.

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Evidence for patients with indicators of high CVD risk

Characteristics of subgroup analysis					Individual Assessment criteria: for all criteria except p-interaction value, input value 1 to 4 (1=lowest credibility, 4=highest credibility) based on respective ICEMAN criteria				
Effect modifier	Intervention	Outcome	Sources (PubMed IDs)	# RCTs	Type of comparison (i.e. between-trial, within-trial, meta-analysis of interactions)	For within-trial comparisons, is direction and magnitude of effect similar from trial to trial?	Use of random effects model within subgroups?	Additional criteria (e.g. 1 for sensitivity analysis corroborating estimate, or -1 point if sensitivity analysis alters effect estimate)	P-interaction value
ASCVD status	SGLT2i	MACE	30424892 & 33031522	3/5	2	2	4	[illegible]	0.0501/0.83
ASCVD status	SGLT2i	CV mortality	30424892 & 33031522	3/5	2	2	4	[illegible]	0.31/0.41
ASCVD status	SGLT2i	All-cause mortality	30424892 & 33031522	3/5	2	3	4	1	0.88/0.54
ASCVD status	SGLT2i	Hospitalisation for heart failure	30424892 & 33031522	3/5	2	3	4	1	0.34/0.26
ASCVD status	SGLT2i	Myocardial infarction	30424892 & 33031522	3/5	2	2	4	[illegible]	0.27
ASCVD status	SGLT2i	Stroke	30424892 & 33031522	3/5	2	2	4	1	0.83
ASCVD status	SGLT2i	Progression of renal disease	30424892 & 33031522	3/5	2	3	4	1	0.71/0.73
ASCVD status	GLP1 RA	MACE	31422062 & 31595457 & 34425083	7/7/8	3	2	4	0	0.24/0.50/0.18

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BMJ 2021;372:m4573

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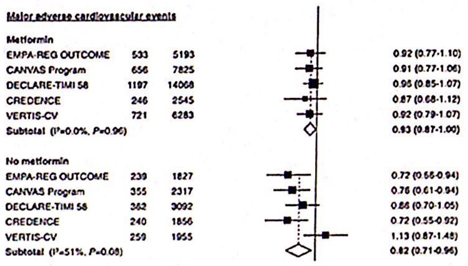
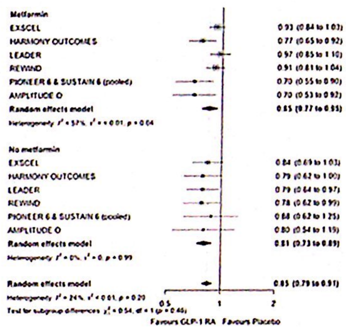
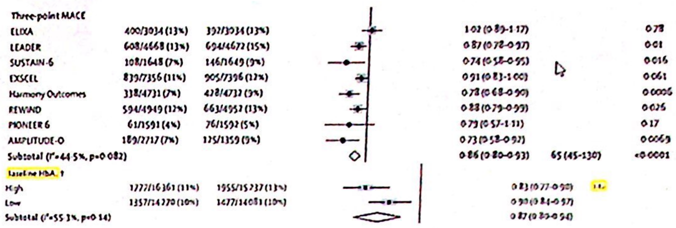
Effect on MACE by background use of metformin or baseline HbA_{1c}

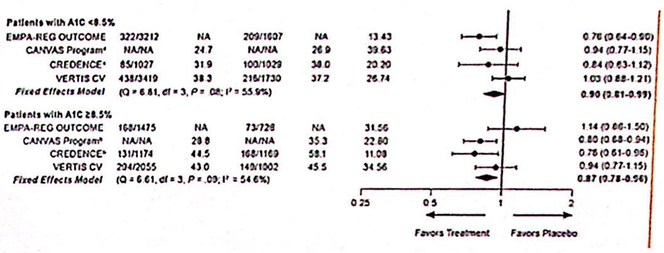




Diab Obes Metab 2021;23:382-390 Diabetes Res Clin Pract. 2021;177:108921 (updated)

0.14





Lancet Diabetes Endocrinol 2021;9:653–62; JAMA Cardiol 2021;6(2):148-158

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Scanned with CamScanner

Consensus recommendations

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

- In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1RA or an SGLT2i with proven benefit should be independent of baseline HbA_{1c}.

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Choosing glucose-lowering medication in people with heart failure

+HF

SGLT2i§ with proven HF benefit in this population

In people with heart failure SGLT2i should be used because they improve heart failure and kidney outcomes.

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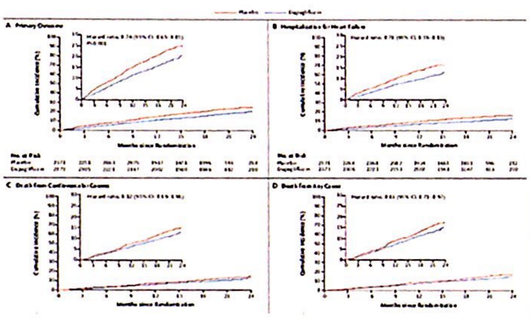
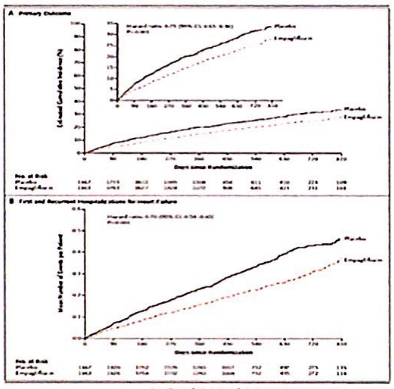
Effect of SGLT2i in people with heart failure

DAPA-HF



N Engl J Med 2019;381:1995-2008

EMPEROR-REDUCED



N Engl J Med 2020;383:1413-1424

EMPEROR-PRESERVED

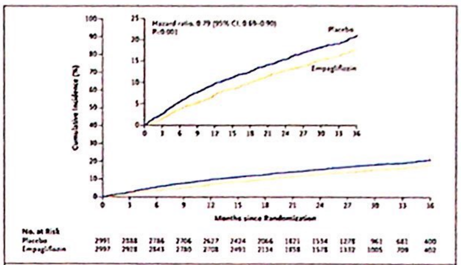


Figure 1. Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure.
The estimated cumulative incidence of the primary outcome in the two groups is shown. The inset shows the same data on an expanded y axis.

N Engl J Med 2021;385:1451-1461

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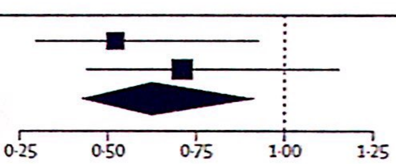
Effect of SGLT2i in people with heart failure

Meta-analysis of HFrEF trials: First Kidney Outcome Composite

	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	18/1863 (1·0%)	33/1867 (1·8%)	0·52 (0·29–0·92)
DAPA-HF	28/2373 (1·2%)	39/2371 (1·6%)	0·71 (0·44–1·16)
Total			**0·62 (0·43–0·90)**



Test for overall treatment effect p=0·013
Test for heterogeneity of effect p=0·42

Kidney composite was defined as time to first occurrence of any of the components of 50% or higher sustained decline in eGFR, end-stage renal disease, or renal death. End-stage renal disease was defined as either sustained eGFR lower than 15 mL/min per 1·73 m^2, chronic dialysis treatment, or receiving a renal transplant.

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Lancet 2020;396:819-29

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Choosing glucose-lowering medication in people with chronic kidney disease

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i[§] with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥ 20 ml/min per 1.73 m^2; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If HbA_{1c} above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

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GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If HbA_{1c} above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

Effects of SGLT2i in people with chronic kidney disease

	CREDENCE[a-c]	DAPA-CKD[d-f]	EMPA-KIDNEY[g-h]
Population	DIABETIC KIDNEY DISEASE ✓ T2D x Non-DM x Non-Albuminuric	PROTEINURIC CHRONIC KIDNEY DISEASE ✓ T2D ✓ Non-DM x Non-Albuminuric	CHRONIC KIDNEY DISEASE ✓ T2D ✓ Non-DM ✓ Non-Albuminuric
No. of patients	4401[b,c]	4304	~6000
Key inclusion criteria	eGFR ≥30 to <90 <u>and</u> UACR >300 mg/g	eGFR ≥25 to ≤75 <u>and</u> UACR ≥200 mg/g	eGFR ≥20 to <45 <u>or</u> eGFR ≥45 to <90 and UACR ≥200 mg/g
Primary composite outcome	ESKD, doubling of creatinine, or renal/CV death	ESKD, ≥50% sustained eGFR decline, or renal/CV death	ESKD, or ≥40% sustained eGFR decline, or renal/CV death
Study start and stop date (announced or planned)	February 2014 [b] July 2018	February 2017 [d] March 2020	November 2018 [g] ~June 2022
Results	+ [c]	+ [f]	+ [g-i] *

DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; TBD, to be determined; UACR, urinary albumin:creatinine ratio. a. Jardine MJ, et al. Am J Nephrol. 2017;46:462-472; b. ClinicalTrials.gov. Accessed November 09, 2021. https://clinicaltrials.gov/ct2/show/NCT02065791; c. Perkovic V, et al. N Engl J Med. 2019;380:2295-2306; d. ClinicalTrials.gov. Accessed November 09, 2021. https://clinicaltrials.gov/ct2/show/NCT03036150; e. Heerspink HJL, et al. Nephrol Dial Transplant. 2020;35:274-282; f. Heerspink HJL, et al. N Engl J Med. 2020;383:1436-1446; g. ClinicalTrials.gov. Accessed November 09, 2021. https://clinicaltrials.gov/ct2/show/ NCT03594110; h. Herrington WG, et al. Clin Kidney J. 2018;11:749-761. i. https://www.boehringer-ingelheim.com/human-health/metabolic-diseases/early-stop-chronic-kidney-disease-trial-efficacy

**published results not yet available*

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Conclusions and recommendations

- In people with CKD, SGLT-2 inhibitors and GLP-1RA reduce risk of MACE independent of eGFR.
- In people with CKD, SGLT2i also reduce risks of HF and kidney outcomes (including end-stage kidney disease).
- In people with CKD and eGFR≥ 20 ml/min per 1.73 m^2, an SGLT2i with proven benefit should be initiated to reduce risks of MACE, HF and kidney outcomes.
- If such treatment is not tolerated or is contraindicated, a GLP-1RA with proven CV outcomes benefit could be considered

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Additional Clinical Considerations

Age

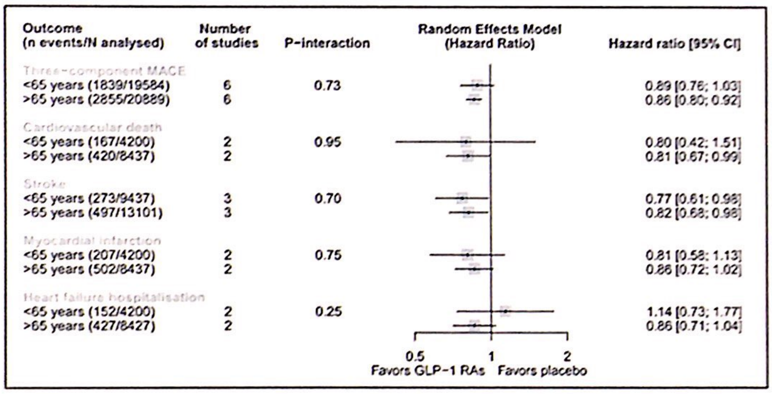
- Type 2 diabetes and older age are associated with frailty, worse outcomes, and less benefit from intensive glycaemic control
- Older (>65 years) and younger (<40 years) adults with diabetes are generally under-represented in clinical trials.
- Therefore, informed decisions regarding treatment of older and younger individuals are limited by an absence of age-specific data

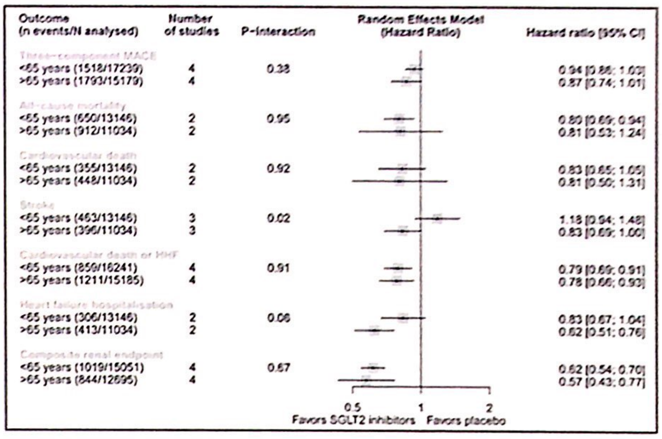
Diabetology 2022;3(1):30-45
Diabetes Res Clin Pract 2021;174:108737

Age

However, a recent MA of 11 large GLP-1RA, SGLT2i outcomes trials found that CV and kidney outcomes in people aged ≥65 years were consistent with the effects seen in the overall trial population

Results in people <65 years and ≥65 years





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Diabetology 2022;3(1):30-45
Diabetes Res Clin Pract 2021;174:108737

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Age

- Selection of medications to improve CV and kidney outcomes should not differ for older people
- Medication choices for people who are frail or who have multiple comorbidities may require modification for safety and tolerability
- Consider de-prescribing to avoid unnecessary medication and/or harmful side effects such as hypoglycaemia and hypotension

Age

- Rates of prediabetes and type 2 diabetes are increasing in the adolescent and young adult population, in concert with increases in obesity
- Younger people with type 2 diabetes are at very high risk for complications, and should be treated correspondingly
- Young people also have more rapid deterioration in glycaemic control and attenuated response to diabetes medications

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JAMA Pediatr 2020;174(2):e194498
Diabetes Care 2018;41(8):1717-1725

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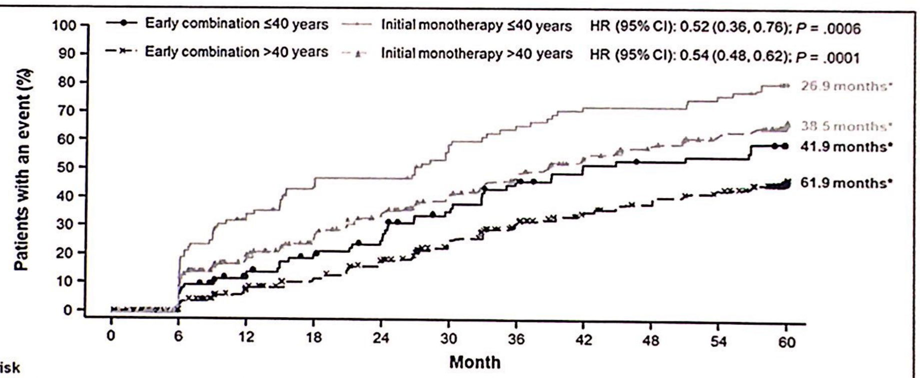
Age

Early use of combination therapy to manage hyperglycaemia may be considered in young people with type 2 diabetes: VERIFY findings suggest superior and more durable glycaemic control with combination vs. metformin monotherapy

Primary treatment failure (HbA1c ≥ 7%) among people with young- and late-onset type 2 diabetes



Patients at risk	0	6	12	18	24	30	36	42	48	54	60
Early combination ≤40	93	92	74	66	60	49	39	33	31	30	15
Initial monotherapy ≤40	90	85	54	44	42	31	26	21	21	18	9
Early combination >40	890	868	788	749	692	622	558	518	478	448	172
Initial monotherapy >40	899	852	679	617	534	472	408	356	316	281	99

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Diabetes Obes Metab 2021;23(1):245-251

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Obesity and Weight-Related Comorbidities

- Care of people with diabetes and weight-related comorbidities such as non-alcoholic fatty liver disease (NAFLD), HF, or obstructive sleep apnea (OSA) should include strategies to achieve weight loss

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Race, Ethnicity and Sex

- Non-White people are disproportionately affected by type 2 diabetes and its complications
- Women have a greater increase in relative risk of CVD from type 2 diabetes than men
- These groups are consistently under-represented in clinical trials and generally have more poorly controlled CV risk factors
- Available data suggest no significant between-group differences in treatment response: beneficial treatments should be utilised irrespective of a person's race, ethnicity, and/or sex

JAMA Netw Open 2022;5(1):e2142078
Diabetes Care 2020;43(5):1157-1163

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Putting it all Together: Strategies for Implementation

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All Speakers
Management of hyperglycaemia in type 2: ADA/EASD Consensus Report 2022

FIGURE 4: HOLISTIC PERSON-CENTRED APPROACH TO T2DM MANAGEMENT

1 = American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S144–76.

ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blockers; ASCVD, Atherosclerotic Cardiovascular Disease; BP, Blood Pressure; CKD, Chronic Kidney Disease; CV, Cardiovascular; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes.

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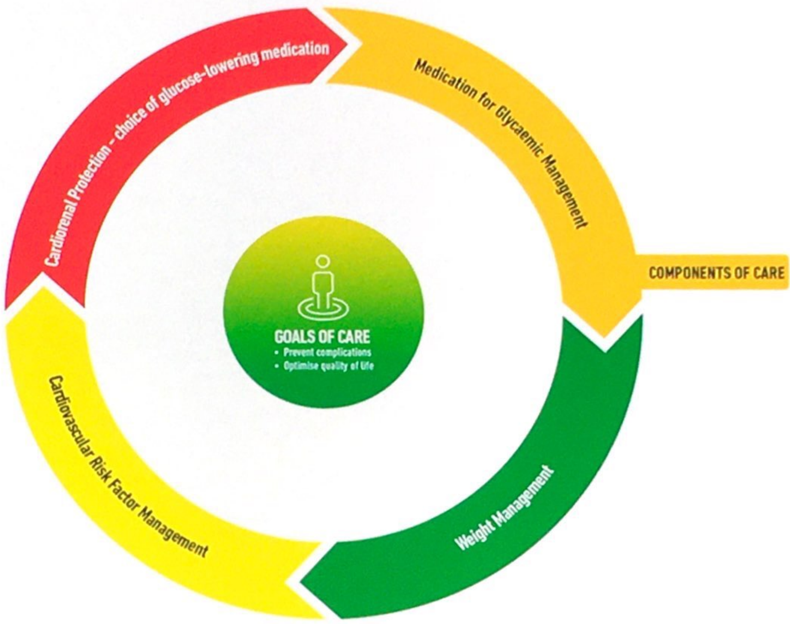

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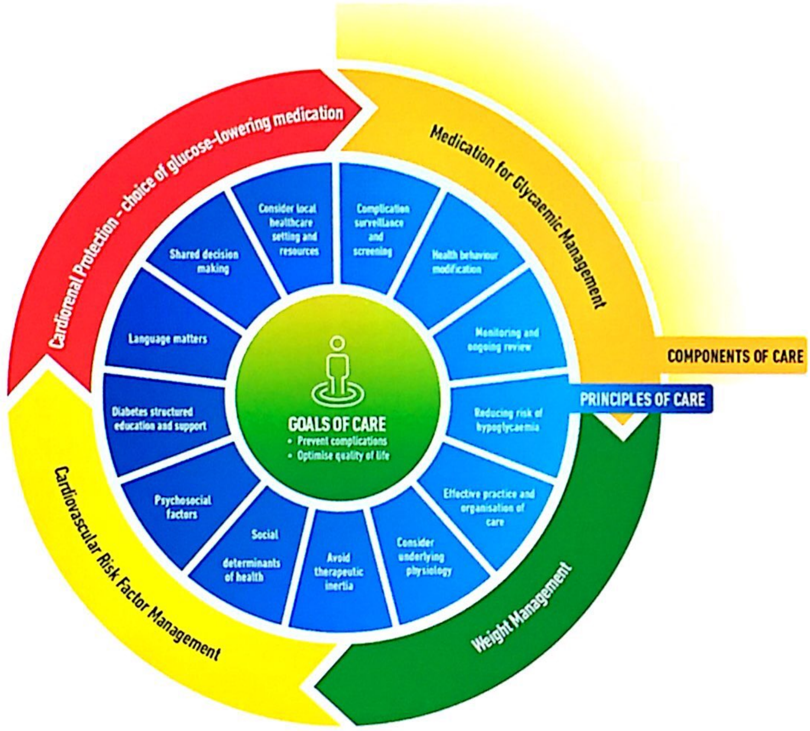

Glycaemic Management: Choose approaches that provide the efficacy to achieve goals:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Consider avoidance of hypoglycaemia a priority in high-risk individuals

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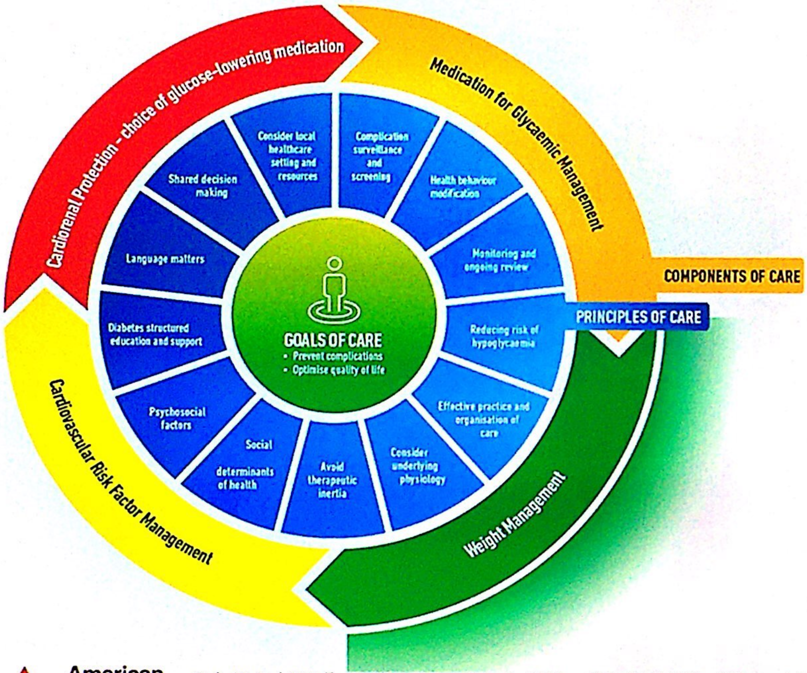

Achievement and Maintenance of Weight Management Goals:

Set individualised weight management goals

General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity	Intensive evidence-based structured weight management programme
Consider medication for weight loss	Consider metabolic surgery

When choosing glucose-lowering therapies:

Consider regimen with high-to-very-high dual glucose and weight efficacy

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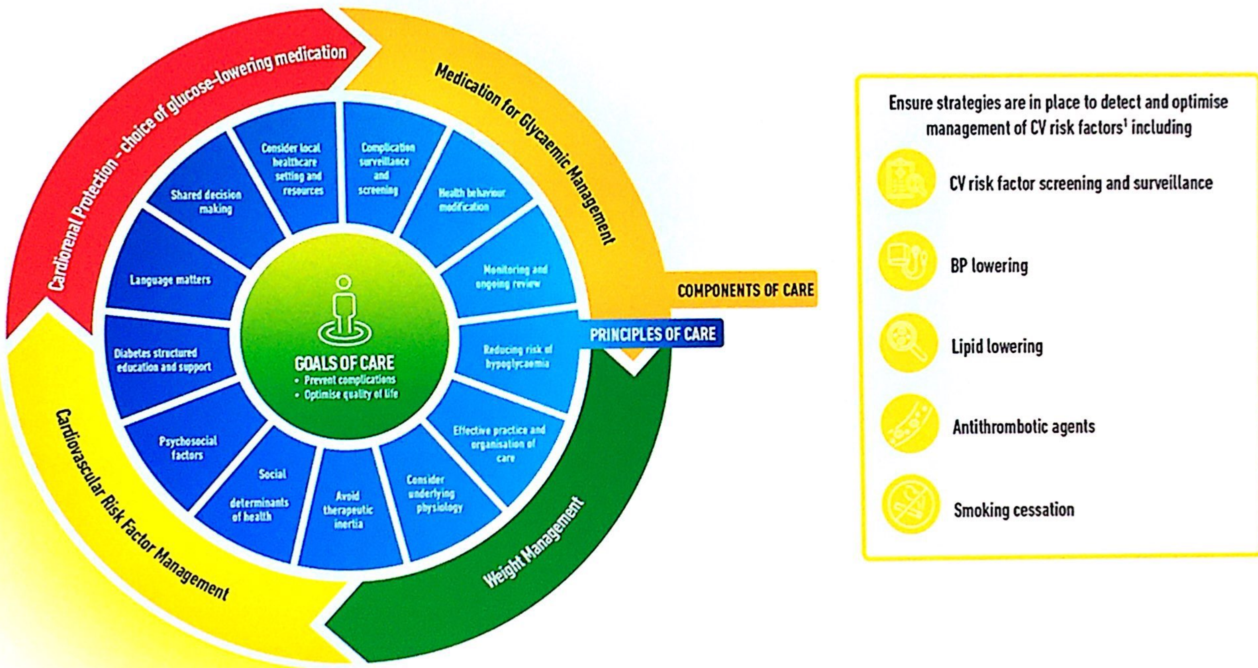

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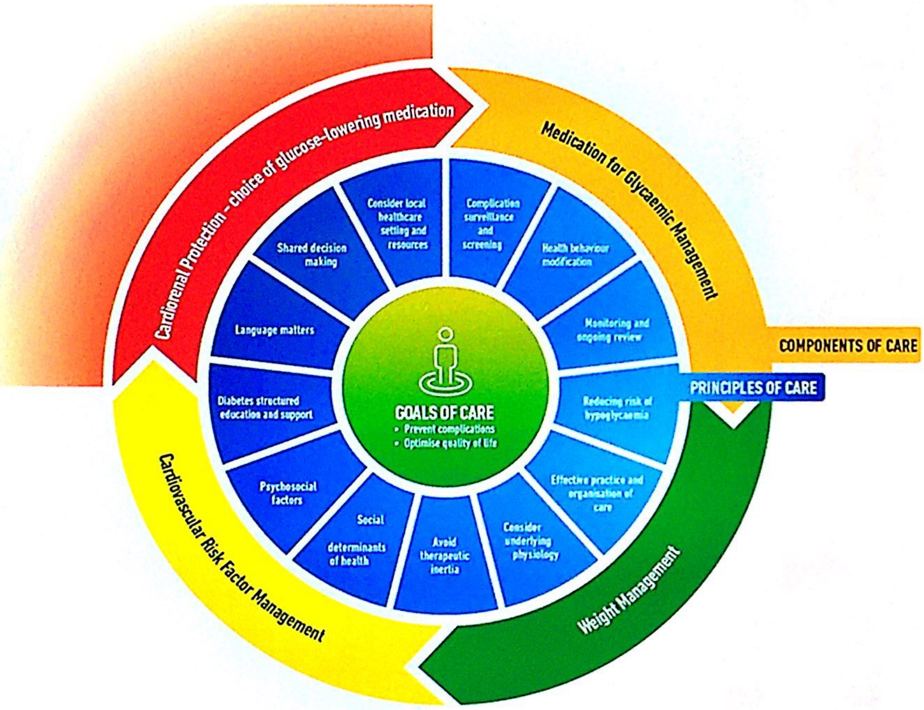

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥ 20 mL/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If additional cardiorenal risk reduction or glycaemic control needed consider combination SGLT2/GLP-1 RA

+ASCVD/Indicators of High Risk

GLP-1 RA with proven CVD benefit — EITHER/OR — SGLT2i with proven CVD benefit

If additional cardiorenal risk reduction or glycaemic control needed consider combination SGLT2/GLP-1 RA

+HF

SGLT2i with proven HF benefit in this population

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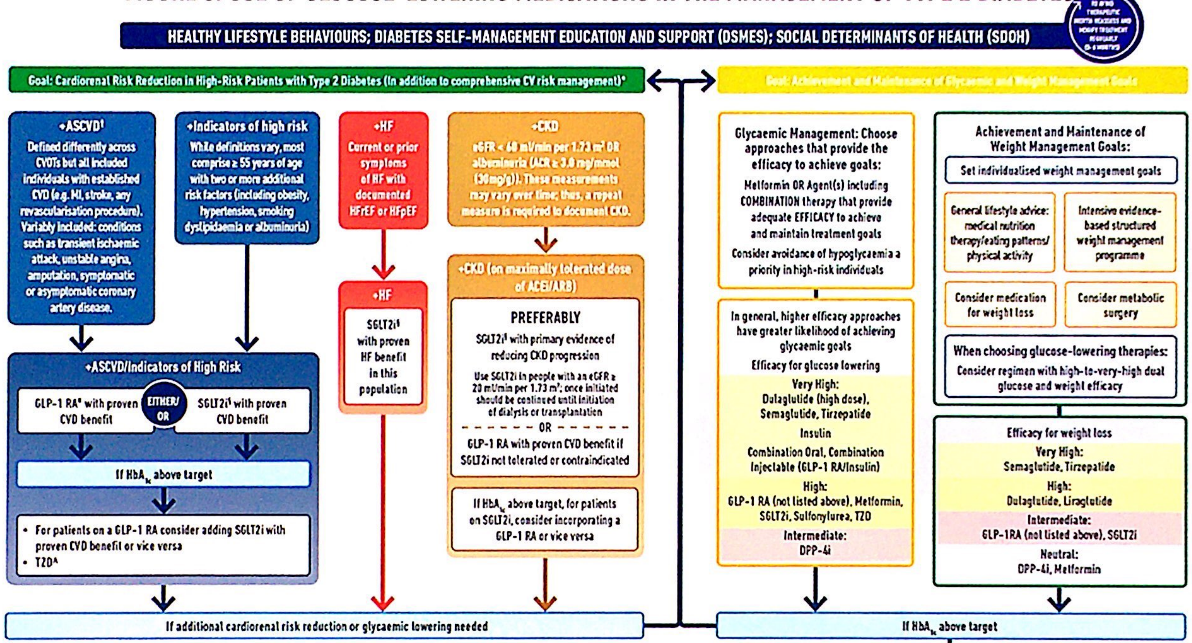
FIGURE 3: USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



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* 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 independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. 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; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke and renal endpoints in individuals with T2D with established/high risk of CVD.

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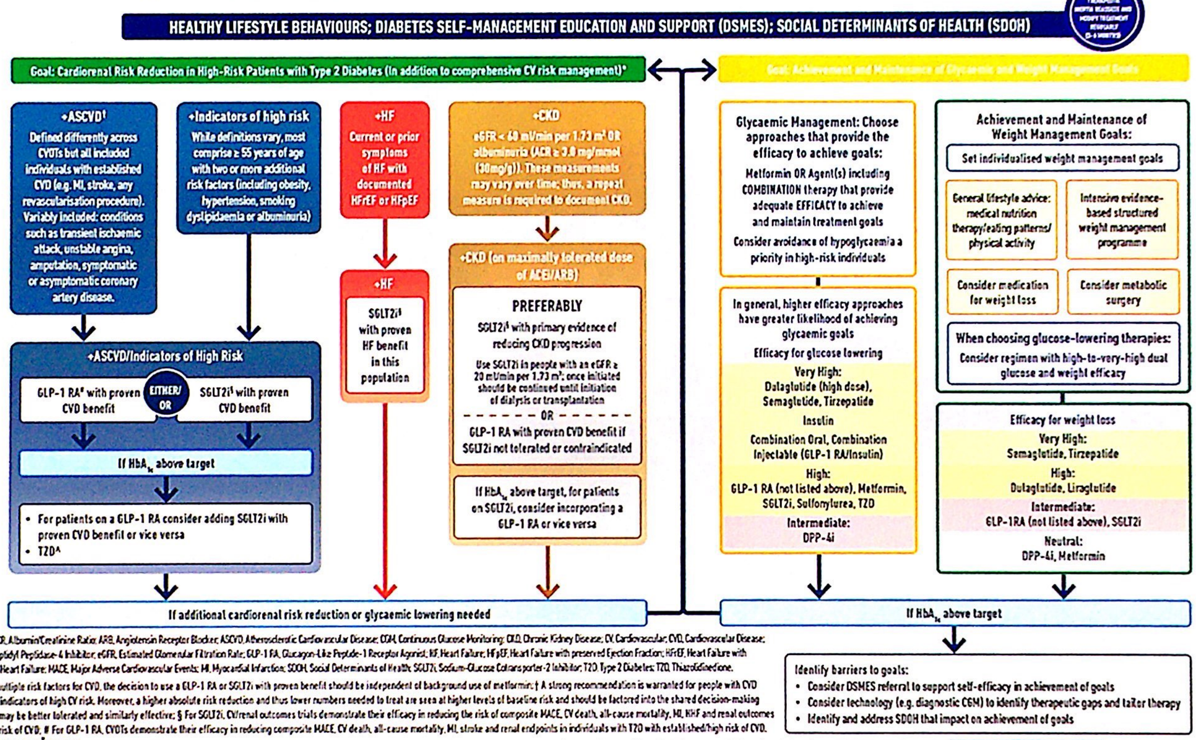

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IMPORTANCE OF INTEGRATED CARE

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IMPORTANCE OF INTEGRATED CARE

Acknowledge the lifelong and evolving nature of type 2 diabetes.

Identify and coordinate with the team.

Know your local resources.

Language matters in diabetes care.

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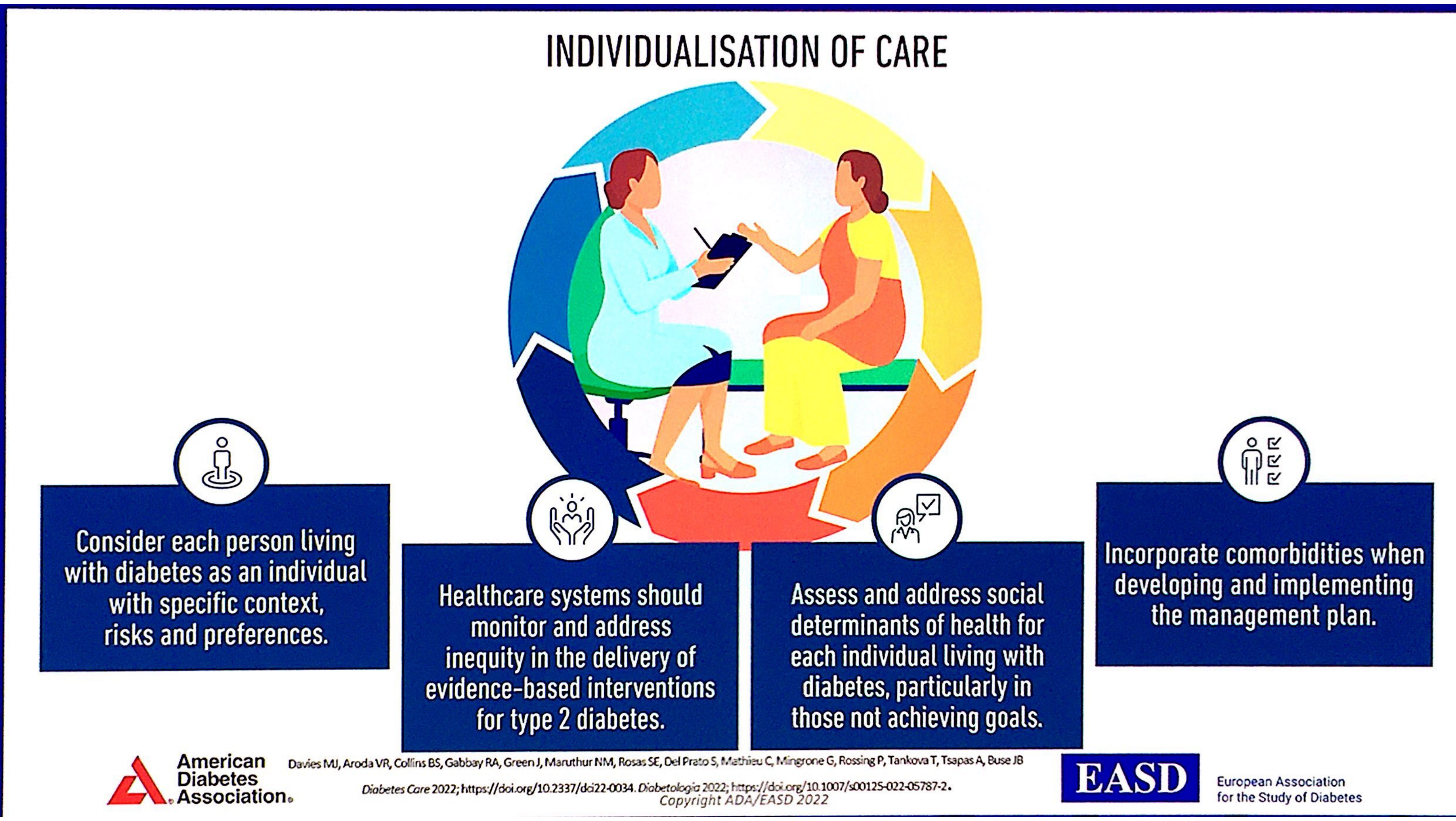
INDIVIDUALISATION OF CARE
Consider each person living with diabetes as an individual with specific context, risks and preferences.
Healthcare systems should monitor and address inequity in the delivery of evidence-based interventions for type 2 diabetes.
Assess and address social determinants of health for each individual living with diabetes, particularly in those not achieving goals.
Incorporate comorbidities when developing and implementing the management plan.
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DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT

Embrace DSMES as being as important as other aspects of diabetes care such as pharmacotherapy.

Identify and know how to access your local DSMES resources.

Impress upon the person and the healthcare team the importance of DSMES in the ongoing holistic approach to the management of type 2 diabetes.

Initiate or refer for DSMES at diagnosis, annually, with changes in social or health status and with transitions of care or life situation.

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FACILITATING HEALTHY BEHAVIOURS AND WEIGHT MANAGEMENT

Specific health behaviour and weight management goals should be agreed upon between the person with type 2 diabetes and the care team; shared decision making is an important component of this discussion.

Emphasise self-monitoring behaviours and review data collected (e.g. glucose monitoring, weight, tracking physical activity) in clinical visits to convey their importance in achieving the desired health behaviour goals.

People taking insulin or a sulfonylurea should be educated about the risk of hypoglycaemia when undertaking physical activity or adopting a specific nutritional plan. Prescribe glucagon in people at high risk of severe hypoglycaemia.

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DSMES and MNT can help the person living with diabetes to identify and address barriers to implementing healthier behaviours.

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CHOICE OF GLUCOSE-LOWERING MEDICATION

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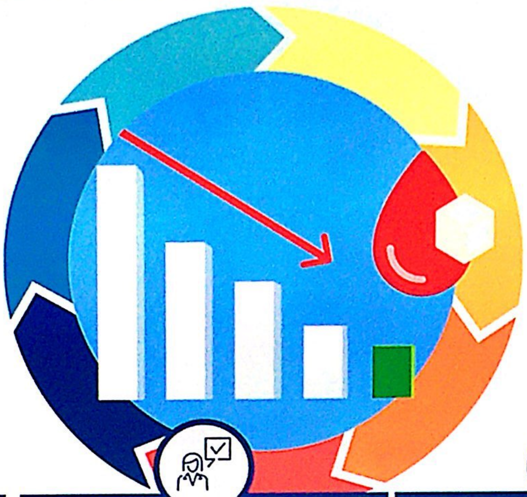

Providers should continually update their knowledge on the efficacy and side effects of diabetes pharmacotherapy (see Table 1).

Identify relevant comorbidities (e.g. obesity, CVD, HF, CKD, NAFLD).

Assess the profile of the person with diabetes (e.g. younger age, frailty, limited life expectancy, cognitive impairment, social determinants of health).

Consider risk factors for medication adverse events (e.g. hypoglycaemia, volume depletion, genital infections, history of pancreatitis).

Prioritise the use of organ-protective medications (GLP-1 RA, SGLT2i, TZD) in those with cardiorenal disease or NASH or at high risk.

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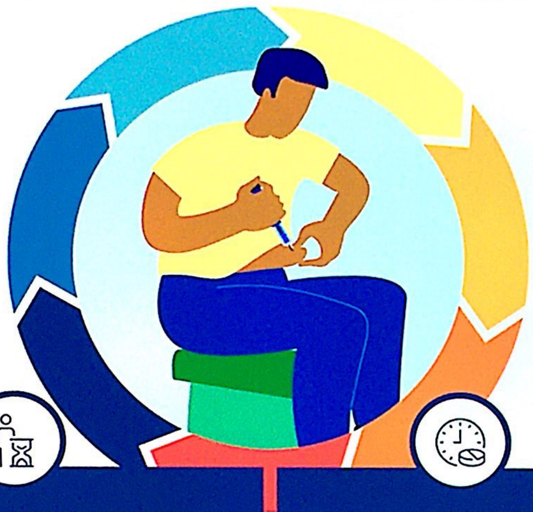
PLACE OF INSULIN IN TYPE 2 DIABETES



The use of a GLP-1 RA should be considered prior to initiation of insulin.

When initiating insulin, start with a basal insulin and intensify the dose in a timely fashion, titrating to achieve the individualised fasting glycaemia target set for every person.

When insulin is initiated, continue organ-protective glucose-lowering medications and metformin.

Refer for DSMES when initiating insulin or advancing to basal-bolus therapy.

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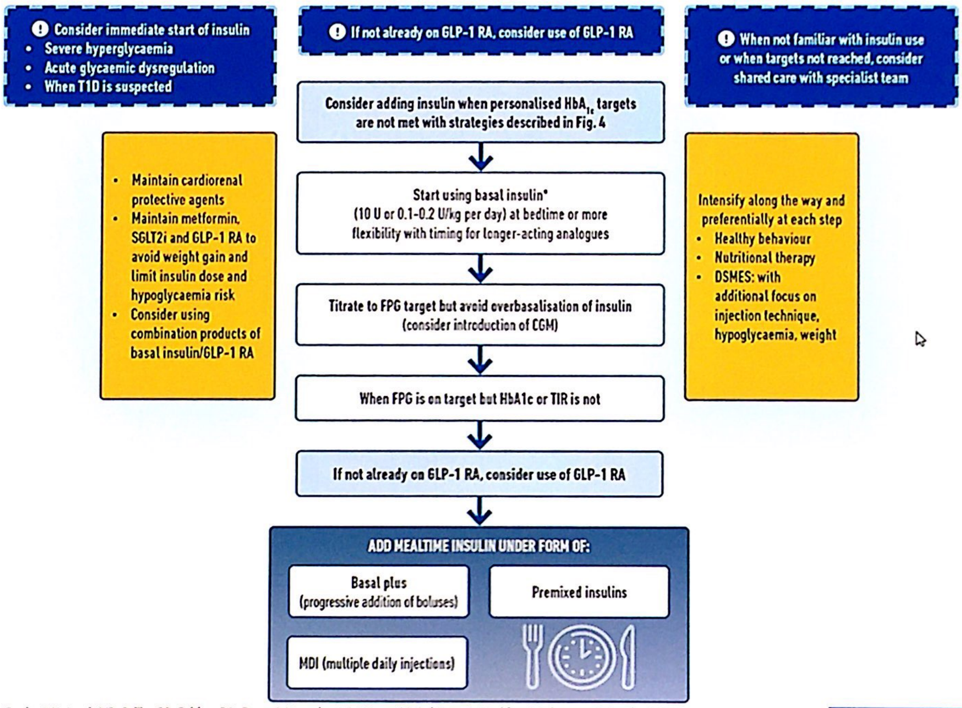
FIGURE 5: PLACE OF INSULIN[1]



*NPH Insulin or preferably analogue to reduce nocturnal hypoglycaemia risk

CGM, Continuous Glucose Monitoring; DSMES, Diabetes Self-Management Education and Support; FPG, Fasting Plasma Glucose; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T1D, Type 1 Diabetes; TIR, Time in Range.

1, More details can be found in Davies M, D'Alessio DA, Fradkin J et al. Management of Hyperglycaemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2018 61(12):2461–2498, and American Diabetes Association Professional Practice Committee, Draznin B, Aroda VR et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S125–43.

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PLACE OF TECHNOLOGY

Technology can be useful in people with type 2 diabetes but needs to be part of an holistic plan of care and supported by DSMES.

Consider CGM in people with type 2 diabetes on insulin.

Adapt the clinic/system to optimise effective use of technology among people with type 2 diabetes, particularly to support behaviour change through self-monitoring.

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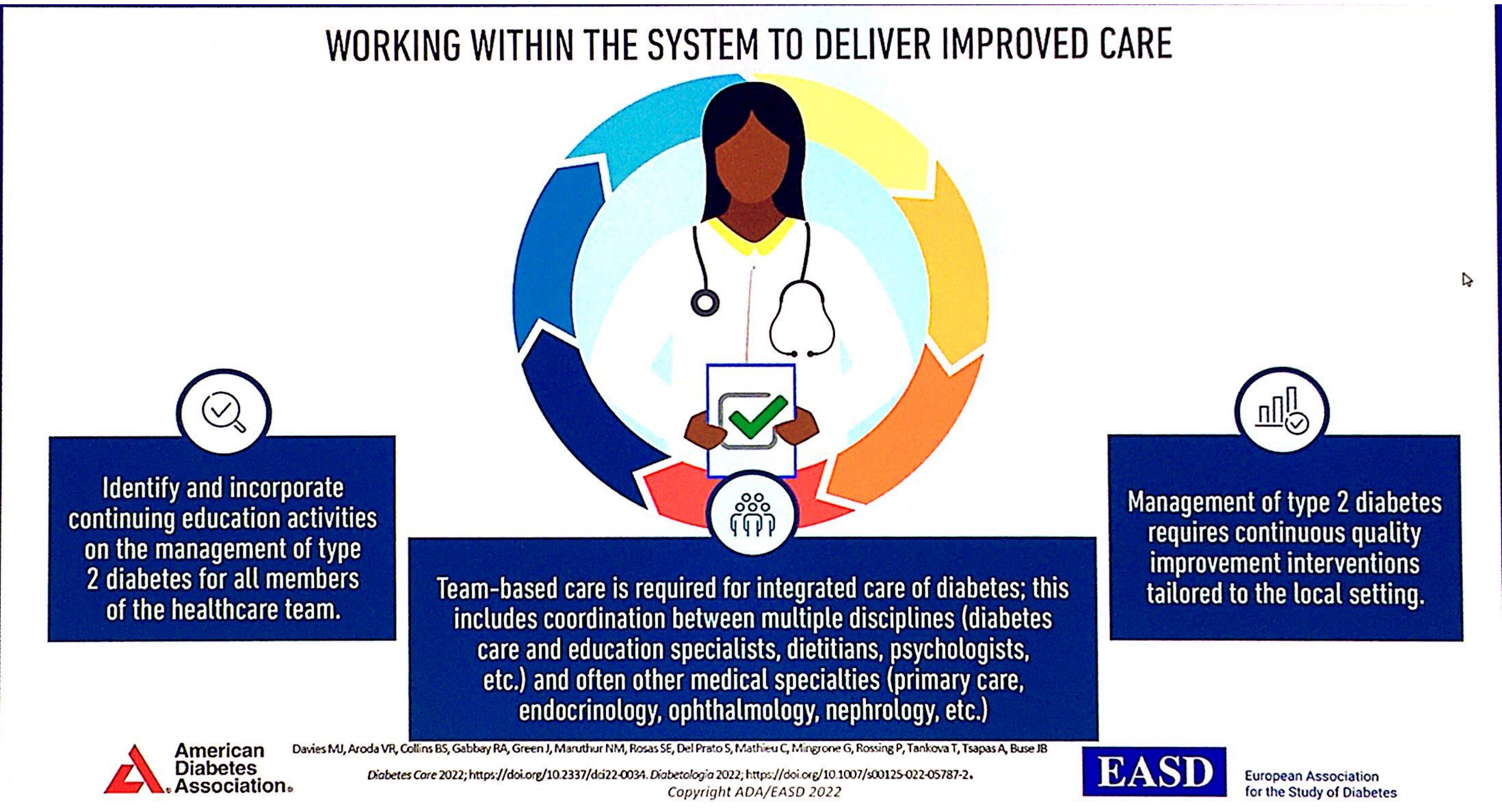
WORKING WITHIN THE SYSTEM TO DELIVER IMPROVED CARE
Identify and incorporate continuing education activities on the management of type 2 diabetes for all members of the healthcare team.
Team-based care is required for integrated care of diabetes; this includes coordination between multiple disciplines (diabetes care and education specialists, dietitians, psychologists, etc.) and often other medical specialties (primary care, endocrinology, ophthalmology, nephrology, etc.)
Management of type 2 diabetes requires continuous quality improvement interventions tailored to the local setting.
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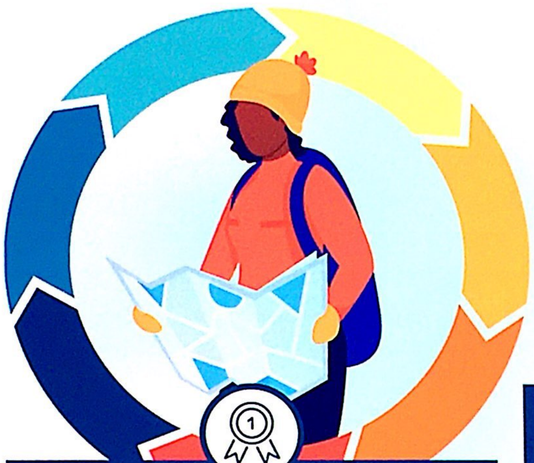
HOW TO REALLY MAKE IT WORK



Delivery arrangements

How, where and by who care is delivered

Coordination of care and management of care processes

Information and communication technology

Governance arrangements: Accountability for health professionals

Training and certification

Quality of practice

Implementation strategies

Health system

Health care setting

Health care workers

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MAKE IT WORK!

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Call to Action

Reflecting on the discovery of insulin 100 years ago and the experience over the last 3 years with COVID-19

The major opportunities to improve diabetes outcomes in the near term come from more effective implementation of best evidence through organisation of care at all levels (national to individual practices) and from addressing social determinants of health

Everyone has a role to play in better implementation with a focus on equity

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Key Opportunities

- Basic science to bring the next generation of interventions
- Implementation science is an essential area for future work, particularly in the context of "learning health care systems" in which internal data is systematically integrated with published evidence to drive quality improvement
- Precision medicine initiatives, whether "omics"-based or focused on social determinants of health, aim to optimally target interventions based on the wide heterogeneity of the population affected by diabetes
- Individualising care to make sure that the right person is getting the right therapy at the right time independent of social determinants of health

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Key Knowledge Gaps

- Study conduct
  - Greater attention to subgroups, in particular vulnerable populations
    - Youth, frailty, >75 years of age
    - Gender balance
  - A minimal first step to enhancing health justice
- Weight management
  - Comparative effectiveness
- Targets: A1c, TIR, weight, remission
- Cardiorenal protection
  - Comparative effectiveness, Combination therapy, Cost effectiveness in low/moderate risk population

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- Glucose monitoring
- Comorbidities
  - NAFLD
  - Cognitive impairment
  - Advanced CKD
- Screening and prevention
- Technology
- Sleep and chronotype

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Overall Summary

- Empathic, person-centred decision-making and support informed by an understanding of local resources and individual social determinants of health
- Consistent efforts to improve health behaviours (nutrition, activity, sleep, self-monitoring) and to provide diabetes self-management education and support
- Acceptance, adherence, and persistence with medical interventions to support cardiorenal health, cardiovascular risk reduction, and attainment of glycaemic and weight goals will prevent complications and optimise quality of life
- We must establish and refine quality improvement efforts in diabetes care at the local level to equitably implement evidence-based interventions to the benefit of all people with type 2 diabetes

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All Speakers
Management of hyperglycaemia in type 2: ADA/EASD Consensus Report 2022


Co-Chair: Melanie J. Davies MB ChB, MD
University of Leicester, UK
Co-Chair: John B. Buse, MD, PhD
UNC School of Medicine, USA
Project Oversight & Integration with SOC Mindy Saraco & Malaika Hill
ADA
The Rationale
Peter Rossing, MD
Steno Diabetes Center Copenhagen, Denmark
Billy Collins, DHSc, PA-C
U.S. Public Health Service, USA
Therapeutic Options
Vanita Aroda, MD
Brigham & Women's Hospital, Boston, USA
Geltrude Mingrone, MD, PhD
Catholic University of the Sacred heart, Rome, Italy
Tsvetalina Tankova, MD, DSC
Medical University, Sofia, Bulgaria
Personalised Approach
Apostolos Tsapas, MD, PhD, MSc
Aristotle University Thessaloniki, Greece
Jennifer Green, MD
Duke University, Durham, USA
Strategies for Implementation
Chantal Mathieu, MD, PhD
KU Leuven, Leuven, Belgium
Nisa Maruthur, MD, MHS
Johns Hopkins Medicine, Baltimore, USA
Sylvia Rosas, MD, MSCE
Joslin Diabetes Center, Boston, USA
Support Across Groups
Robert Gabbay, MD, PhD
ADA
Stefano Del Prato, MD
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Copies of the manuscript and slides are available at

For today only

https://diabetologia-journal.org/wpcontent/uploads/2022/09/ADAEASDConsensusReport.pdf

Consensus report (EASD):	https://doi.org/10.1007/s00125-022-05787-2
Slide deck (EASD):	https://tinyurl.com/ysxjwtm3
Consensus report (ADA):	https://doi.org/10.2337/dci22-0034
Slide deck (ADA):	https://professional.diabetes.org/2022ADA/EASDconsensus

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