“Time in Range”: a Practical Guide

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HbA1c – The gold standard

HbA1c
The gold standard

Advantages

- Easy to measure and standardize
- Relatively cheap
- Predictive of vascular complications
- Often used to guide management decisions

Limitations

- HbA1c is a poor indicator of glucose variability
- Potential confounding by some conditions (e.g. renal failure)
- Only provides an average measure of glycemia

There is a need for metrics beyond HbA1c to address these limitations

Aijan RA. Diabetes Technol Ther 2017;19:S27–S36

HealthPartners
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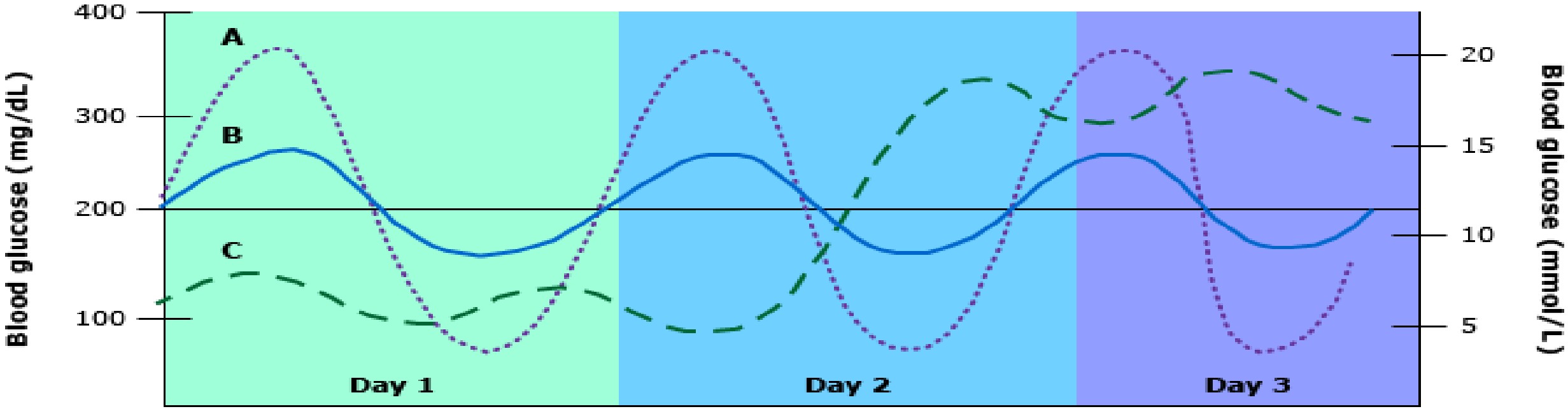
Patterns of blood glucose control



Blood glucose excursions in 3 hypothetical patients who have the same mean blood glucose concentration of approximately 200 mg/dL (11.1 mmol/L, equivalent to an A1C value of approximately 8.2%) but who have different overall blood glucose control

Blank space .....

Date	Breakfast			Lunch			Dinner			Bedtime	Comments
Month	Before	Carbs/ Insulin	2 Hours After	Before	Carbs/ Insulin	2 Hours After	Before	Carbs/ Insulin	2 Hours After		
Sun											
Mon											
Tue											
Wed											
Thu											
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Sat											
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Thu											
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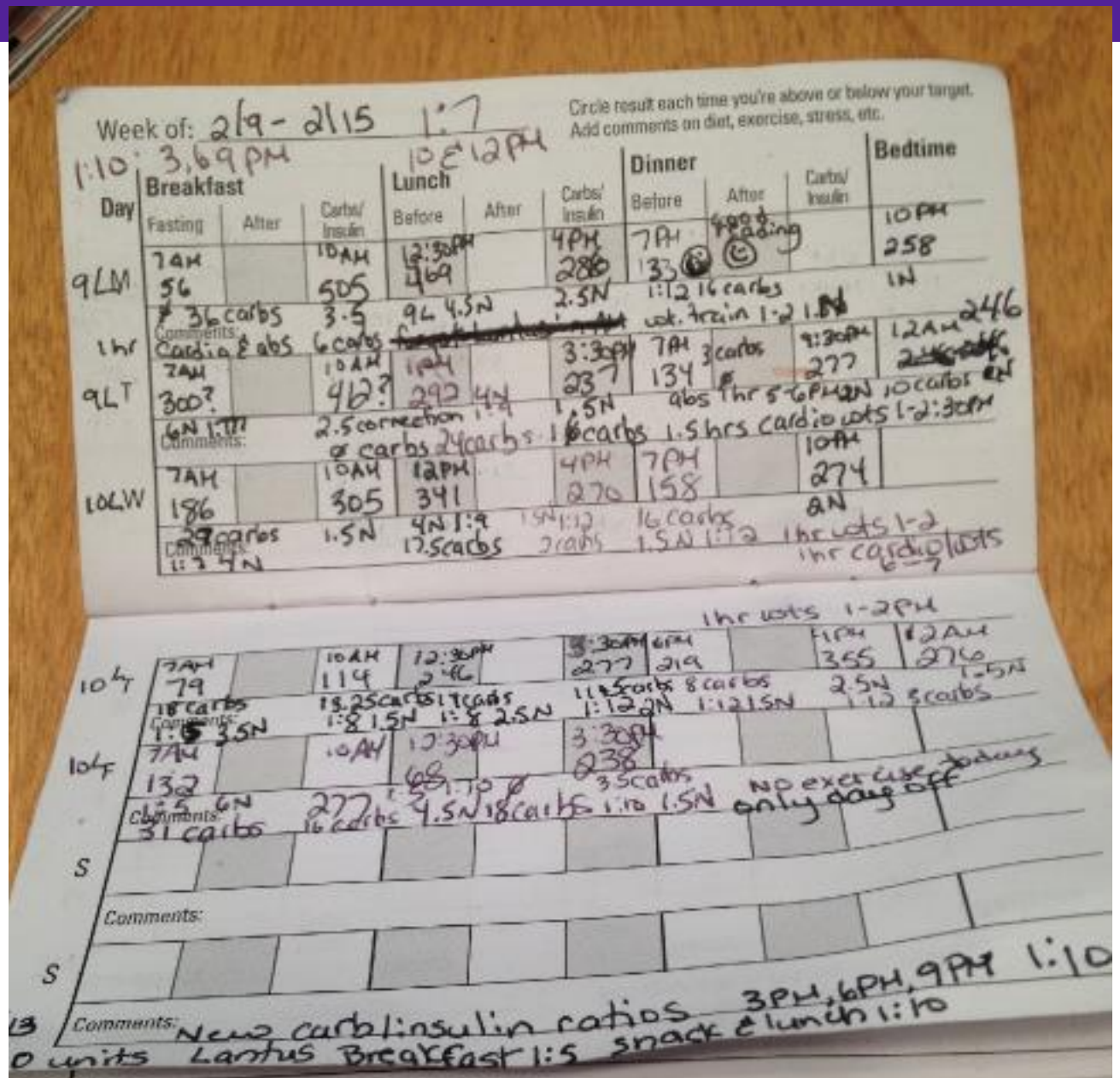
Sat											

CHAOS.....


Week of: 2/9 - 2/15
Circle result each time you're above or below your target.
Add comments on diet, exercise, stress, etc.
Day
Breakfast
Fasting
After
Carbs/ Insulin
Lunch
Before
After
Carbs/ Insulin
Dinner
Before
After
Carbs/ Insulin
Bedtime
Comments:
Comments:
Comments:
Comments:
Comments:
New carb:insulin ratios 3PM, 6PM, 9PM 1:10
units Lantus Breakfast 1:5 snack & lunch 1:10

Either way……


TIME
FOR
CHANGE


Daily Graph
(mmol/L)
OK
21
15
9
00:00
12:00
24:00
02 Mar
Tuesday


Glucose Monitor
Add Note
In Range
108
mg
dL
90 Day Overview
Recent Events

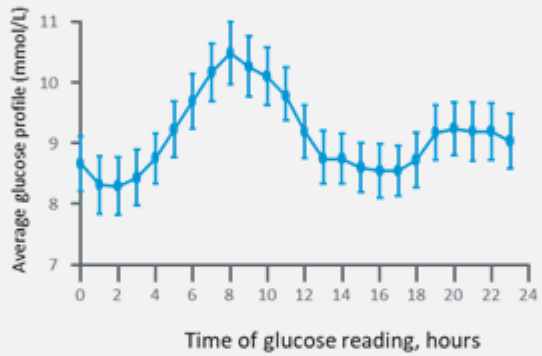

6.1
3 Hours
6
12
24
22
18
13.9
3.9
8:00
9:00
10:00
Now
6.1
Clarity
3 Days
7
14
30
90

Continuous Glucose Monitoring
From 7-Point SMBG to Ambulatory Glucose Profile (cont)

7-Point SMBG

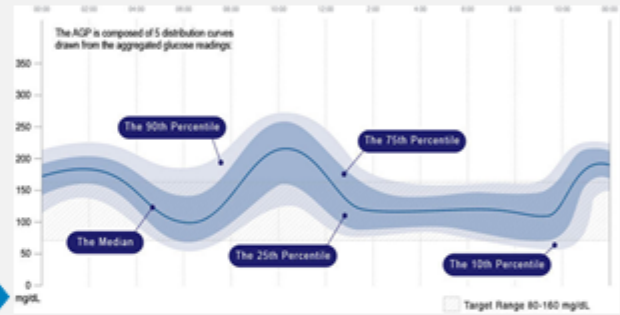
Distinguishes between **fasting**, **pre-prandial**, and **postprandial glucose excursions**, but only provides a snapshot[a]

Typical CGM Profile



Provides information on **direction**, **magnitude**, and **frequency of fluctuations** in blood glucose over 24 hours[b]

Ambulatory Glucose Profile



Average of CGM profiles to generate a **modal day** single curve, which can help in **identifying trends**[c] and visually represent **glycemic patterns**[d]

a. Parkin CG, et al. *J Diabetes Sci Technol.* 2009;3:500-508; b. De Block C, et al. *J Diabetes Sci Technol.* 2008;2:718-727; c. Hammond P. *Br J Diabetes.* 2016;16:S10-S15; d. Bergenstal RM, et al. *J Diabetes Sci Technol.* 2013;7:562-578.

AGP report

Metrics and targets

AGP profile (13 days)

Daily views

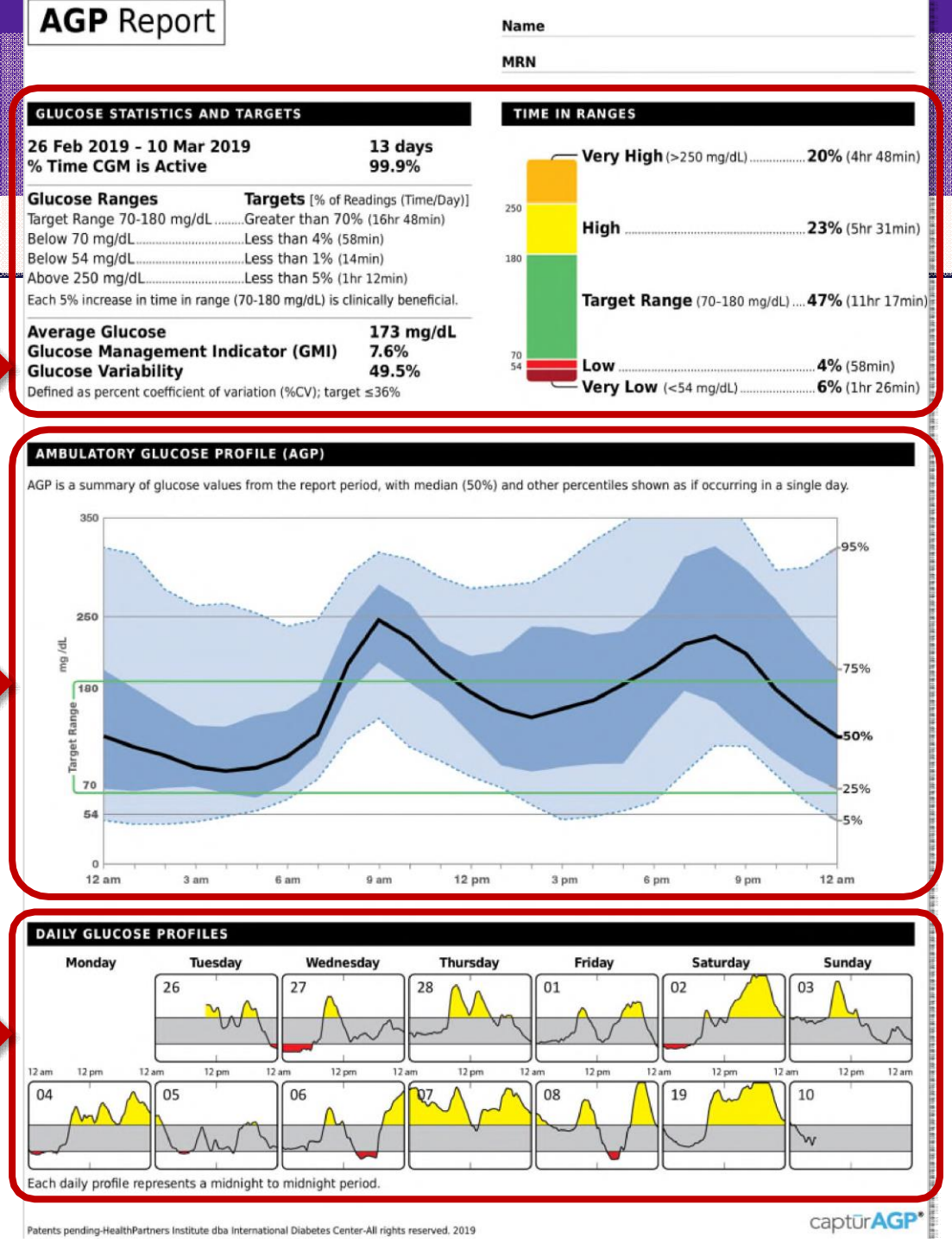


Image: http://www.agpreport.org/agp/agpreports

TIR – HbA1c correlation[1]

TIR 70% ≈ HbA1c 7%

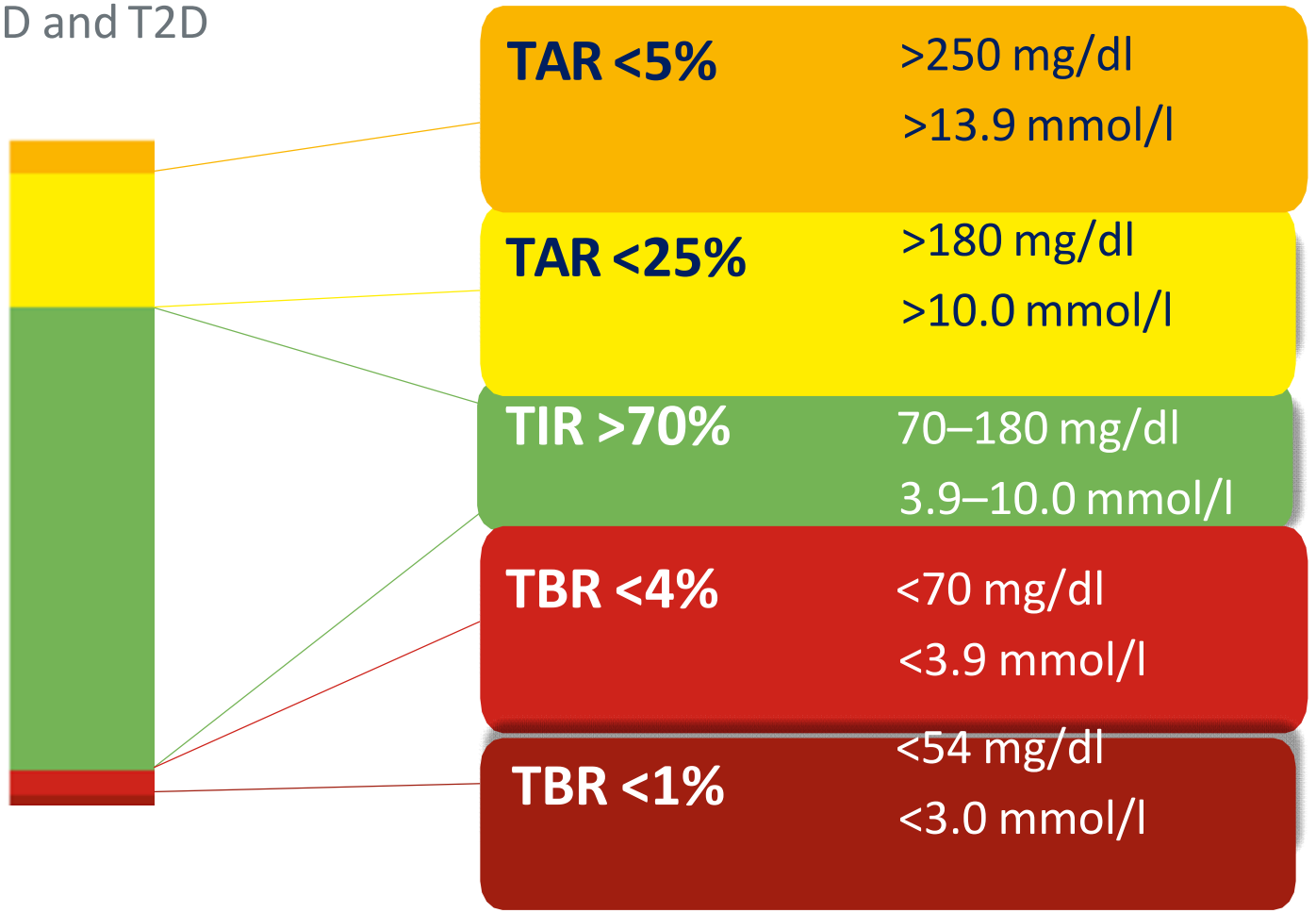
TIR 50% ≈ HbA1c 8%

10% ΔTIR ≈ 0.5% ΔHbA1c

AGP benefits:

- ✓ **Standardized and organized CGM data**
- ✓ **User-friendly / time-saving**

CGM TIR targets for most with T1D and T2D



High risk individuals (with complications or comorbidities & pregnancy) have different targets
Battelino T, et al. Diabetes Care 2019;42:1593–603

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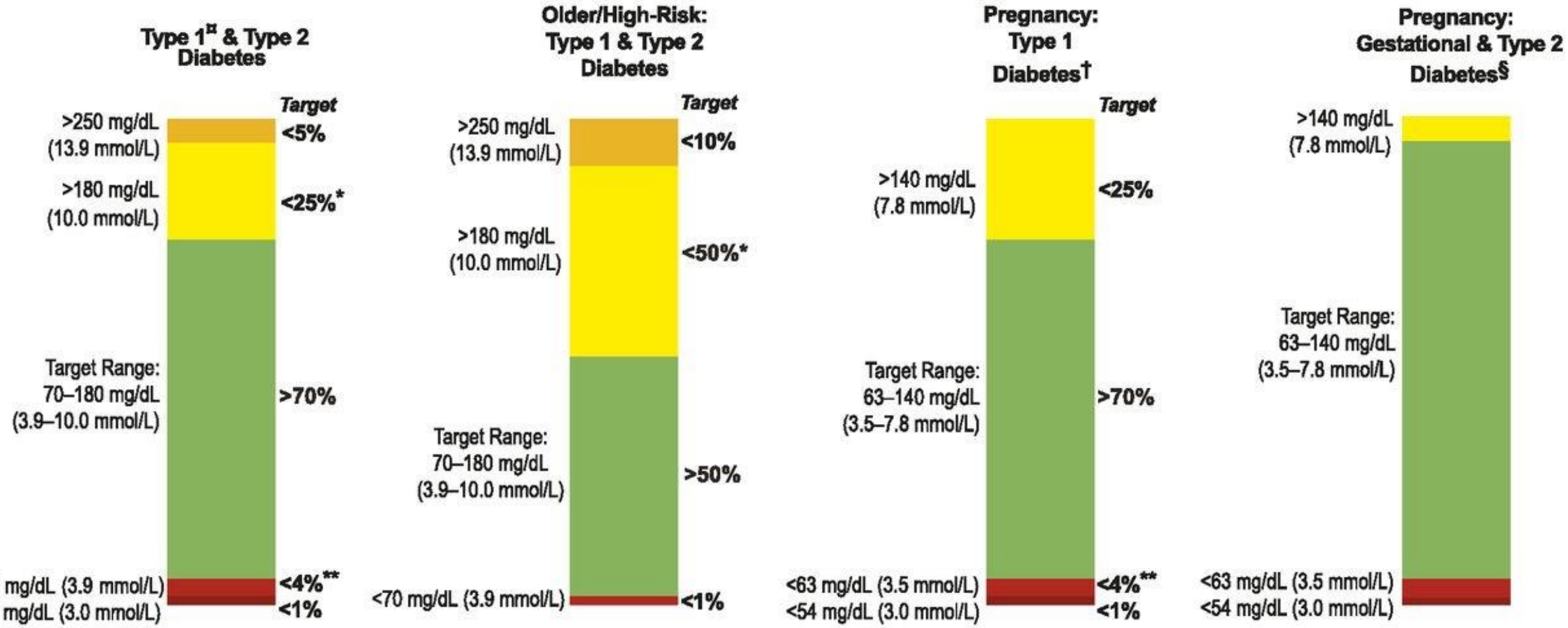


¤ For age <25 yr., if the A1C goal is 7.5%, then set TIR target to approximately 60%. (See *Clinical Applications of Time in Ranges* section in the text for additional information regarding target goal setting in pediatric management.)

† Percentages of time in ranges are based on limited evidence. More research is needed.

§ Percentages of time in ranges have not been included because there is very limited evidence in this area. More research is needed. Please see *Pregnancy* section in text for more considerations on targets for these groups.

* Includes percentage of values >250 mg/dL (13.9 mmol/L).

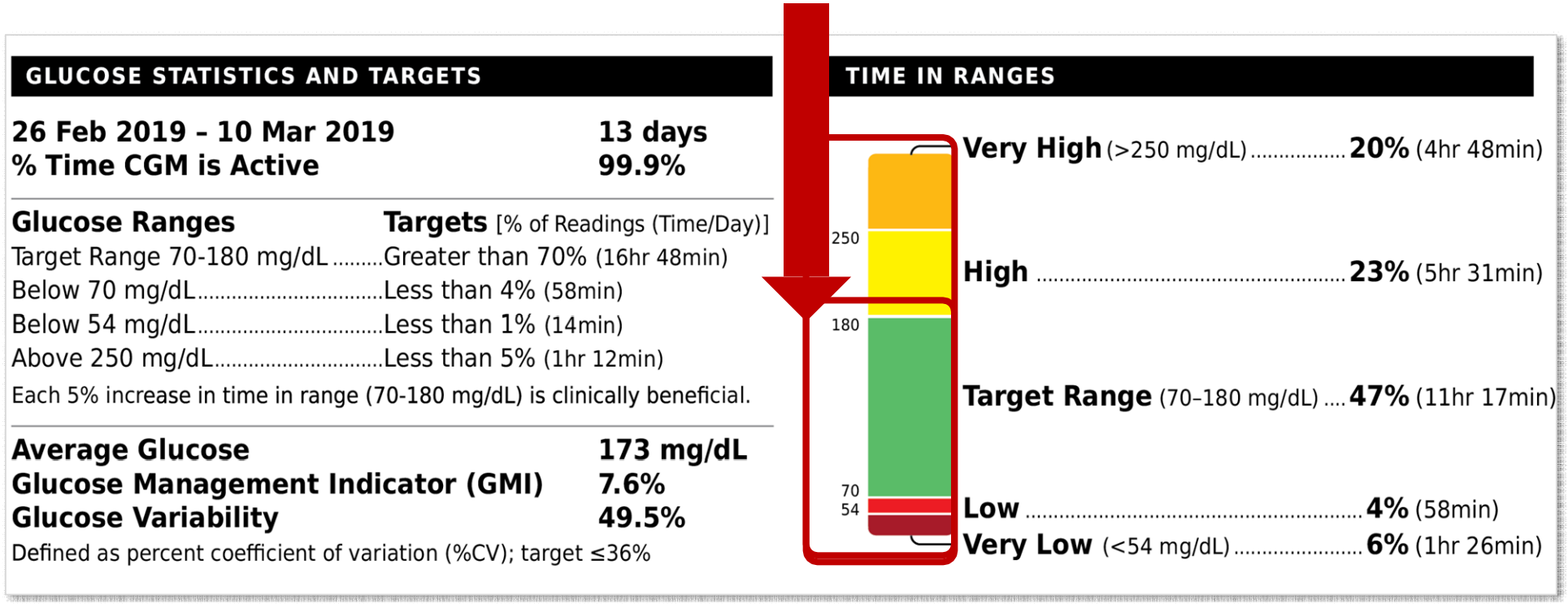
** Includes percentage of values <54 mg/dL (3.0 mmol/L).

Clinical Targets for Continuous Glucose Monitoring Data interpretation: Recommendations From the International Consensus on Time in Range Diabetes Care 2019 Aug; 42(8): 1593-1603.

AGP report

MG LR

MORE GREEN LESS RED



GLUCOSE STATISTICS AND TARGETS

26 Feb 2019 – 10 Mar 2019	**13 days**
% Time CGM is Active	**99.9%**

Glucose Ranges	**Targets** [% of Readings (Time/Day)]
Target Range 70-180 mg/dL	Greater than 70% (16hr 48min)
Below 70 mg/dL	Less than 4% (58min)
Below 54 mg/dL	Less than 1% (14min)
Above 250 mg/dL	Less than 5% (1hr 12min)

Each 5% increase in time in range (70-180 mg/dL) is clinically beneficial.

Average Glucose	**173 mg/dL**
Glucose Management Indicator (GMI)	**7.6%**
Glucose Variability	**49.5%**

Defined as percent coefficient of variation (%CV); target ≤36%

TIME IN RANGES

Very High (>250 mg/dL) **20%** (4hr 48min)

High **23%** (5hr 31min)

Target Range (70–180 mg/dL) **47%** (11hr 17min)

Low **4%** (58min)

Very Low (<54 mg/dL) **6%** (1hr 26min)

Image: http://www.agpreport.org/agp/agpreports

Correlation with HbA1C:

- TIR 70%: A1C 7%
- TIR 50%: A1C 8%

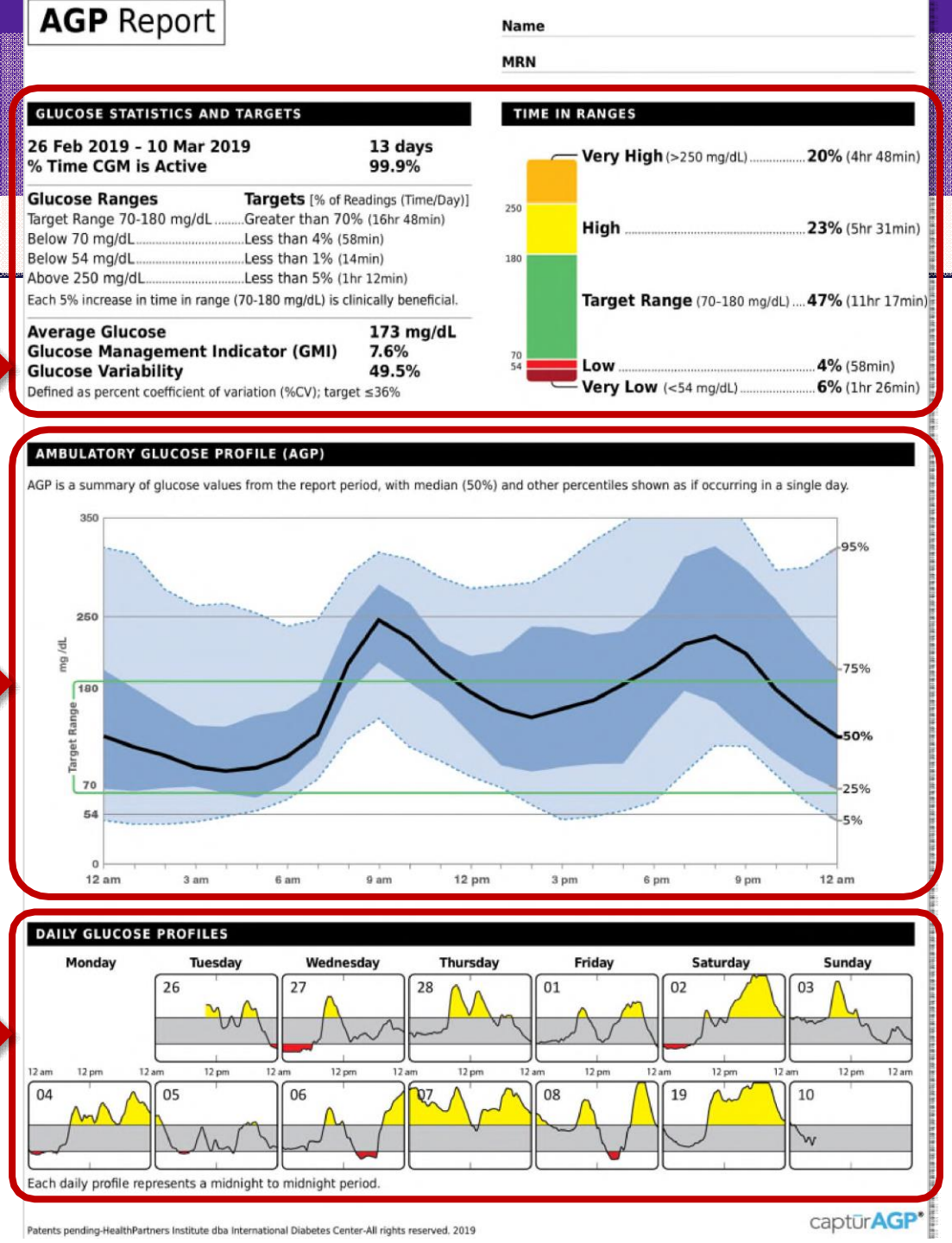
- Increase of TIR by 10% - decreases A1C by 0.5%

AGP report

Metrics and targets

AGP profile (13 days)

Daily views



AGP Report

Name

MRN

GLUCOSE STATISTICS AND TARGETS

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TIME IN RANGES

250 / 180 / 70 / 54

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High 23% (5hr 31min)
Target Range (70-180 mg/dL) 47% (11hr 17min)
Low 4% (58min)
Very Low (<54 mg/dL) 6% (1hr 26min)

AMBULATORY GLUCOSE PROFILE (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if occurring in a single day.

mg/dL: 350, 250, 180 (Target Range), 70, 54, 0
95%, 75%, 50%, 25%, 5%
12 am, 3 am, 6 am, 9 am, 12 pm, 3 pm, 6 pm, 9 pm, 12 am

DAILY GLUCOSE PROFILES

Monday 26 | Tuesday 27 | Wednesday 28 | Thursday 01 | Friday 02 | Saturday 03 | Sunday
04 | 05 | 06 | 07 | 08 | 19 | 10

Each daily profile represents a midnight to midnight period.

Patents pending-HealthPartners Institute dba International Diabetes Center-All rights reserved. 2019

captürAGP®

Image: http://www.agpreport.org/agp/agpreports

TIR – HbA1c correlation[1]

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TIR 50% ≈ HbA1c 8%

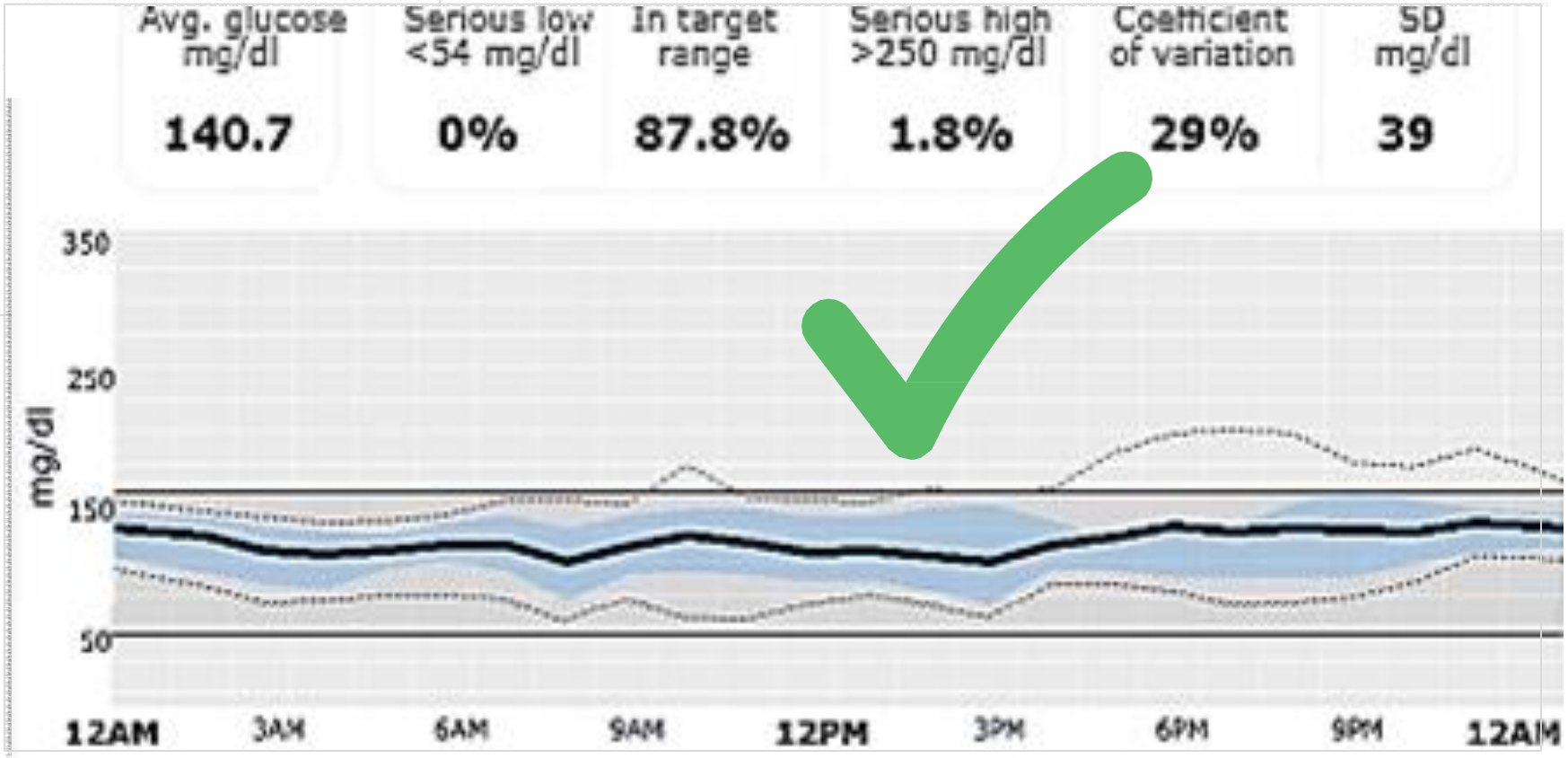
10% ΔTIR ≈ 0.5% ΔHbA1c

AGP benefits:

- ✓ **Standardized and organized CGM data**
- ✓ **User-friendly / time-saving**

What are we striving for in a CGM/AGP profile?

FNIR



Flat, narrow and in range!

GLUCOSE STATISTICS AND TARGETS

12 May 2022 - 25 May 2022	**14 Days**
% Time Sensor is Active	**93%**

Ranges And Targets For — Type 1 or Type 2 Diabetes

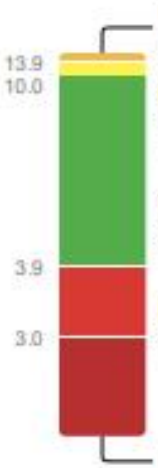
Glucose Ranges	**Targets** % of Readings (Time/Day)
Target Range 3.9-10.0 mmol/L	Greater than 70% (16h 48min)
Below 3.9 mmol/L	Less than 4% (58min)
Below 3.0 mmol/L	Less than 1% (14min)
Above 10.0 mmol/L	Less than 25% (6h)
Above 13.9 mmol/L	Less than 5% (1h 12min)

Each 5% increase in time in range (3.9-10.0 mmol/L) is clinically beneficial.

Average Glucose	**6.6** mmol/L
Glucose Management Indicator (GMI)	**6.2% or 44 mmol/mol**
Glucose Variability	**54.9%**

Defined as percent coefficient of variation (%CV); target ≤36%

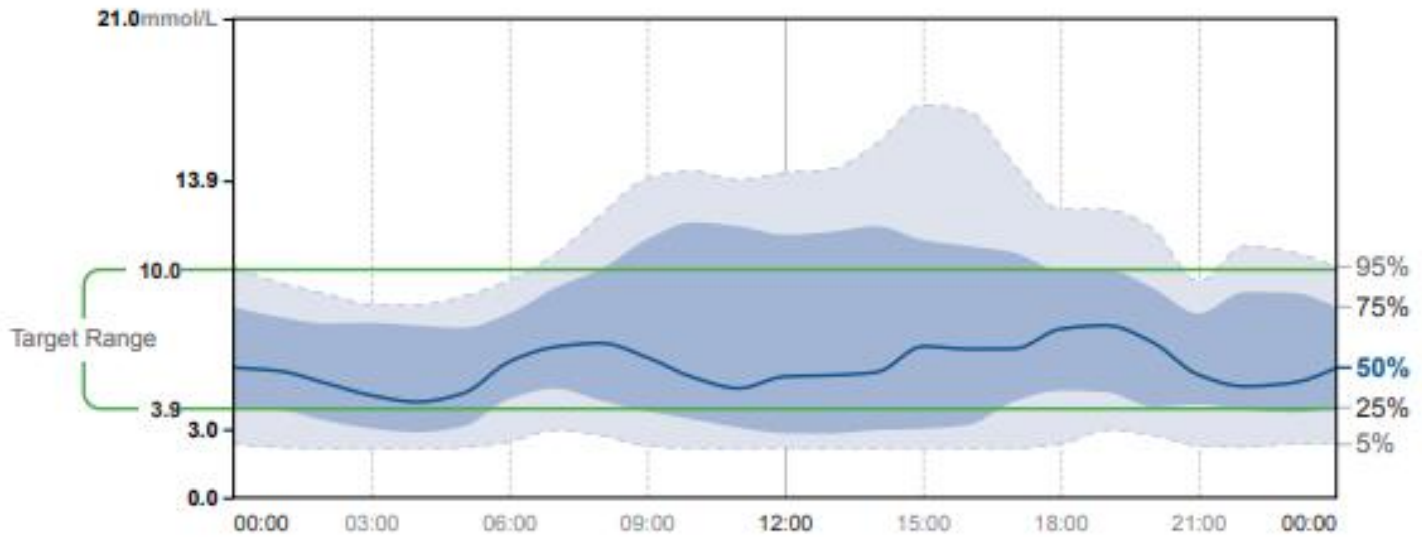
TIME IN RANGES



Very High	>13.9 mmol/L	**0%** (0min)
High	10.1 - 13.9 mmol/L	**1%** (14min)
Target Range	3.9 - 10.0 mmol/L	**54%** (12h 58min)
Low	3.0 - 3.8 mmol/L	**18%** (4h 19min)
Very Low	<3.0 mmol/L	**27%** (6h 29min)

AMBULATORY GLUCOSE PROFILE (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if occurring in a single day.

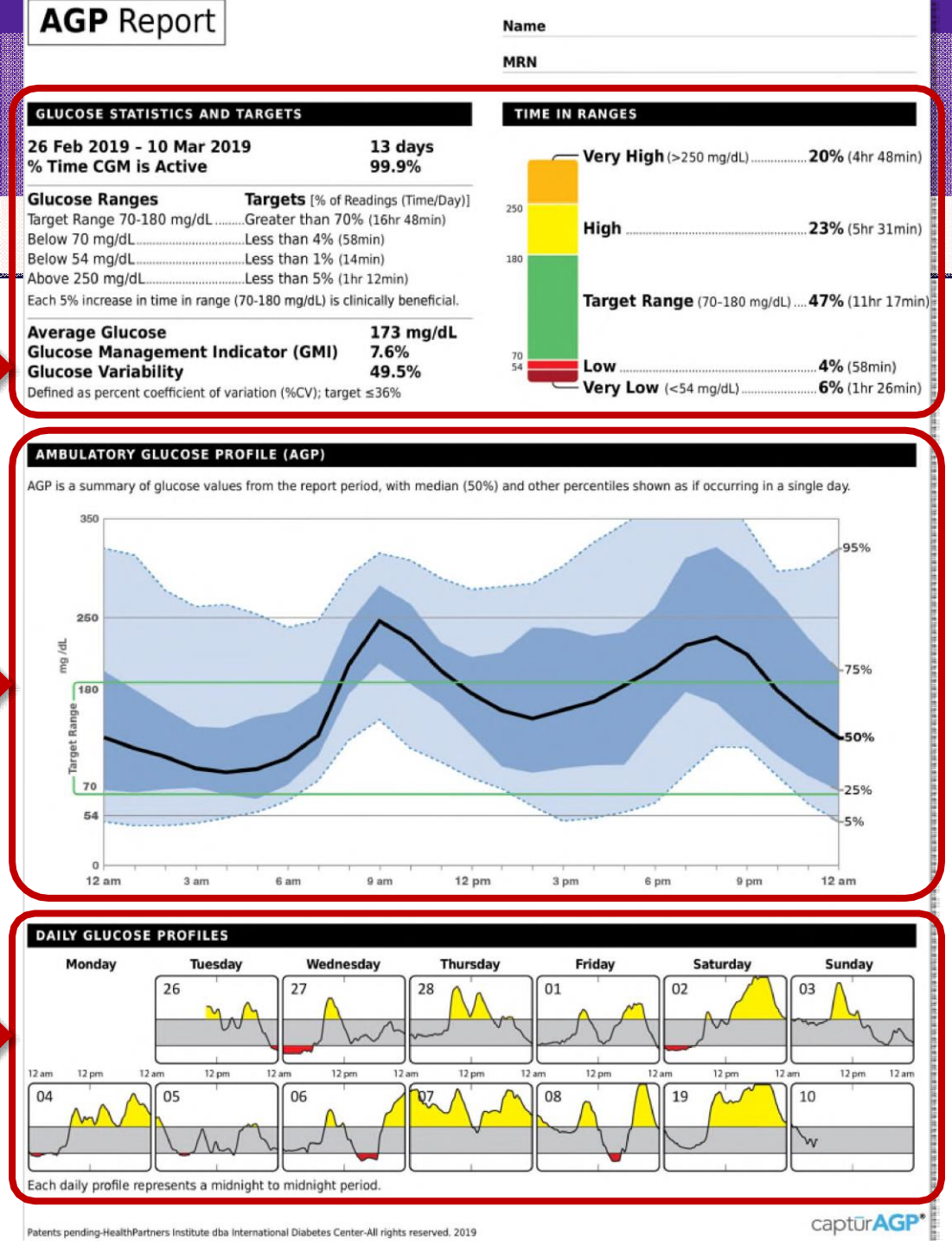


AGP report

Metrics and targets

AGP profile (13 days)

Daily views



Ima… http… …w.agpreport.org/agp/agpreports

TIR – HbA1c correlation[1]

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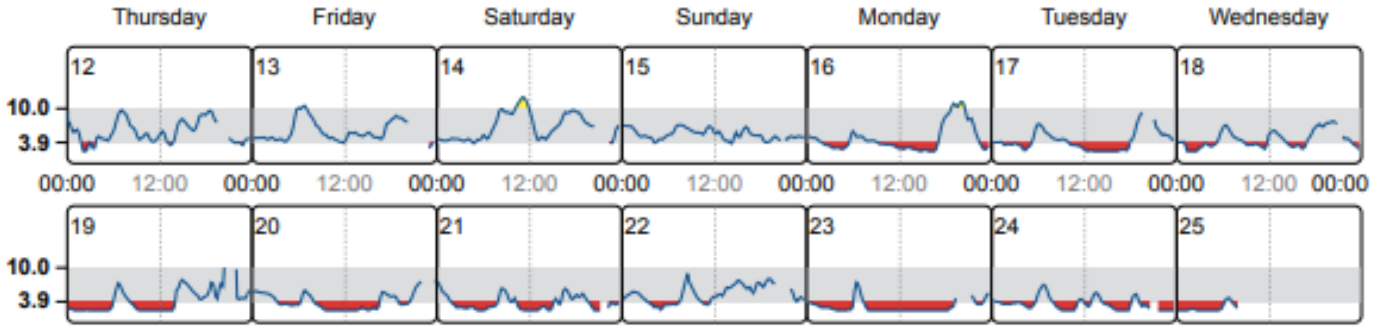
DAILY GLUCOSE PROFILES

Each daily profile represents a midnight to midnight period with the date displayed in the top-left corner.



Source: Battelino, Tadej, et al. "Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range." Diabetes Care, American Diabetes Association, 7 June 2019, https://doi.org/10.2337/dci19-0028.

Glucose Pattern Insights

LibreView

Generated: 01/06/2022 Page: 1 of 1

Selected dates: 12 May – 25 May 2022 (14 Days)

% Time Sensor is Active **93%**

Time in Ranges

Very High	>13.9 mmol/L	0%	1%
High	10.1 - 13.9	1%	Goal: <25%
Target	3.9 - 10.0	54%	>70%
Low	3.0 - 3.8	18%	45%
Very Low	<3.0	27%	<4%

Glucose Statistics

Average Glucose

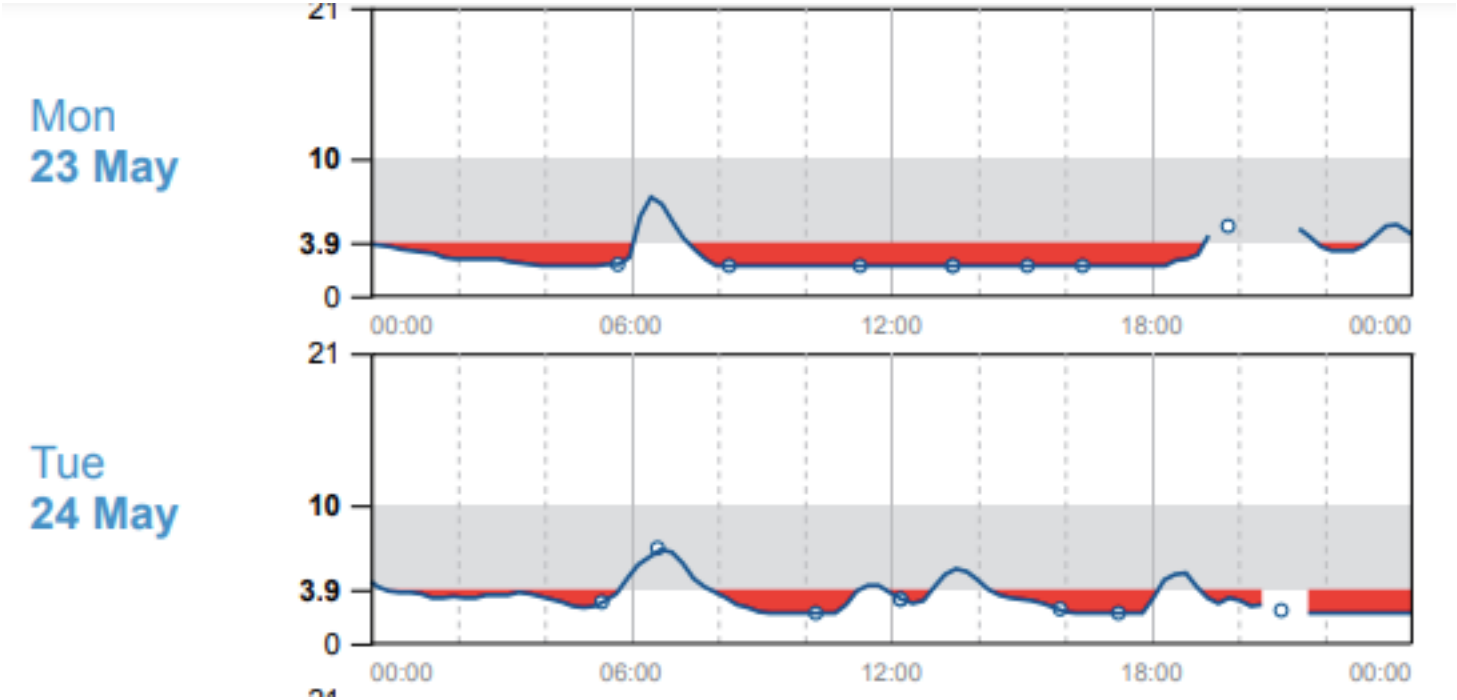
6.6 mmol/L Goal: ≤8.6 mmol/L

Glucose Management Indicator (GMI)

Approximate A1C level based on average CGM glucose level.

6.2% Goal: ≤7.0% | 44 mmol/mol Goal: ≤53 mmol/mol

Daily views


Mon
23 May
21
10
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0
00:00
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Tue
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18:00
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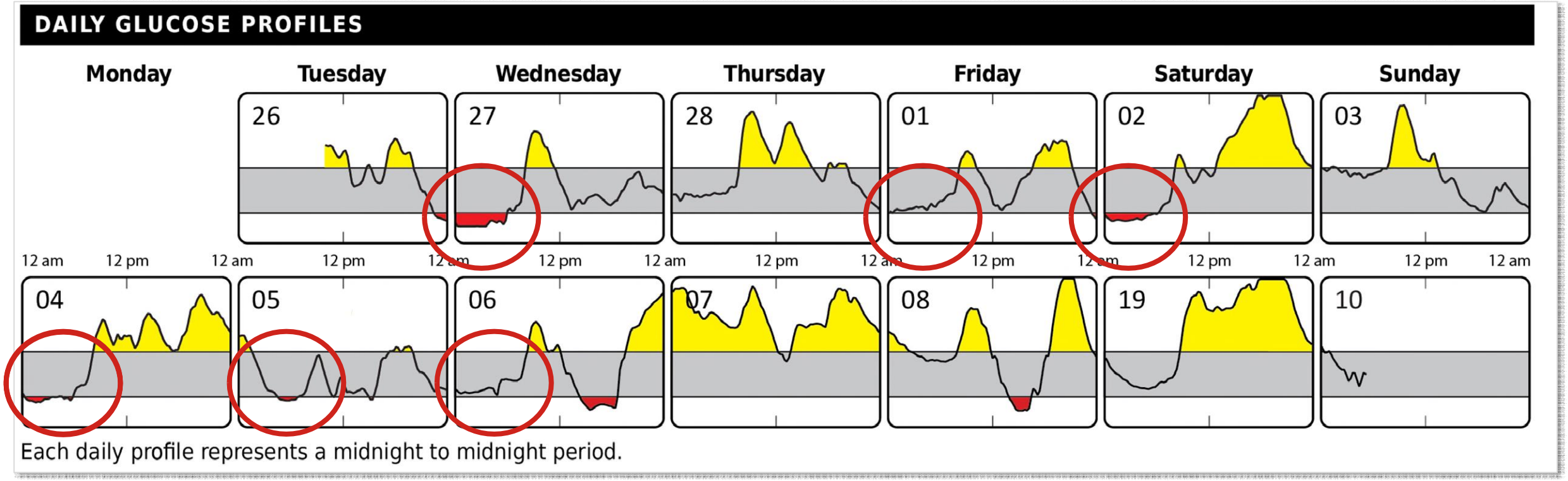
AGP report



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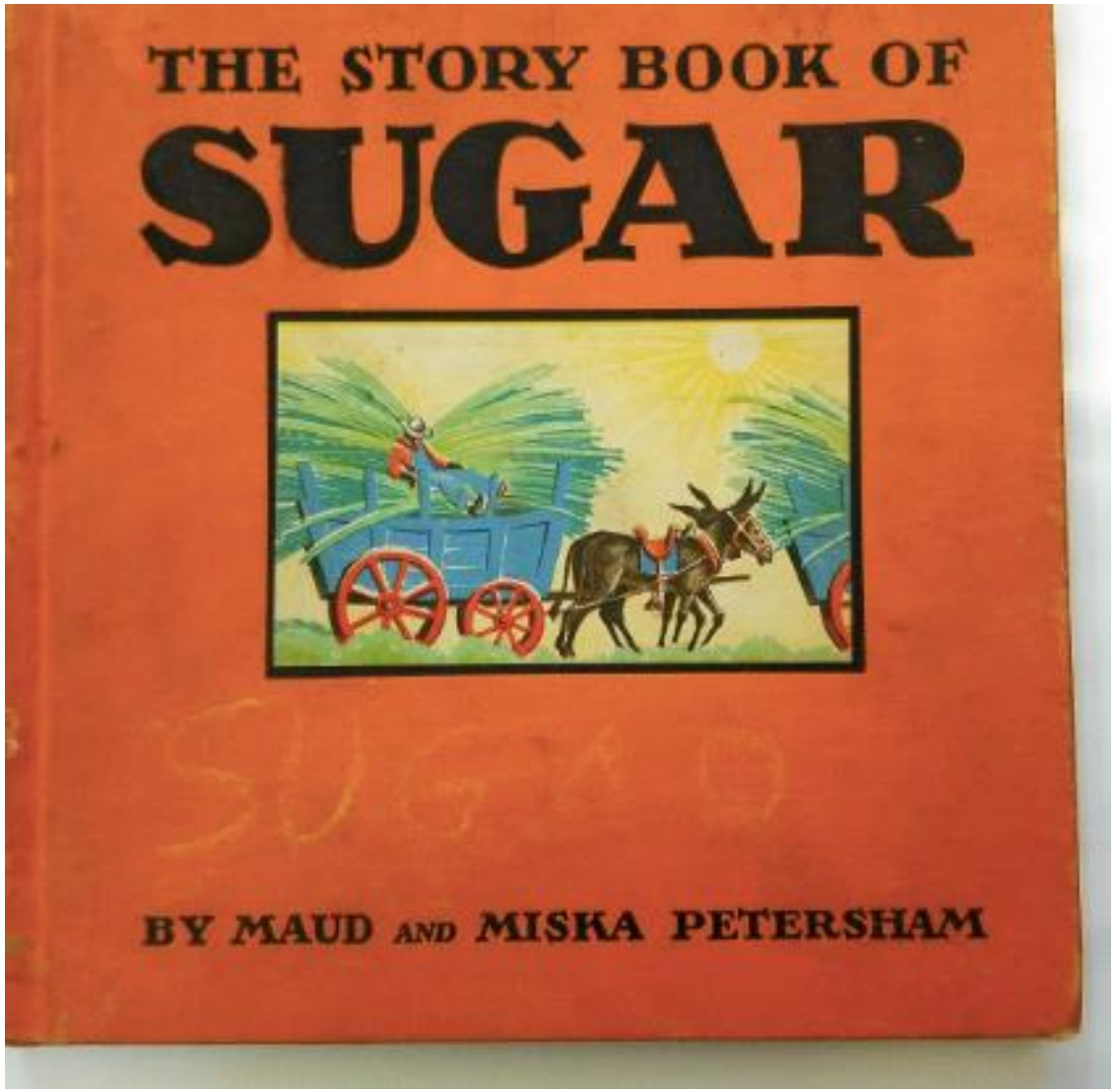
THE STORY BOOK OF
SUGAR
BY MAUD AND MISKA PETERSHAM

Take home points

1. **HbA1c:** A good indicator of population risk of diabetes complications but not a good glucose management guide

2. **CGM:**

   - **Metrics, targets & the AGP report** are now standardized and **endorsed by ADA, EASD, JDRF and others**
   - **CGM data tells a story to allow care to be personalised** through interventions including change in lifestyle and medications, use of technology and possibly adjunctive therapy

CGM / AGP can help us navigate the waters of diabetes management

RCT EVIDENCE ON TIME-IN-RANGE IN TYPE 1 DIABETES (**in Range Study**)

The **primary objective** of **InRange** (NCT04075513) was to demonstrate non-inferiority of Gla-300 versus IDeg-100 on **glycaemic control,** as measured by **TIR** and **variability, using blinded CGM in adults with T1D**

Tadej Battelino, MD, PhD[1], Thomas Danne, MD[2], Steve V. Edelman, MD[3], Pratik Choudhary, MD[4], Eric Renard, MD[5], Jukka Westerbacka, MD, PhD[6], Bhaswati Mukherjee, MD[6], Valerie Pilorget, MD[6], Pascaline Picard, MSc[7], R ichard M. Bergenstal, MD[8]

15 YEARS ANNIVERSARY
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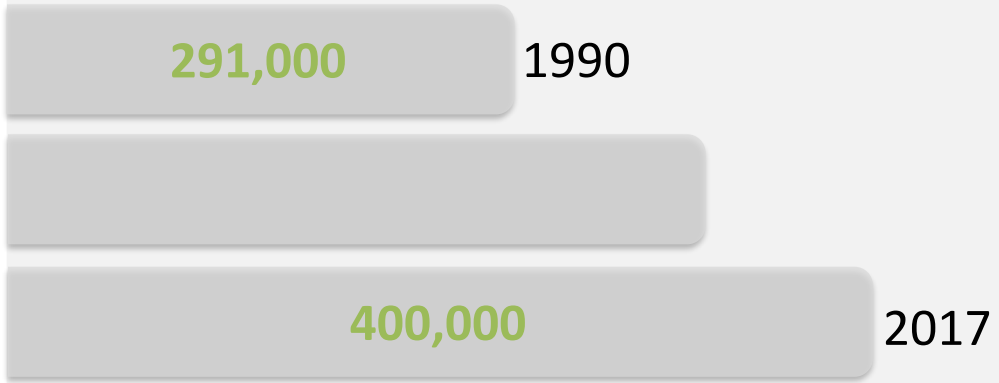
Background and rationale

Global burden of T1D

- Affects ~10% of the diabetes population[1]
- Incidence: 15 per 100,000 people[1]
- Prevalence: 9.5 per 10,000 people[1]

Incidence of T1D is increasing globally[2]



115; 2. Liu, J., et al. *BMC Public Health* 2020;**20**:1415

Background and rationale

Earlier implementation of intensive therapy in T1D is associated with greater reduction in risk of macrovascular and microvascular complications[1]

- Increased risk of **hypoglycaemia** may present a **barrier** to achieving appropriate glycaemic control[2]
- A recent US study of electronic health records from >30,000 people with T1D found that **80% had HbA_{1c} ≥7.0 %**, with mean HbA_{1c} of 8.8 %[3]
- The global SAGE study found **less than 25% of people with T1D had HbA_{1c} <7.0 %** (mean HbA_{1c} 7.95 %), with differences across regions[4]

1. Lachin J.M., et al., *Diabetes Care* 2021;**44**:2225-2230; 2.. Anderbro, T., et al., *Diabet Med* 2010;**27**(10):1151-1158; 3. Pettus J.H., et al., *Diabetes Obes Metab* 2020;**22**:622-630; 4. Renard, E., et al., *Diabetes Metab Res Rev.* 2021;**37**(7):e3430.

SD, standard deviation; T1D, type 1 diabetes

Background and rationale

- **Second-generation BI analogues** Gla-300 and IDeg-100 offer **more stable** and prolonged pharmacokinetic and pharmacodynamic **profiles** versus the first-generation Gla-100, with **less hypoglycaemia**[1,2]
- There are limited data available directly comparing Gla-300 and IDeg-100, in people with T1D and **no RCTs using CGM-derived time in range (TIR) as the primary endpoint**

- Use of **CGM** is associated with improved metabolic control in adults with diabetes versus standard blood glucose monitoring[3]
- It has been shown that standard blood glucose monitoring underestimates **hypoglycaemia and hyperglycaemia** versus CGM[4]
- CGM metrics can be used to **compare different treatment options** in clinical trials

1. Heise, T., et al. *Expert Opin Drug Metab Toxicol* 2015;**11**(8):1193-201; 2. Becker, R. H. A., et al., Diabetes Care 2015;**38**:637–643; 3. Beck, R.W., et al., *JAMA* 2017;**317**(4):371-378. 4. Mangrola, D., et al., *Endocr Pract* 2018;**24**:47-52

BI, basal insulin; CGM, continuous glucose monitoring; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; IDeg-100, insulin degludec 100 U/mL; RCT, randomised controlled trial; T1D, type 1 diabetes; TIR, time in range

Study design

12-week, multicentre, randomized, active-controlled, parallel-group, open-label study

Study population (N=343)

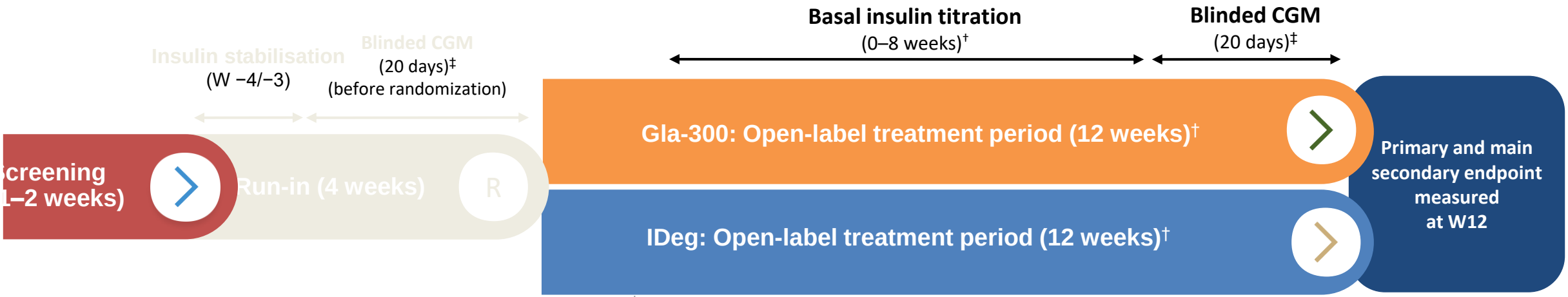
- Adults aged 18–70 years with T1D
- HbA_{1c} ≥7 % to ≤10 %
- MDI regimen with any
  - Basal insulin analogue
  - Rapid-acting insulin analogue
- No Gla-300 or IDeg-100 in last 30 days

During the titration period, doses of Gla-300 or IDeg-100 were titrated to achieve the target fasting self-measured plasma glucose (SMPG) of ≥70 to <100 mg/dL

Mealtime insulin analogue was titrated to achieve 2-hour post-prandial SMPG target of ≥130 to ≤180 mg/dL while avoiding hypoglycaemia

CGM data was blinded to both investigators and participants

Post-treatment safety information was collected 2–4 days after the last insulin dose



Randomisation stratified by screening HbA1c values of <8.0 % vs ≥8.0 %; †Telephone calls by investigators to monitor insulin titration weekly between site visits for all participants, unless participants attended the study site for sensor replacement (participant had option to visit the site on day –10 and 74 for sensor replacement). BI dose adjustments were based on a median of fasting SMPG values from last 3 days. Mealtime insulin dose adjustments were based on a pattern of post-meal SMPG data from last 3 days OR the carbohydrate content of the meal. ‡Baseline CGM data collection was started in W –3 and stopped at randomization visit. Endpoint CGM data was collected over 20 consecutive days during W10–W12

CGM, continuous glucose monitoring; Gla-300, insulin glargine 300 U/mL; IDeg-100, insulin degludec 100 U/mL; MDI, multiple daily injections; R, randomisation; SMPG, self-measured plasma glucose; T1D, type 1 diabetes

Study endpoints

Primary endpoint

% TIR ≥70 to ≤180 mg/dL at Week 12

Main secondary endpoint

Glucose total CV at Week 12 (as a measure of glycaemic variability)

Hierarchical testing procedure

Step 1 Demonstrate **non-inferiority** of Gla-300 vs IDeg-100 on **primary endpoint**

↓

Step 2 Demonstrate **non-inferiority** of Gla-300 vs IDeg-100 on **main secondary endpoint**

↓

Step 3 Demonstrate **superiority** of Gla-300 over IDeg-100 on **primary endpoint**

Non-inferiority was tested after multiplicity adjustment with a one-sided type I error of 2.5%, with a **relative** non-inferiority margin of 10% (note: not difference in %-units).
Statistics for all other endpoints were for descriptive purposes only
CV, coefficient of variation; Gla-300, insulin glargine 300 U/mL; IDeg-100, insulin degludec 100 U/mL; TIR, time in range

Other study endpoints

Descriptive statistics presented for other efficacy and safety variables

Secondary efficacy endpoints

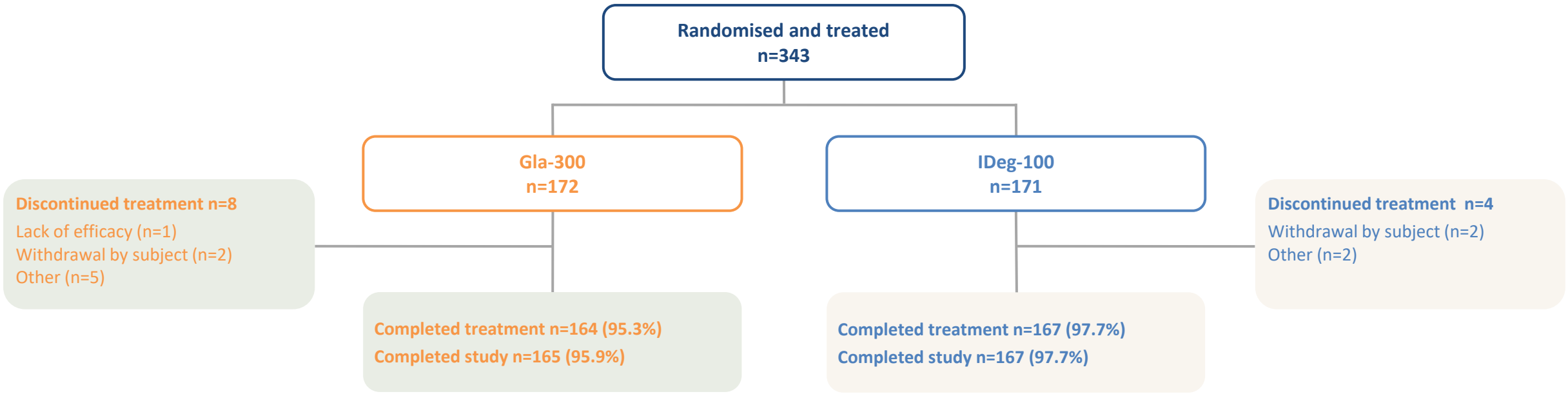
- Changes in HbA_{1c}
- % TAR per day >180 mg/dL at Week 12
- % TBR per day <70 mg/dL at Week 12

Safety/other endpoints:

- Incidence and event rates of hypoglycaemia (defined by SMPG)
  - Nocturnal/diurnal
  - <70 mg/dL
  - <70 mg/dL and ≥54 mg/dL (ADA Level 1)
  - <54 mg/dL (ADA Level 2)
  - Severe (ADA Level 3)
- Incidence of adverse events
- Changes in insulin dose

ADA, American Diabetes Association; SMPG, self-measured plasma glucose; TAR, time above range; TBR, time below range

Study disposition



All patients randomised were treated as planned and were included in the safety and ITT populations

Gla-300, insulin glargine 300 U/mL; IDeg-100, insulin degludec 100 U/mL; ITT, intention-to-treat

Baseline characteristics

eline characteristics were comparable between groups

Baseline Characteristic	Gla-300 (N=172)	IDeg-100 (N=171)	All (N=343)
Age, years, mean (SD)	42.9 (13.53)	42.8 (13.05)	**42.8 (13.28)**
Sex, female, n (%)	86 (50)	74 (43.3)	**160 (46.6)**
Body weight, kg, mean (SD)	80.5 (15.95)	78.8 (14.57)	**79.6 (15.28)**
BMI, kg/m^2, mean (SD)	27.6 (5.07)	27.0 (4.44)	**27.3 (4.77)**
Time since T1D diagnosis, years, mean (SD)	20.74 (12.47)	20.31 (13.12)	**20.53 (12.78)**
HbA$_{1c}$ ≥8 %, n (%)	106 (61.6)	106 (62.0)	**212 (61.8)**
Age at diagnosis, years, mean (SD)	22.74 (13.22)	23.14 (12.84)	**22.94 (13.01)**
Time since first intake of BI analogue treatment, years, mean (SD)	8.08 (6.20)	9.05 (6.26)	**8.56 (6.24)**
Time since first intake of mealtime insulin analogue treatment, years, mean (SD)	8.56 (7.22)	9.78 (7.28)	**9.17 (7.27)**

BI, basal insulin; BMI, body mass index; Gla-300, insulin glargine 300 U/mL; IDeg-100, insulin degludec 100 U/mL; SD, standard deviation; T1D, type 1 diabetes.

Baseline characteristics

eline characteristics were comparable between groups

Baseline Characteristic	Gla-300 (N=172)	IDeg-100 (N=171)	All (N=343)
Diabetic complications, n (%)			
At least one	60 (35.1)	55 (32.5)	**115 (33.8)**
Diabetic retinopathy	30 (17.5)	36 (21.3)	**66 (19.4)**
Non-proliferative diabetic retinopathy	25 (14.6)	31 (18.3)	**56 (16.5)**
Proliferative diabetic retinopathy	4 (2.3)	5 (3.0)	**9 (2.6)**
Diabetic neuropathy	32 (18.7)	32 (18.9)	**64 (18.8)**
Diabetic nephropathy	13 (7.6)	8 (4.7)	**21 (6.2)**

Gla-300, insulin glargine 300 U/mL; IDeg-100, insulin degludec 100 U/mL

The InRange study is the first RCT comparing second-generation BI analogues, Gla-300 and IDeg-100, in T1D using TIR as the primary endpoint

Primary endpoint met	Main secondary endpoint met	Hypoglycaemia and safety profile
		
Non-inferiority for glycaemic control (% TIR)	**Non-inferiority for glycaemic variability** (total glucose CV)	**Similar occurrences of hypoglycaemia, with no unexpected safety findings**

Gla-300 is non-inferior to IDeg-100 in people with T1D in terms of glycaemic control (TIR), and in terms of glycaemic variability, with no difference in occurrences of hypoglycaemia or safety profiles

BI, basal insulin; CV, coefficient of variation; Gla-300, insulin glargine 300 U/mL; IDeg-100, insulin degludec 100 U/mL; MDI, multiple daily injections; RCT, randomised controlled trial; T1D, type 1 diabetes; TIR, time in range

Observations from InRange

CGM as an outcome measure can be clinically useful – can studies like this make it useful from a regulatory standpoint?

HbA_{1c} dropped from 8.34 / 8.29 % to 7.38 / 7.51 % with targeted dose titration

- Result of lower variability?
- Why can't we replicate that in clinical care?

Total daily dose didn't change much (from approx. 0.6 U/kg)

- Slight increase in Gla-300 dose as expected

Hypoglycaemia was similar to that reported in many clinical studies

- Severe hypoglycaemia was very low (<6% patients; <30 events / 100 patient year)

CGM was NOT used clinically to titrate insulin – so there are even better results to be achieved

CGM, continuous glucose monitoring; Gla-300, insulin glargine 300 U/mL

CGM summary

- ?way forward
  - insulin requiring diabetes
  - and /or those at risk for hypoglycaemia
- NB:
  - it's a tool… can't simply buy it and slap it on!
  - patient to 'own' their diabetes management
  - understand concepts: TIR / interpret graphs and CGM daily profile
  - clear clinical targets set

The Diabetic with Heart Failure

Dr joanna Skelton

Endocrinologist and Diabetologist, KZN

CVR 0722002

DISCLAIMER:

“This presentation is intended for educational purposes only and does not replace independent professional judgment.

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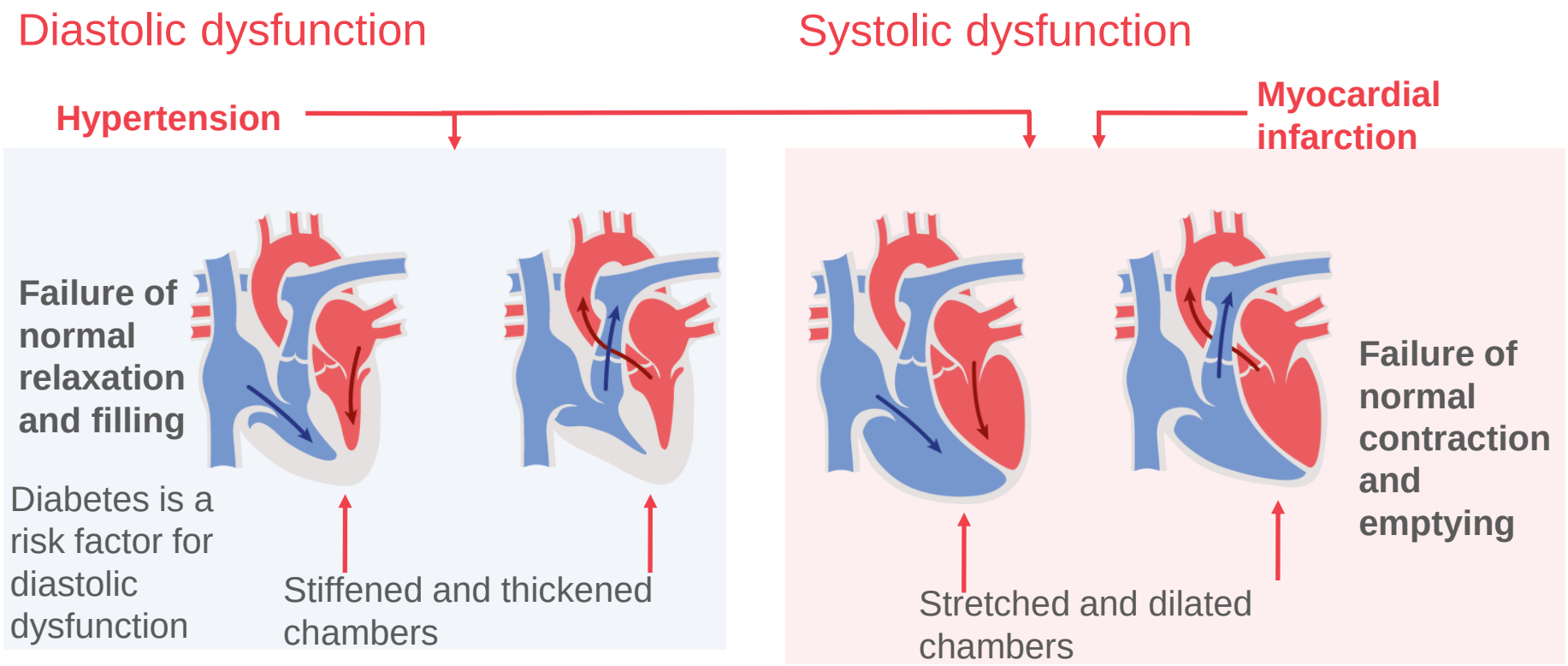
AstraZeneca does not endorse or approve, and assumes no responsibility for, the content, accuracy or completeness of the information presented.”.

The Definition

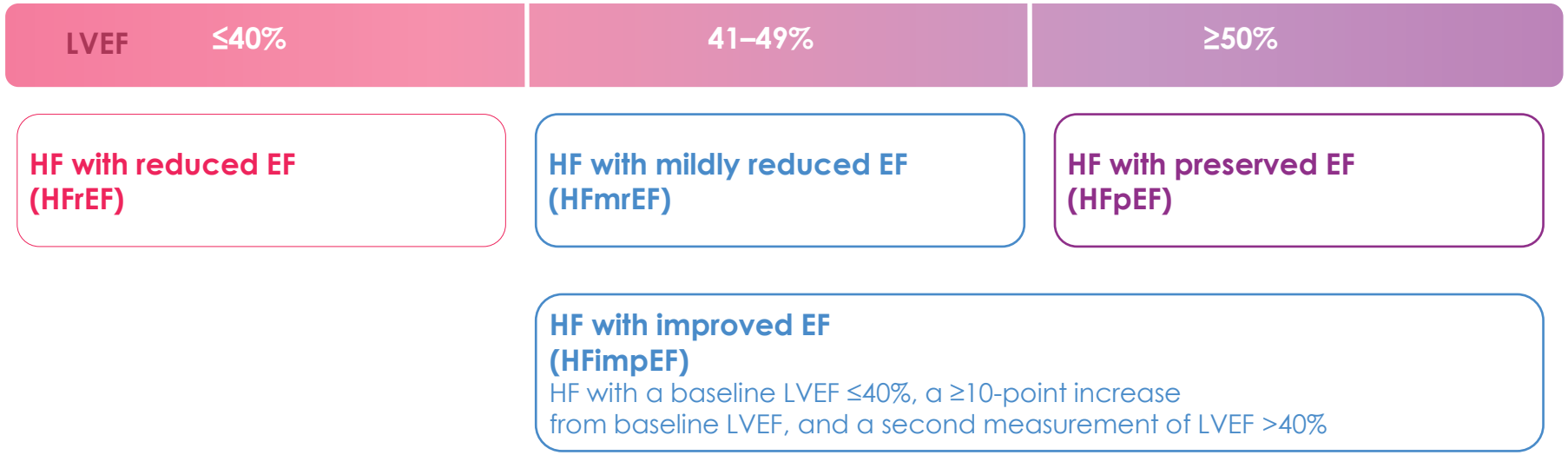
left ventricular heart failure



CAD, coronary artery disease; T2D, type 2 diabetes

McMurray JVV *et al. Lancet Diabetes Endocrinol* 2014;2:843

The new universal definition of heart failure classifies the different phenotypes according to LVEF



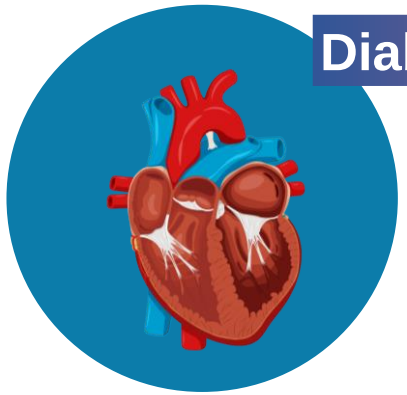
EF, ejection fraction; LVEF, left ventricular ejection fraction.
Bozkurt B *et al*. *Eur J Heart Fail.* 2021;23:352.

WHY WORRY?

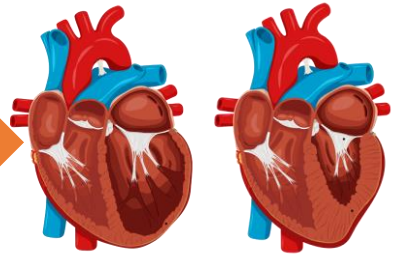
T2D Contributes to Early Cardiac Dysfunction

Downstream Effects of T2D[1-5]

- RAAS activation
- Arterial stiffness
- Fluid expansion
- HTN
- Renal hyperfiltration



Diabetic Cardiomyopathy[1]



68% of patients with T2D for a median of 5 years had evidence of asymptomatic LV dysfunction[6,a]

HFrEF **HFpEF**

Up to **1 in 2** patients with T2D may develop HF[8]

aProspective study in Italy, evaluating clinical and echocardiographic characteristics of individuals with T2D (N=386) who were determined to be free from cardiac disease. Median duration of diabetes was 5 years; mean A1C was 7.1%; bACC/AHA Stage C/D HF.7

A1C=glycated hemoglobin; ACC=American College of Cardiology; AHA=American Heart Association; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; RAAS=renin-angiotensin-aldosterone system.

1. Dunlay SM et al. *Circulation*. 2019;140(7):e294-e324; 2. Standl E. *Diabetes Mellitus*. 2018;21(5):399-403; 3. Low Wang CC et al. *Circulation*. 2016;133(24):2459-2502; 4. Ofstad AP et al. *Heart Fail Rev*. 2018;23(3):303-323; 5. Devereux RB et al. *Circulation*. 2000;101(19):2271-2276; 6. Faden G et al. *Diabetes Res Clin Pract*. 2013;101(3):309-316; 7. Yancy CW et al. *J Am Coll Cardiol.* 2013;62(16):e147-e239; 8. American Diabetes Association. *Diabetes Care*. 2020;43(suppl 1):S1-S212.

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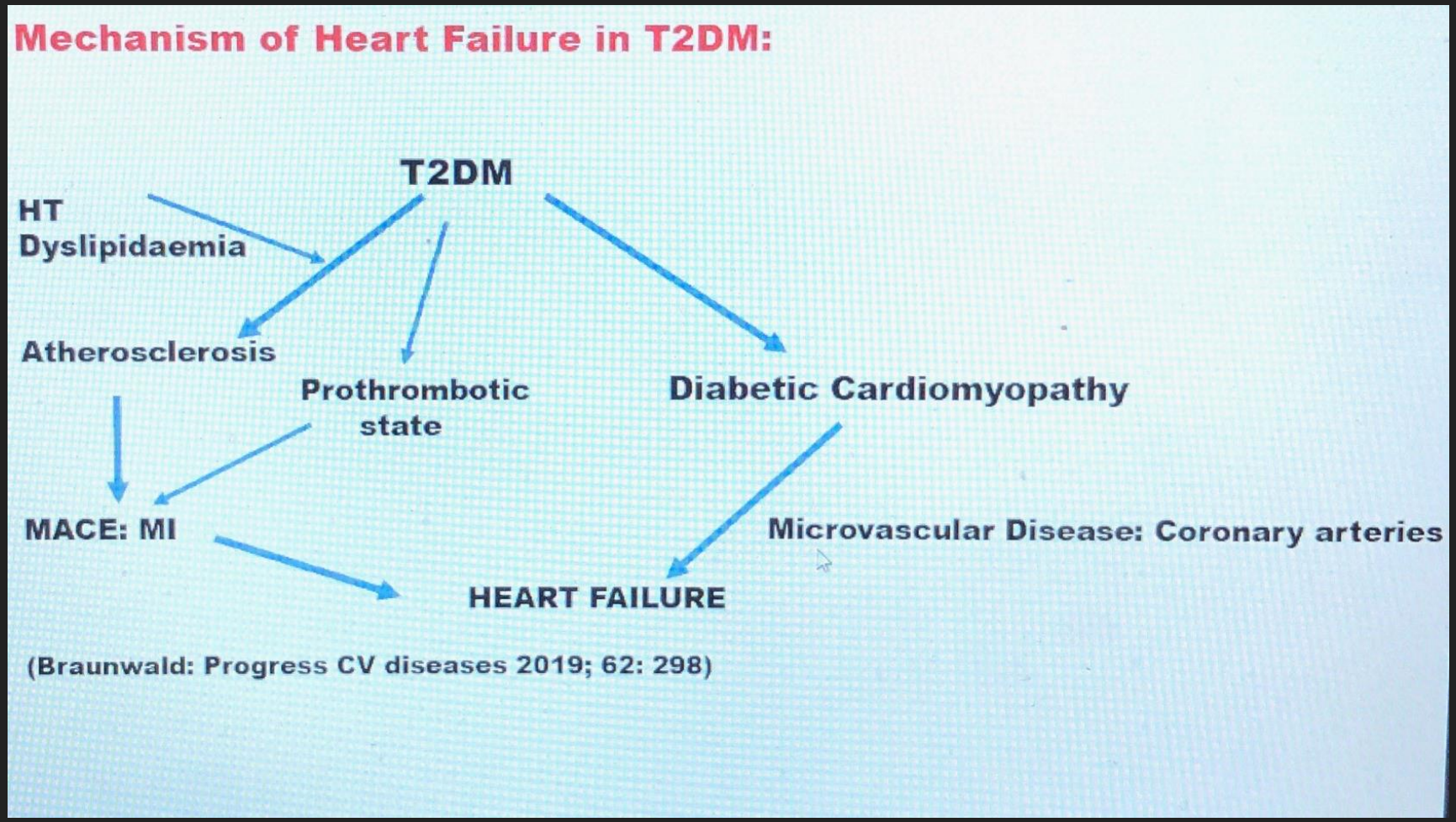
Mechanism of Heart Failure in T2DM:
T2DM
HT
Dyslipidaemia
Atherosclerosis
Prothrombotic state
Diabetic Cardiomyopathy
MACE: MI
Microvascular Disease: Coronary arteries
HEART FAILURE
(Braunwald: Progress CV diseases 2019; 62: 298)

Just treat the sugar…

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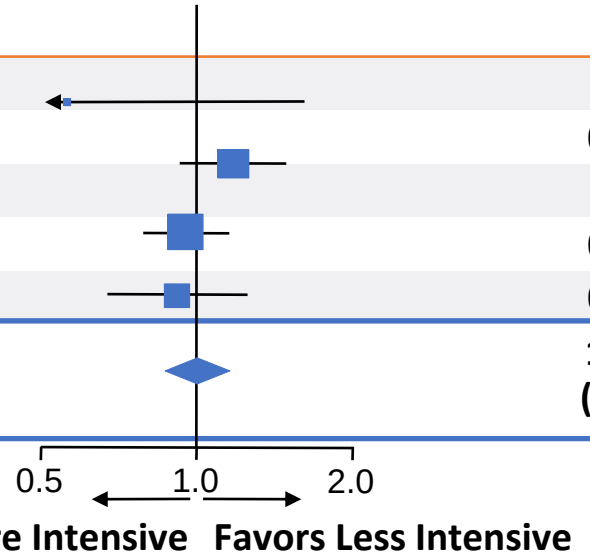
While Glucose Control is Fundamental to the

Trials	Number of Events (annual event rate, %): More intensive	Less intensive	Change in A1C (%)	HR (95% CI)
Hospitalized/Fatal HF				
UKPDS	8 (0.06)	6 (0.11)	–0.66	0.55 (0.19–1.60)
ACCORD	152 (0.90)	124 (0.75)	–1.01	1.18 (0.93–1.49)
ADVANCE	220 (0.83)	231 (0.88)	–0.72	0.95 (0.79–1.14)
VADT	79 (1.80)	85 (1.94)	–1.16	0.92 (0.68–1.25)
Overall	**459**	**446**	**–0.88**	**1.00 (0.86–1.16) (Q=3.59, p=0.31, I^2=16.4%)**



A1C = glycosylated hemoglobin; ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; HF = heart failure; HR = hazard ratio; T2D = type 2 diabetes; UKPDS = UK Prospective Diabetes Study; VADT = Veterans Affairs Diabetes Trial.

Turnbull FM et al. *Diabetologia.* 2009;52:2288-2298.

‘CV BENEFIT’

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CV disease occurs early and is the leading cause of mortality in patients with T2D

CV disease can occur

10–15 years earlier

in patients with diabetes compared with those without diabetes[1]

Despite advances in standard of care, most patients with T2D

die from CV disease[2]

CV, cardiovascular; T2D, type 2 diabetes

1. Booth GL *et al. Lancet* 2006;368:29; 2. Morrish NJ *et al. Diabetologia* 2001;44(Suppl 2):S14 3. das sr et al JACC , 2 0 1 8 : 3 2 0 0 – 2 3

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Science…

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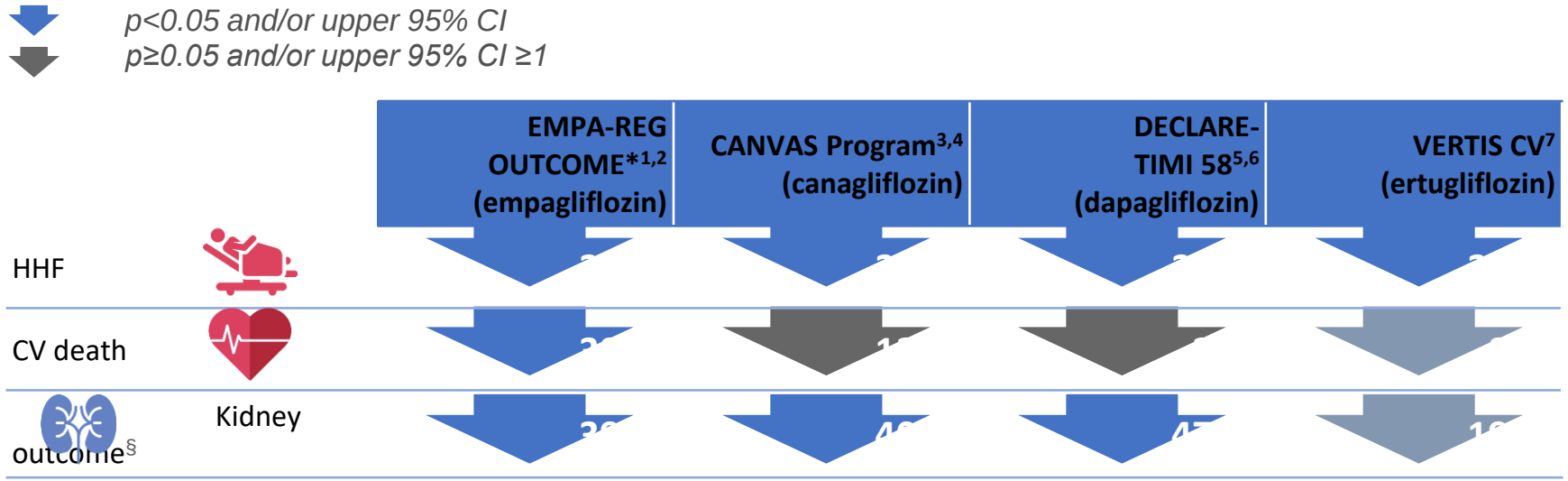
In CVOTs, SGLT2 inhibitors have demonstrated



See slide notes for footnotes

Comparison of studies should be interpreted with caution due to differences in study design, populations and methodology

CV, cardiovascular; CVOT, cardiovascular outcomes trial; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HHF, hospitalisation for heart failure;
RRT, renal replacement therapy; SGLT2, sodium-glucose co-transporter-2; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio

1. Zinman B *et al. N Engl J Med* 2015;373:2117; 2. Wanner C *et al. N Engl J Med* 2016;375:323; 3. Neal B *et al. N Engl J Med* 2017;377:644; 4. Radholm K *et al. Circulation* 2018;138:458–68; 5. Wiviott SD *et al. N Engl J Med* 2019;380:347; 6. Mosenzon O *et al. Lancet Diabetes Endocrinol* 2019;7:606; 7. Cannon CP *et al*. *N Engl J Med* 2020;383:1425

EMPA-REG OUTCOME[2]

(N=7,020)

Placebo MACE rate
43.9/1000 pt-yrs

CANVAS[3]

(N=10,142)

Placebo MACE rate
31.5/1000 pt-yrs

DECLARE[4,5]

(N=17,160)

Placebo MACE rate
24.2/1000 pt-yrs

CV, cardiovascular; eCVD, established CV disease; MACE, major CV events; SGLT-2i, sodium glucose co-transporter 2 inhibitor; T2D, type 2 diabetes

1. Einarson TR, et al. *Cardiovasc Diabetol* 2018;17:83; **2**. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128; **3**. Neal B, et al. *N Engl J Med* 2017;377:644–657; **4**. Raz I, et al. *Diabetes Obes Metab* 2018;20:1102–1110; **5** Wiviott SD et al. Online ahead of print. *N Engl J Med*. 2018

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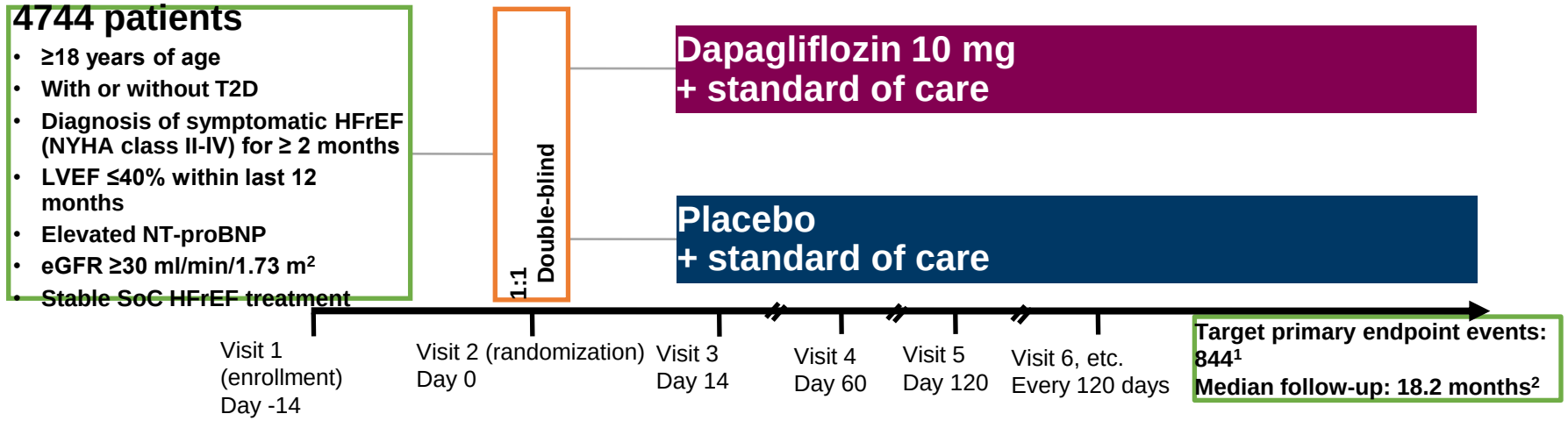
Dapagliflozin

DAPA-HF Assessing Dapagliflozin in Patients with



Primary Endpoint

- Time to first occurrence of any of the components of the composite: CV death or hHF or an urgent HF visit

Secondary Endpoints

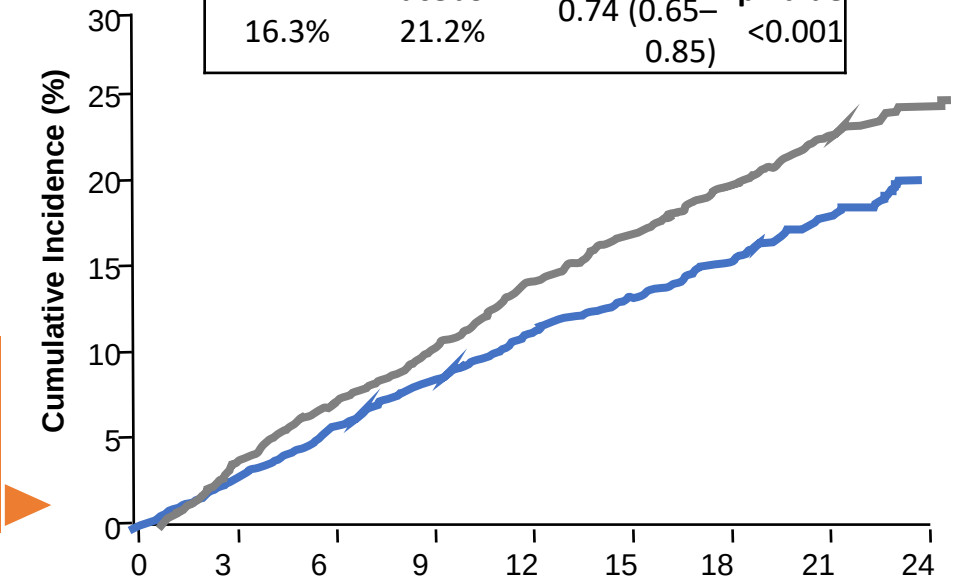
- Time to first occurrence of either of the components of the composite: CV death or hHF
- Total number of (first and recurrent) hHF and CV death
- Change from baseline measured at 8 months in the total symptom score of the KCCQ
- Time to first occurrence of any of the components of the composite: ≥50% sustained decline in eGFR or reaching ESRD or renal death
- Time to death from any cause

CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease; HbA1c = glycated hemoglobin; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; hHF = hospitalization for heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; SoC = standard of care; T2D = type 2 diabetes.

1. McMurray JJV et al. Article and supplementary appendix. *Eur J Heart Fail.* 2019;21:665-675; 2. McMurray J. Presentation at: European Society of Cardiology Congress. September 1, 2019; Paris, France; 3. Study NCT03036124. ClinicalTrials.gov website. Accessed August 19, 2019. 4. McMurray JJV et al. *Eur J Heart Fail.* 2019;doi: 10.1002/ejhf.1548. Accessed July 16, 2019.

Dapagliflozin Significantly Reduced the Relative Risk of CV Death or Worsening HF[a] on

DAPA	Placebo	HR (95% CI)	p-value
16.3%	21.2%	0.74 (0.65–0.85)	<0.001



26% RRR

4.9% ARR

NNT=21

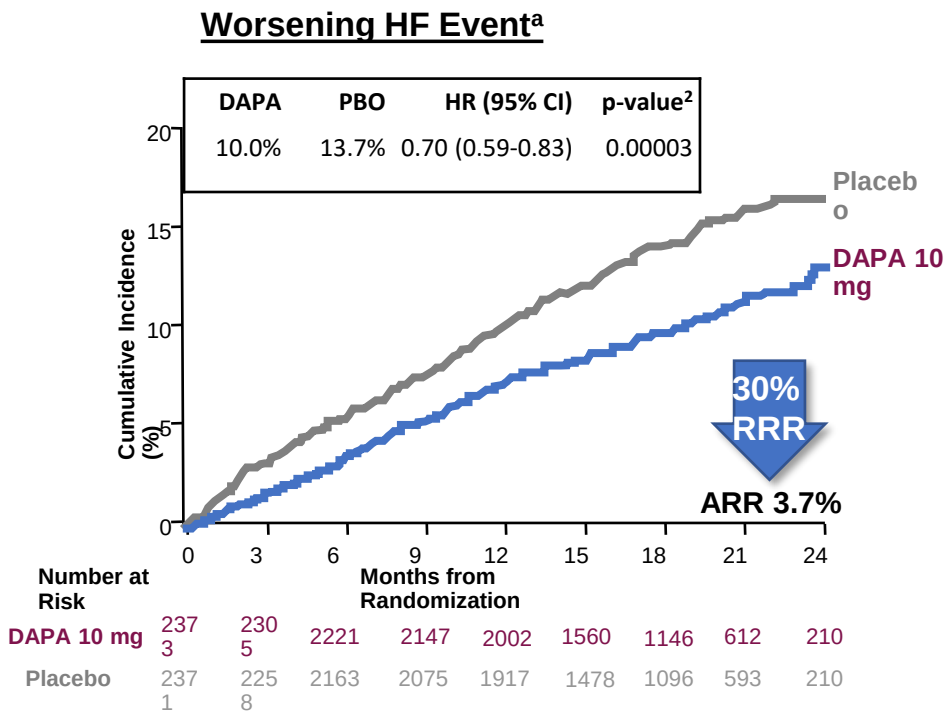
Primary endpoint was statistically significant as early as Day 28[2]

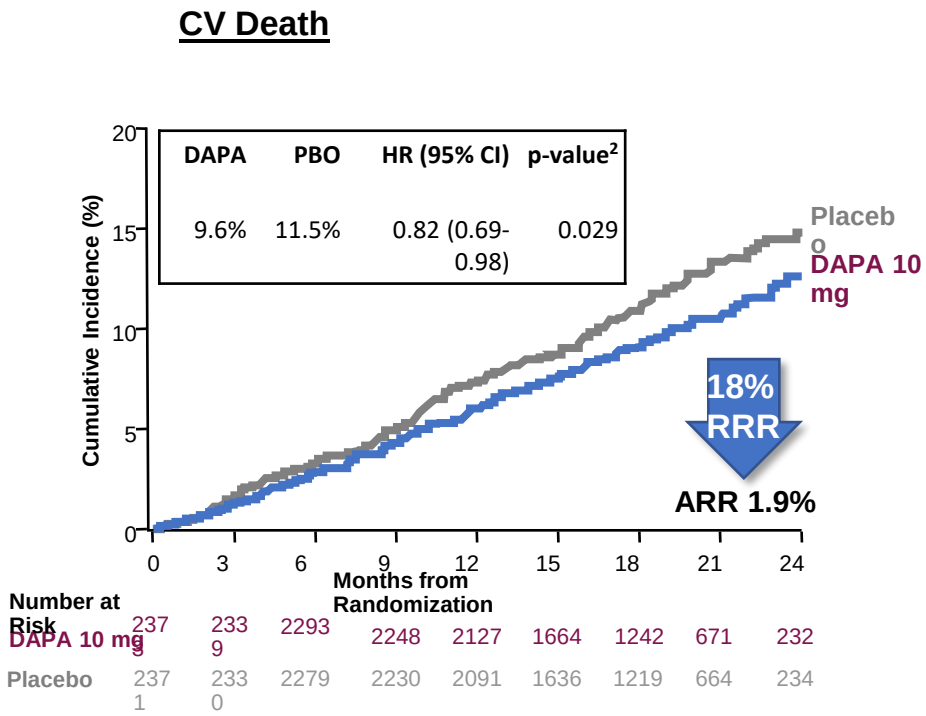
Number at Risk

DAPA 10 mg	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

[a]Worsening HF includes hHF or urgent HF visit.
ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; NNT = number needed to treat; RRR = relative risk reduction.
1. McMurray JJV et al. *N Engl J Med*. 2019;381:1995-2008; 2. Sabatine MS et al. Presented at: AHA Scientific Sessions; November 16-18, 2019; Philadelphia, PA.

Individual Components of the Primary





[a]Worsening HF includes hHF or urgent HF visit.
ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; HR = hazard ratio; PBO = placebo; RRR = relative risk reduction.
1. McMurray JJV et al. *N Engl J Med*. 2019;381:1995-2008; 2. McMurray J. Presented at: ESC Congress; August 31-September 4, 2019; Paris, France.

Empagliflozin

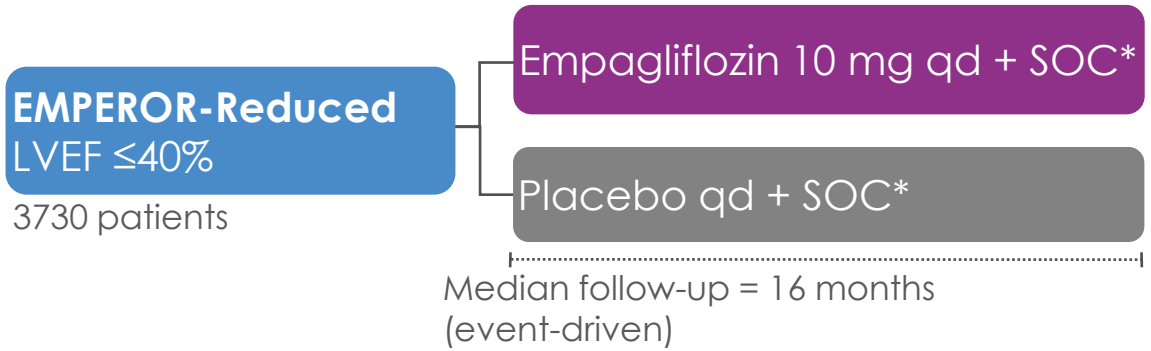
EMPEROR-Reduced

Phase III randomised double-blind placebo-controlled trial

Aim: To investigate the safety and efficacy of empagliflozin versus placebo on top of guideline-directed medical therapy in patients with HF with reduced ejection fraction

Population: T2D and non-T2D, aged ≥18 years, chronic HF (NYHA class II–IV)

Study design[1-3]



Confirmatory endpoints[1,2]

COMPOSITE PRIMARY ENDPOINT

Time to first event of adjudicated CV death or adjudicated HHF

SECONDARY ENDPOINTS

- First and recurrent adjudicated HHF events
- Slope of change in eGFR (CKD-EPI) from baseline

*Guideline-directed medical therapy

CV, cardiovascular; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalisation for heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; qd, once daily; SOC, standard of care; T2D, type 2 diabetes

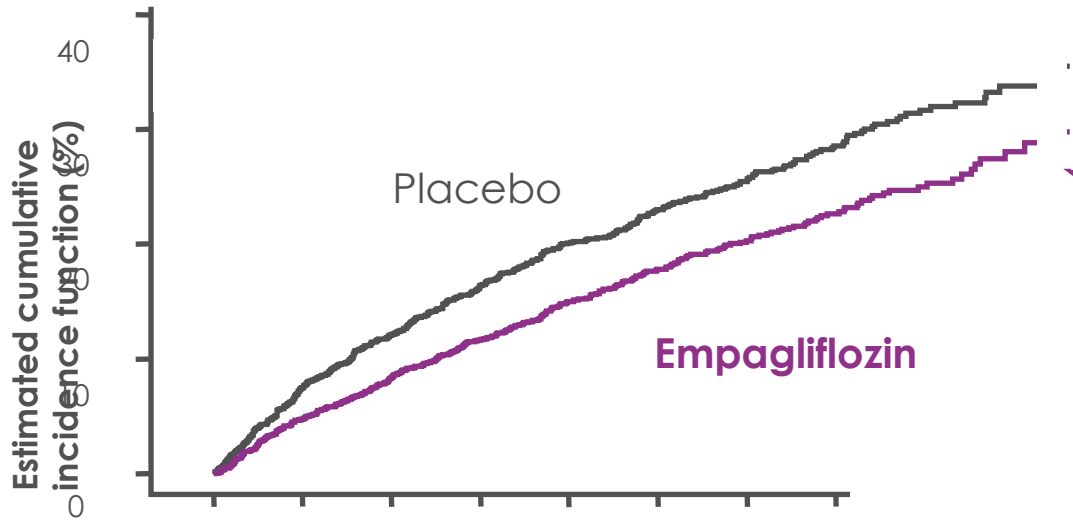
1. ClinicalTrials.gov. NCT03057977 (accessed Jan 2021); 2. Packer M *et al. Eur J Heart Fail* 2019;21:1270; 3. Packer M *et al. N Engl J Med* 2020;383(15):1413.

Trial inclusion and exclusion criteria

Inclusion criteria[1,2]	
Age ≥18 years (Japan, age ≥20 years) at screening	
Chronic HF NYHA class II–IV	
HFrEF (LVEF ≤40%) and elevated NT-proBNP	
EF (%)	**NT-proBNP (pg/ml)** Patients without AF*
≥36 to ≤40	≥2500
≥31 to ≤35	≥1000
≤30	≥600
Dose of medical therapy for HF that is consistent with CV guidelines stable for ≥1 week prior to screening and throughout screening period	
Further inclusion criteria apply	

Exclusion criteria[1,2]
MI, coronary artery bypass graft surgery or other major CV surgery, stroke or TIA ≤90 days before Visit 1
Heart transplant recipient, or listed for heart transplant
Acute decompensated HF
SBP ≥180 mmHg at Visit 2
Symptomatic hypotension and/or a SBP <100 mmHg
eGFR <20 ml/min/1.73 m^2 or requiring dialysis
Further exclusion criteria apply

Primary endpoint: First adjudicated CV death or hospitalisation for heart failure



Patients at risk										
Placebo	1867	1715	1612	1345	1108	854	611	410	224	109
Empagliflozin	1863	1763	1677	1424	1172	909	645	423	231	101

RR
5%

RR
2%

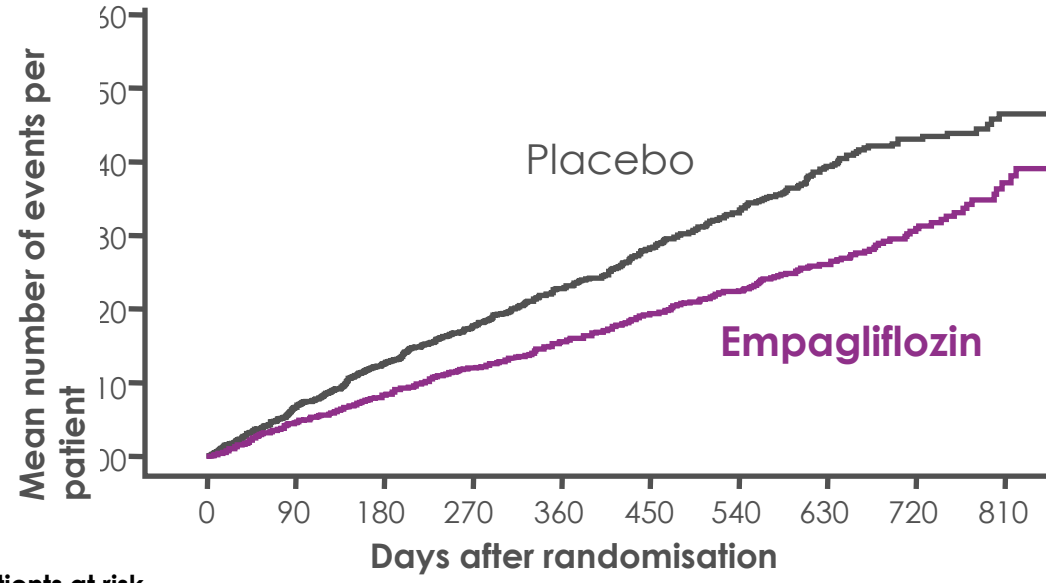
NNT = 19

HR 0.75
(95% CI 0.65, 0.86)
p<0.001

Empagliflozin:
361 patients with event
Rate: 15.8/100 patient-years

Placebo:
462 patients with event
Rate: 21.0/100 patient-years

Cox regression model including covariates age, baseline eGFR, geographic region, baseline diabetes status, sex, LVEF and treatment
ARR, absolute risk reduction; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LVEF, left ventricular ejection fraction; NNT, Number needed to treat; RRR, relative risk reduction.
Packer M *et al. N Engl J Med* 2020;383(15):1413.



Patients at risk

Placebo	1867	1820	1762	1526	1285	1017	732	497	275	135
Empagliflozin	1863	1826	1768	1532	1283	1008	732	495	272	118

RR
0%

HR 0.70
(95% CI 0.58, 0.85)
p<0.001

Emagliflozin: 388 events
Placebo: 553 events

Analysis of first and recurrent HHF accounting for CV death as terminal event using a joint frailty model. Model includes covariates age, baseline eGFR, treatment, region, baseline diabetes status, sex, and baseline LVEF, estimated dependence between adjudicated HHF and adjudicated CV death, and variance of frailty. CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalisation for heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction

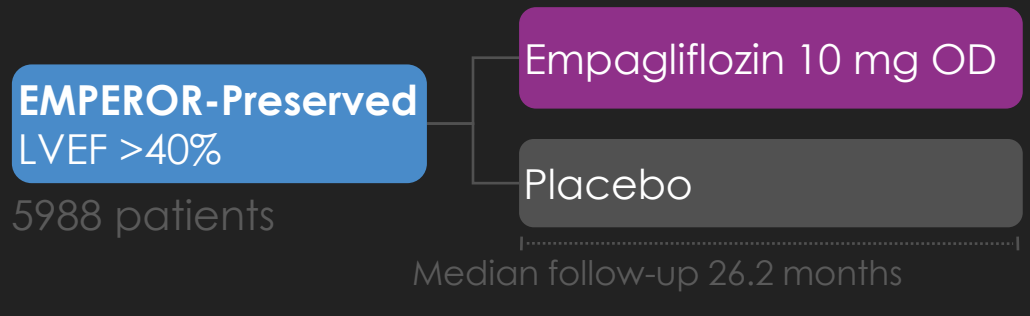
Packer M *et al. N Engl J Med* 2020;383(15):1413.

EMPEROR-PRESERVED STUDY DESIGN

Phase III trial* in patients with HFpEF

Aim: To investigate the safety and efficacy of empagliflozin versus placebo in patients with HF with preserved ejection fraction

Population: T2D and non-T2D, aged ≥18 years, chronic HF (NYHA class II–IV)



COMPOSITE PRIMARY ENDPOINT

Time to first event of adjudicated CV death or adjudicated HHF

CONFIRMATORY KEY SECONDARY ENDPOINTS

First and recurrent adjudicated HHF

Slope of change in eGFR (CKD-EPI) from baseline

*Randomized, double-blind, placebo-controlled trial.

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; OD, once daily.

Anker S *et al. N Engl J Med*. 2021;XX:XXX.

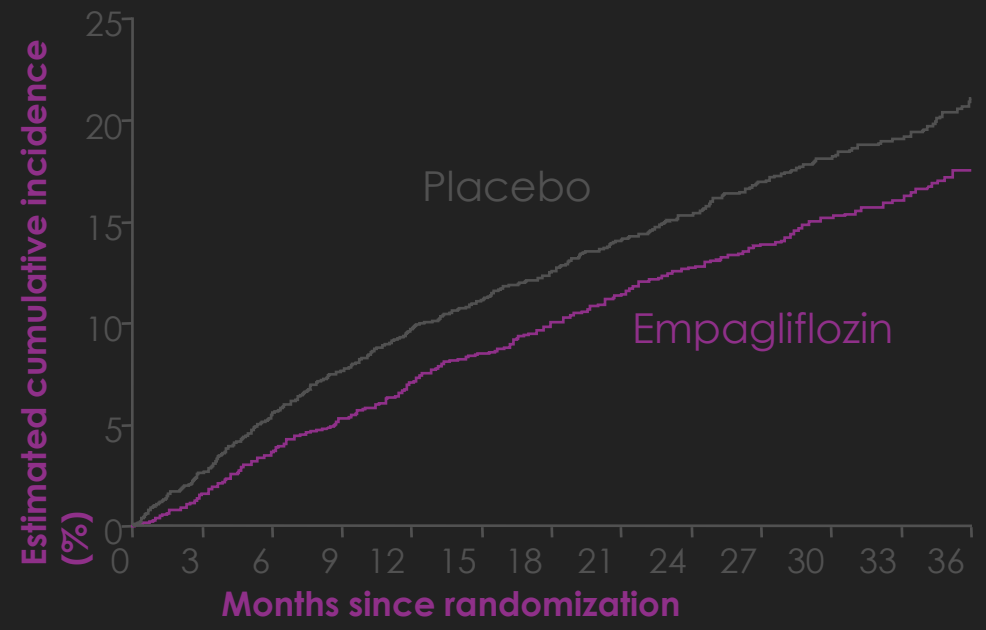
EMPEROR-PRESERVED: INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria	Exclusion criteria

• Age ≥18 years
• Chronic HF NYHA class II–IV
• **LVEF >40%**
• **NT-proBNP:**
  • **>300 pg/mL** in patients without AF
  • **>900 pg/mL** in patients with AF
• **Structural changes in the heart** (increases in left atrial size or left ventricular mass) **or HHF within 12 months of screening**
	• MI, coronary artery bypass graft surgery or other major CV surgery, stroke or TIA ≤90 days before visit
	• Heart transplant recipient, or listed for heart transplant
	• Acute decompensated HF
	• SBP ≥180 mmHg at randomization
	• Symptomatic hypotension and/or SBP <100 mmHg
	• eGFR <20 mL/min/1.73 m^2 or requiring dialysis
	
	Further criteria apply

SBP, systolic blood pressure; TIA, transient ischaemic attack.
Anker S *et al. N Engl J Med*. 2021;XX:XXX.

EMPAGLIFLOZIN DEMONSTRATED A CLINICALLY MEANINGFUL 21% RRR IN THE COMPOSITE PRIMARY ENDPOINT OF CV DEATH OR HHF



Patients at risk													
Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

RRR 21%

ARR 3.3%

NNT*=31

HR: 0.79
(95% CI: 0.69, 0.90)
p<0.001

Empagliflozin:
415 (13.8%) patients with event
Rate: 6.9/100 patient-years

Placebo:
511 (17.1%) patients with event
Rate: 8.7/100 patient-years

still to come

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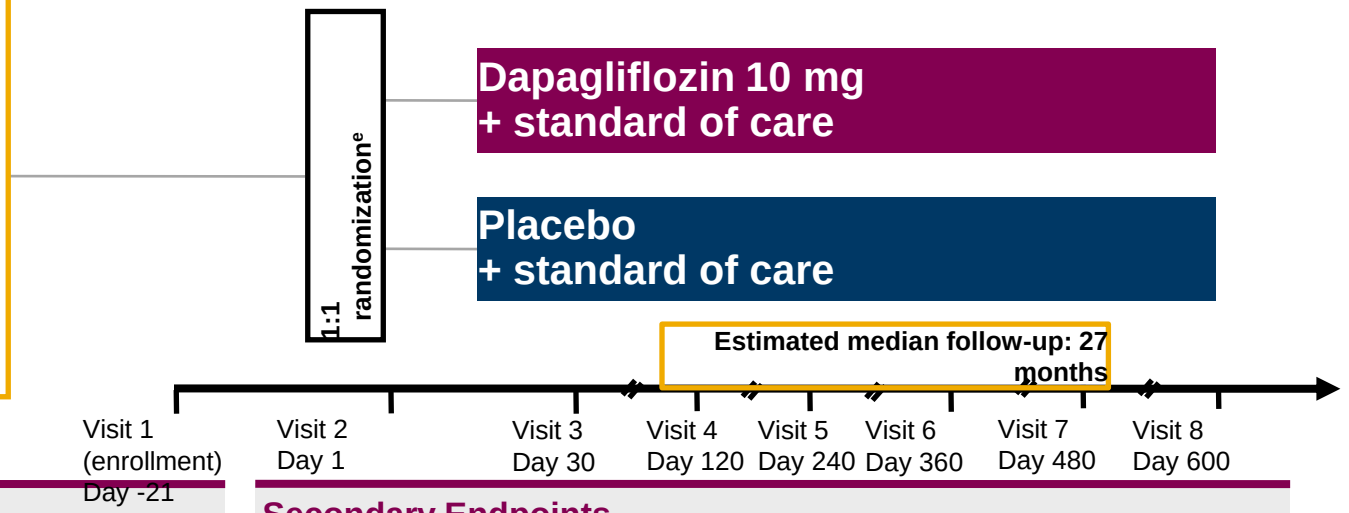
6263 Patients

- ≥40 years of age with or without T2D
- LVEF >40%[a] and evidence of structural heart disease[b] within 12 months
- Symptomatic NYHA Class II-IV HF at enrollment and typical signs/symptoms of HF ≥6 weeks before enrollment with at least intermittent need for diuretic treatment
- Elevated NT-proBNP levels
- eGFR[c] ≥25 mL/min/1.73 m^2
- Ambulatory or hospitalized off IV HF therapy[d] for ≥24 hours



Primary Endpoint

- Time to first occurrence of any component of the composite of CV death or worsening HF events (hHF or urgent HF visit) assessed in dual primary analyses
  - ✞ Full patient population
  - ✞ Patients with LVEF <60%

Secondary Endpoints

- Total number of HF events (first and recurrent) and CV deaths in the full patient population and in patients with LVEF <60%
- Change from baseline in KCCQ-TSS at 8 months
- Time to occurrence of CV death
- Time to occurrence of death from any cause

A prespecified pooled analysis from DAPA-HF and DELIVER is planned to assess the effect of dapagliflozin across the range of LVEF

[a]Patients with an LVEF <40% before the qualifying LVEF measurement could be included; [b]LV hypertrophy or LA enlargement; [c]Based on Chronic Kidney Disease-Epidemiology Collaboration Equation; [d]Including diuretics; [e]Stratified by T2D status (established diagnosis/HbA1c ≥6.5% at enrollment).

1. Solomon SD et al. *Eur J Heart Fail.* 2021;23(7):1217-1225; 2. Solomon SD et al. *JACC Heart Fail*. 2022;10(3):184-197.

WhERE to

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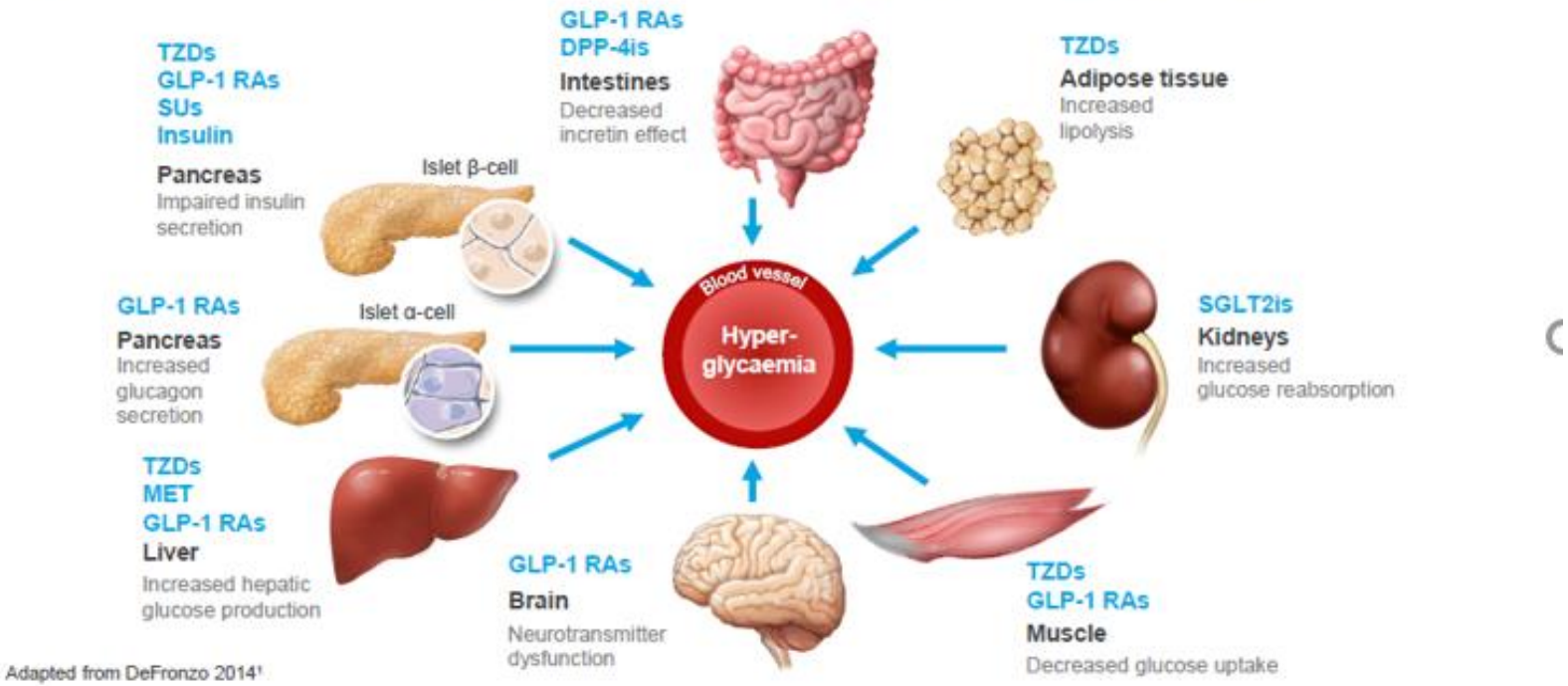
Classes of Diabetes Therapies

There are a number of different classes of antidiabetic agents for T2D, with varying targets as shown below.[1-3] This section will cover each drug class in more detail.



Adapted from DeFronzo 2014[1]

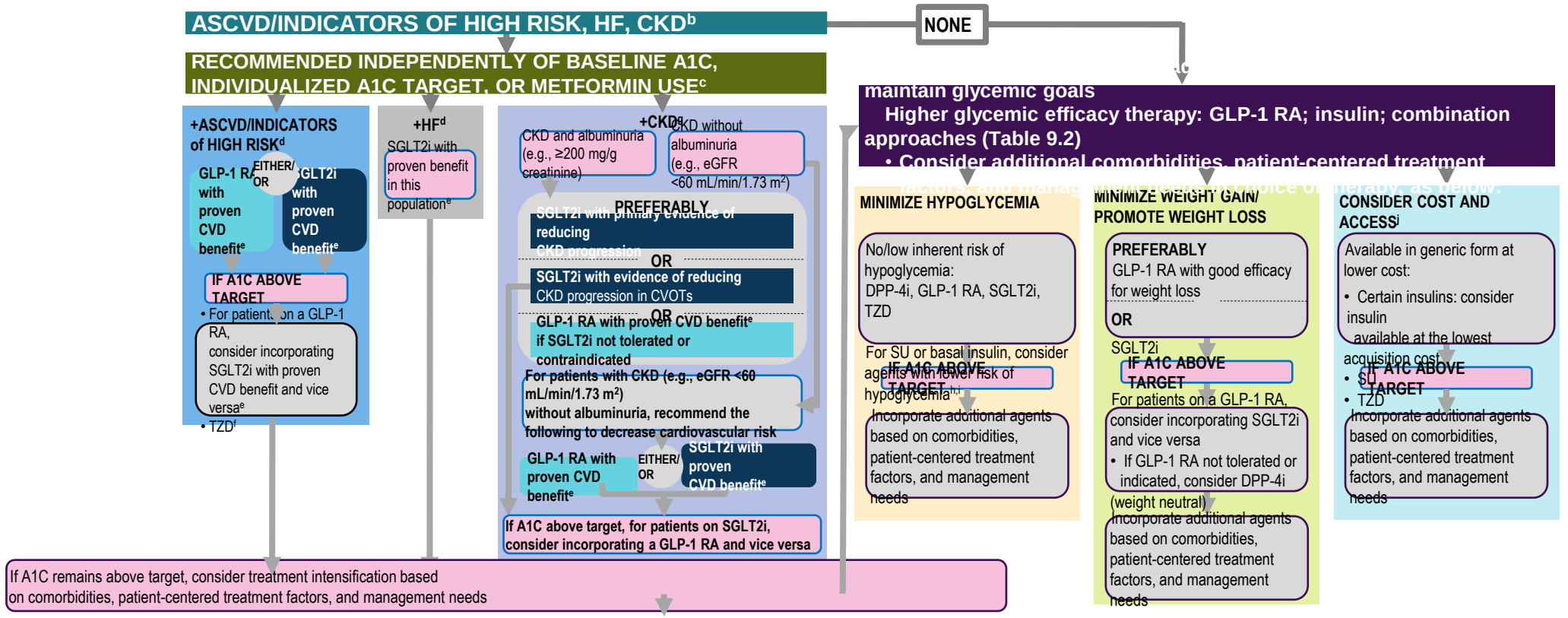
1. DeFronzo RA, et al. *Diabetes spectr* 2014;27(4):100-112. 2. Smith CJ et al. *Br J Cardiol* 2010;17:279-282. 3. Cavaiola TS, Pettus J, *Management Of Type 2 Diabetes: Selecting Amongst Available Pharmacological Agents*. Available at: https://www.ncbi.nlm.nih.gov/books/NBK425702. Accessed: July 2018.

2017 SEMDSA algorithm for the management of type 2 diabetes in non-pregnant adults without metabolic decompensation or cardiovascular disease

2022 ADA Standards of Care
Pharmacologic Treatment of Hyperglycemia in Adults with T2D

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

FIRST-LINE THERAPY depends on comorbidities, patient-centered treatment factors, including cost and access considerations, and management needs and generally includes metformin and comprehensive lifestyle modification[a]

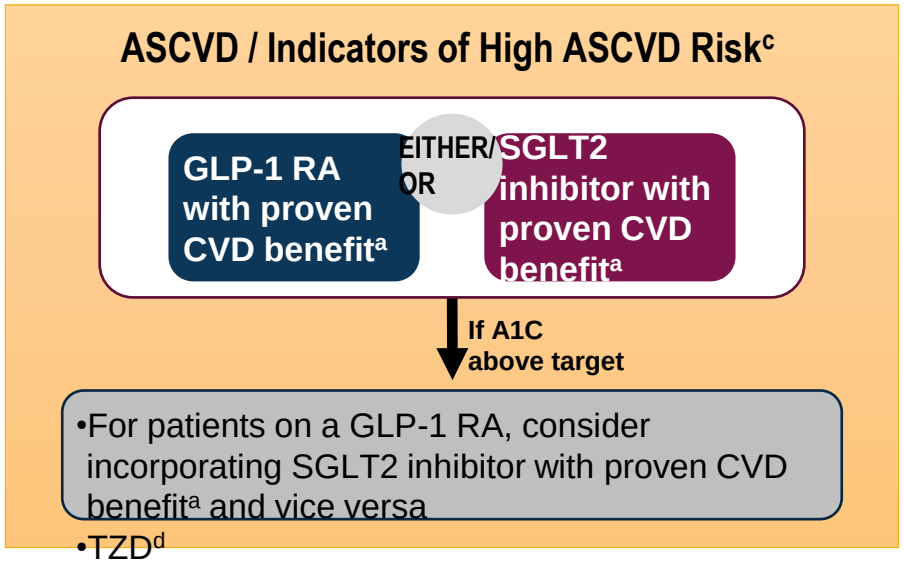


To avoid therapeutic inertia reassess and modify treatment regularly (3-6 months). [a]For adults with overweight or obesity, lifestyle modification to achieve and maintain ≥5% weight loss and ≥150 min/week of moderate- to vigorous-intensity physical activity is recommended (See Section 5: Facilitating Behavior Change and Well-being to Improve Health Outcomes); [b]Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications; [c]Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy; [d]Refer to Section 10: Cardiovascular Disease and Risk Management; [e]Proven benefit refers to label indication (see Table 9.2); [f]Low dose may be better tolerated though less well studied for CVD effects; [g]Refer to Section 11: Chronic Kidney Disease and Risk Management and specific medication label for eGFR criteria; [h]Choose later generation SU to lower risk of hypoglycemia; [i]Risk of hypoglycemia: degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin; [j]Consider country- and region-specific cost of drugs.

American Diabetes Association. *Diabetes Care*. 2022;45(suppl 1):S1-S264.

2022 ADA Standards of Care
Treatment of Patients With T2D and ASCVD/Indicators of High

Use of SGLT2 inhibitors or GLP-1 receptor agonists with proven CVD benefit[a] recommended regardless of baseline A1C, individualized A1C target, or metformin use[b]

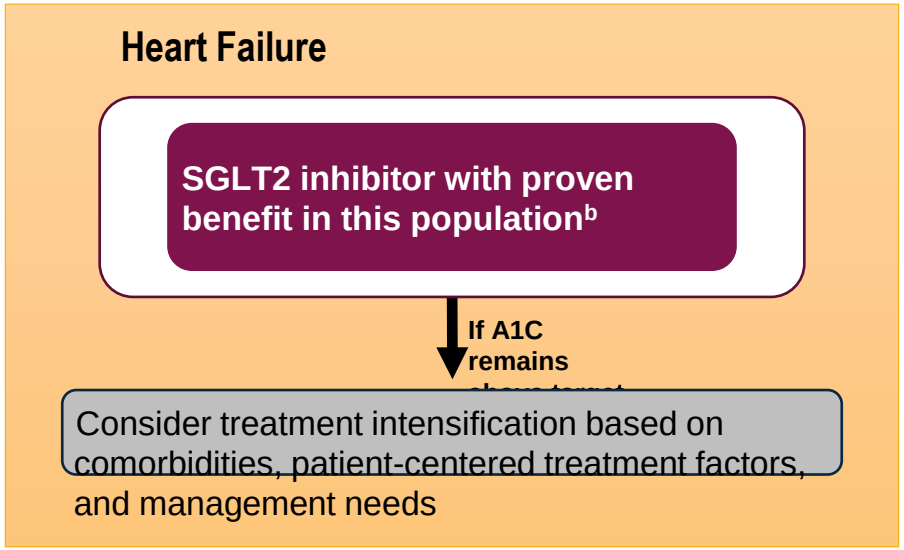


[a]Proven benefit refers to label indication; [b]Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy; [c]Age ≥55 years with coronary, carotid or lower-extremity artery stenosis >50% or LVH; [d]Low dose may be better tolerated though less well studied for CVD effects.

A1C = glycated hemoglobin; ADA = American Diabetes Association; ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; GLP-1 RA = glucagon-like peptide-1 receptor antagonist; LVH = left ventricular hypertrophy; SGLT2 = sodium-glucose cotransporter 2; T2D = type 2 diabetes; TZD = thiazolidinedione.

Adapted from American Diabetes Association. Diabetes Care. 2022;45(suppl 1):S1-S264.

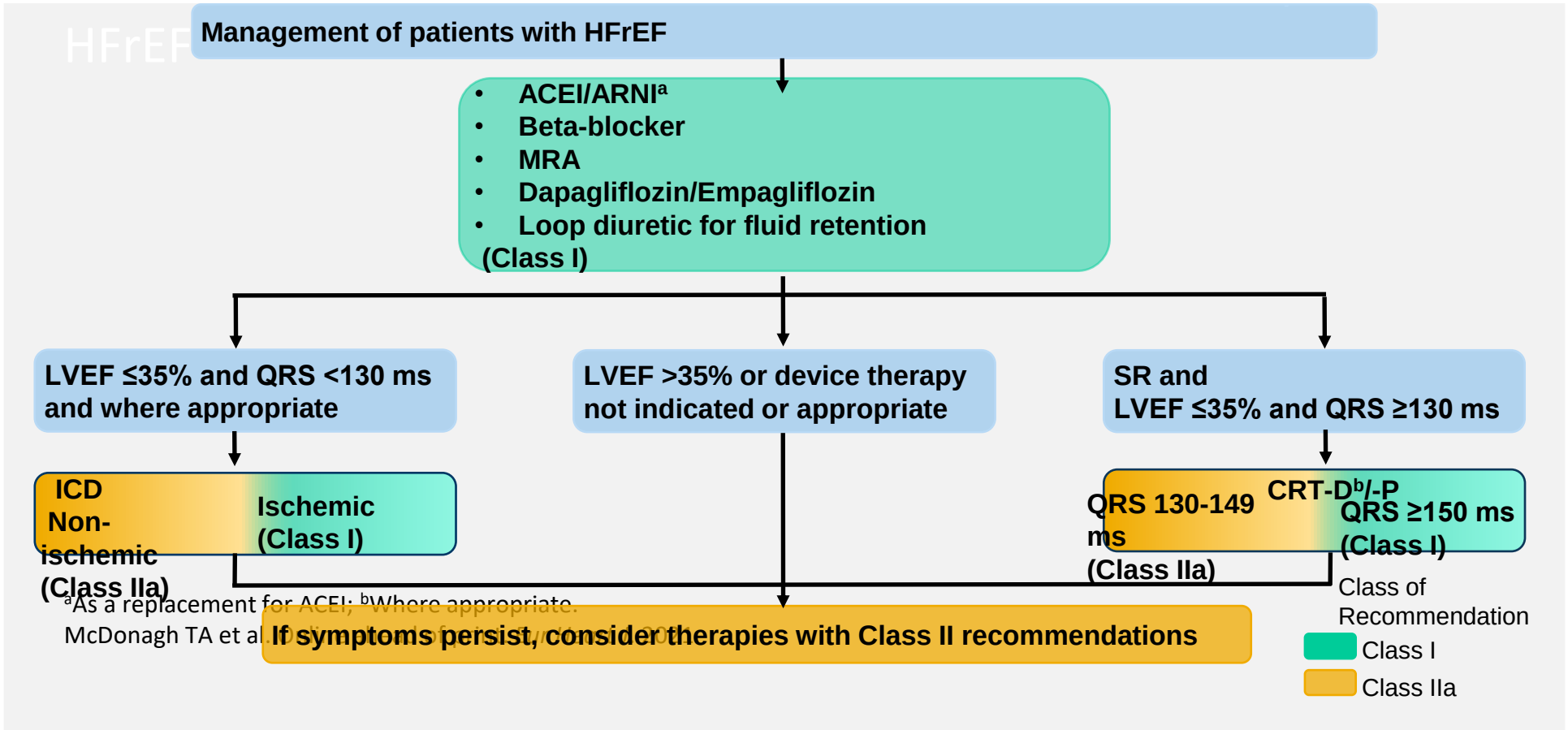
Use of SGLT2 inhibitors recommended regardless of baseline A1C, individualized A1C target, or metformin use[a]



[a]Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy; [b]Proven benefit refers to label indication.

A1C = glycated hemoglobin; ADA = American Diabetes Association; SGLT2 = sodium-glucose cotransporter 2; T2D = type 2 diabetes.

Adapted from American Diabetes Association. *Diabetes Care*. 2022;45(suppl 1):S1-S264.



[a]As a replacement for ACEI; [b]Where appropriate.

McDonagh TA et al.

TAKE HOME MESSAGE:

DM2
Established CVD
High CVD risk
HF

CONSIDER SGLT2I (read PI!)