# DIABETES MELLITUS IN SPECIAL GROUPS

DIABETIC KIDNEY DISEASE

THE ELDERLY

ADOLESCENTS

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# EDUCATIONAL OBJECTIVES

1. **DM in patients with DKD**
   a) What should be the blood pressure treatment goals?
   b) What are the preferred treatment agents for hypertension?
   c) What should be the HbA1c goal?
   d) Update: Roles of newer DM agents in patients with DKD
   e) Adjusting DM medications in CKD
2. **DM in the elderly**
   a) Simplifying insulin treatment
   b) Choosing non-insulin DM drugs
3. **DM in adolescents**
   a) Clinical points to note

1)

# BP GOALS

## IN DIABETIC KIDNEY DISEASE

# 1) BP GOALS IN CKD

A 52 year old Chinese man with T2DM complicated by retinopathy, neuropathy and stage 3 CKD (eGFR 40ml/min) from diabetic nephropathy comes to your office for routine follow-up care.

He is currently treated with basal insulin glargine 12 units at bedtime, linagliptin 5mg OM and glipizide 5mg OM.

His BP is 150/95mmHg.

Key laboratory values include: serum potassium 4.7 mmol/L, serum creatinine 1.5mg/dL (132umol/L), urine albumin:creatinine ratio 90mg/mmol/ (severe albuminuria), HbA1c 7.1%.

**What should the BP goal be for this patient ?**

a) Although lower BP decreases cardiovascular events, it has no impact on clinically meaningful renal outcomes

b) 140/90 mmHg

c) 130/80 mmHg

d) It depends on the patient's age, with a goal of <150/95 mmHg in patients older than 65 years

# 1) BP GOALS IN CKD

"Several large scale land mark clinical RCTs have consistently demonstrated the benefit of BP lowering and incident nephropathy (defined as progression of albuminuria and/or worsening of serum creatinine). **A target blood pressure of 130/80 mmHg appears reasonable. The benefit of further blood pressure lowering is unproven and may potentially be hazardous in individuals with pre-existing coronary artery disease.** "

Singapore MOH DM Guidelines 2014

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Singapore MOH DM Guidelines 2014

# 1) BP GOALS IN CKD

"Randomised clinical trials have demonstrated unequivocally that treatment of hypertension to blood pressure <140/90 mmHg reduces cardiovascular events as well as microvascular complicatons. **Therefore, patients with type 1 or type diabetes who have hypertension should, at minimum, be treated to blood pressure targets of <140/90mmHg…it may be reasonable to target blood pressure <130/80 mmHg among patients with diabetes and either clinically diagnosed cardiovascular disease (particularly stroke) or 10-year ASCVD risk >=15% if it can be attained safely.** "

American Diabetes Association Standards of Medical Care in Diabetes 2019

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American Diabetes Association Standards of Medical Care in Diabetes 2019

# 1) BP GOALS IN CKD


## How do I ascertain a high10-year ASCVD risk?

| Risk Level | Clinical Presentation of Individuals |
|---|---|
| Very high risk | (1) Individuals with established CAD, atherosclerotic cerebrovascular disease, aortic aneurysm or peripheral artery disease<br>(2) Individuals with diabetes mellitus with chronic kidney disease<br>(3) Individuals with familial hypercholesterolemia which should be suspected in patients with low density lipoprotein cholesterol (LDL cholesterol) >4.9mmol/L (190mg/dL) with diagnosis based on criteria presented on page 59). |
| High risk | (1) Individuals with moderate to severe chronic kidney disease (estimated glomerular filtration rate [eGFR] <60ml/min/1.73 $m^2$)<br>(2) Individuals with diabetes mellitus without established CAD, atherosclerotic cerebrovascular disease, aortic aneurysm or peripheral artery disease or chronic kidney disease. |

Derived from the Framingham-based NCEP ATP III 10-year Risk Score which takes into consideration age, TC, HDL, smoking and BP into the risk calculation.
These have been re-calibrated based on epidemiological data derived within each of the three ethnic groups in Singapore.
(Other risk scores tend to under-estimate CV risk in our local population)

Singapore MOH Lipids Guidelines 2016

**Table A-1 Estimation of 10-Year Coronary Artery Disease Risk for Men (CPG pg. 29)**

| Age | Points |
|---|---|
| 20-34 | -9 |
| 35-39 | -4 |
| 40-44 | 0 |
| 45-49 | 3 |
| 50-54 | 6 |
| 55-59 | 8 |
| 60-64 | 10 |
| 65-69 | 11 |
| 70-74 | 12 |
| 75-79 | 13 |

1. Estimate the individual's 10-year CAD risk by allocating points based on his age, total and HDL cholesterol levels, smoking status and systolic blood pressure (BP).
2. Check the total points against Table A-2 to estimate that individual's 10-year CAD risk.

| Total Cholesterol mmol/L (mg/dL) | Points | | | | |
|---|---|---|---|---|---|
| | Age 20-39 | Age 40-49 | Age 50-59 | Age 60-69 | Age 70-79 |
| < 4.1 (160) | 0 | 0 | 0 | 0 | 0 |
| 4.1-5.1 (160-199) | 4 | 3 | 2 | 1 | 0 |
| 5.2-6.1 (200-239) | 7 | 5 | 3 | 1 | 0 |
| 6.2-7.2 (240-279) | 9 | 6 | 4 | 2 | 1 |
| ≥ 7.3 (280) | 11 | 8 | 5 | 3 | 1 |

| Smoker | Points | | | | |
|---|---|---|---|---|---|
| | Age 20-39 | Age 40-49 | Age 50-59 | Age 60-69 | Age 70-79 |
| No | 0 | 0 | 0 | 0 | 0 |
| Yes | 8 | 5 | 3 | 1 | 0 |

| HDL Cholesterol mmol/L (mg/dL) | Points |
|---|---|
| ≥ 1.6 (60) | -1 |
| 1.3-1.5 (50-59) | 0 |
| 1.0-1.2 (40-49) | 1 |
| < 1.0 (40) | 2 |

| Systolic BP (mmHg) | Points | |
|---|---|---|
| | If untreated | If treated |
| < 120 | 0 | 0 |
| 120-129 | 0 | 1 |
| 130-139 | 1 | 2 |
| 140-159 | 1 | 2 |
| ≥ 160 | 2 | 3 |

**Table A-3 Estimation of 10-Year Coronary Artery Disease Risk for Women (CPG pg. 31)**

| Age | Points |
|---|---|
| 20-34 | -7 |
| 35-39 | -3 |
| 40-44 | 0 |
| 45-49 | 3 |
| 50-54 | 6 |
| 55-59 | 8 |
| 60-64 | 10 |
| 65-69 | 12 |
| 70-74 | 14 |
| 75-79 | 16 |

1. Estimate the individual's 10-year CAD risk by allocating points based on her age, total and HDL cholesterol levels, smoking status and systolic blood pressure (BP).
2. Check the total points against Table A-4 to estimate that individual's 10-year CAD risk.

| Total Cholesterol mmol/L (mg/dL) | Points | | | | |
|---|---|---|---|---|---|
| | Age 20-39 | Age 40-49 | Age 50-59 | Age 60-69 | Age 70-79 |
| < 4.1 (160) | 0 | 0 | 0 | 0 | 0 |
| 4.1-5.1 (160-199) | 4 | 3 | 2 | 1 | 1 |
| 5.2-6.1 (200-239) | 8 | 6 | 4 | 2 | 1 |
| 6.2-7.2 (240-279) | 11 | 8 | 5 | 3 | 2 |
| ≥ 7.3 (280) | 13 | 10 | 7 | 4 | 2 |

| Smoker | Points | | | | |
|---|---|---|---|---|---|
| | Age 20-39 | Age 40-49 | Age 50-59 | Age 60-69 | Age 70-79 |
| No | 0 | 0 | 0 | 0 | 0 |
| Yes | 9 | 7 | 4 | 2 | 1 |

| HDL Cholesterol mmol/L (mg/dL) | Points |
|---|---|
| ≥ 1.6 (60) | -1 |
| 1.3-1.5 (50-59) | 0 |
| 1.0-1.2 (40-49) | 1 |
| < 1.0 (40) | 2 |

| Systolic BP (mmHg) | Points | |
|---|---|---|
| | If untreated | If treated |
| < 120 | 0 | 0 |
| 120-129 | 1 | 3 |
| 130-139 | 2 | 4 |
| 140-159 | 3 | 5 |
| ≥ 160 | 4 | 6 |

**Table A-2 Estimation of 10-Year Coronary Artery Disease Risk for Men (CPG pg. 30)**

| Total Points | 10-Year Risk (%) | | |
|---|---|---|---|
| | Chinese | Malay | Indian |
| -1 | < 1 | < 1 | 1 |
| 0 | < 1 | < 1 | 1 |
| 1 | < 1 | 1 | 1 |
| 2 | 1 | 1 | 1 |
| 3 | 1 | 1 | 2 |
| 4 | 1 | 1 | 2 |
| 5 | 1 | 1 | 3 |
| 6 | 1 | 2 | 3 |
| 7 | 2 | 2 | 4 |
| 8 | 2 | 3 | 5 |
| 9 | 3 | 4 | 7 |
| 10 | 4 | 5 | 9 |
| 11 | 5 | 6 | 11 |
| 12 | 6 | 8 | 14 |
| 13 | 8 | 11 | 18 |
| 14 | 11 | 13 | > 20 |
| 15 | 13 | 17 | > 20 |
| 16 | 17 | > 20 | > 20 |
| ≥ 17 | > 20 | > 20 | > 20 |

**Table A-4 Estimation of 10-Year Coronary Artery Disease Risk for Women (CPG pg. 32)**

| Total Points | 10-Year Risk (%) | | |
|---|---|---|---|
| | Chinese | Malay | Indian |
| 5 | < 1 | < 1 | 1 |
| 6 | < 1 | < 1 | 1 |
| 7 | < 1 | 1 | 1 |
| 8 | < 1 | 1 | 1 |
| 9 | 1 | 1 | 2 |
| 10 | 1 | 1 | 2 |
| 11 | 1 | 2 | 3 |
| 12 | 1 | 2 | 3 |
| 13 | 1 | 3 | 4 |
| 14 | 2 | 4 | 6 |
| 15 | 3 | 5 | 7 |
| 16 | 3 | 6 | 10 |
| 17 | 4 | 8 | 12 |
| 18 | 5 | 10 | 16 |
| 19 | 7 | 13 | 20 |
| 20 | 9 | 16 | > 20 |
| 21 | 12 | 20 | > 20 |
| 22 | 15 | > 20 | > 20 |
| 23 | 19 | > 20 | > 20 |
| ≥ 24 | > 20 | > 20 | > 20 |


# VD risk?

or CV risk score >20%

Derived from the Framingham-based NCEP ATP III 10-year Risk Score which takes into consideration age, TC, HDL, smoking and BP into the risk calculation.
These have been re-calibrated based on epidemiological data derived within each of the three ethnic groups in Singapore.
(Other risk scores tend to under-estimate CV risk in our local population)

Singapore MOH Lipids Guidelines 2016

# 1) BP GOALS IN CKD

A 52 year old Chinese man wit[illegible]athy, neuropathy and stage 3 CKD (eGFR 40ml/min) from diabetic[illegible]ice for routine follow-up care.

High/Very high CV risk

He is currently treated with basal insulin glargine 12 units at bedtime, linagliptin 5mg OM and glipizide 5mg OM.

His BP is 150/95mmHg.

Key laboratory values include: serum potassium 4.7 mmol/L, serum creatinine 1.5mg/dL (132umol/L), urine albumin:creatinine ratio 90mg/mmol/ (severe albuminuria), HbA1c 7.1%.

**What should the BP goal be for this patient ?**

a) Although lower BP decreases cardiovascular events, it has no impact on clinically meaningful renal outcomes

b) 140/90 mmHg

c) 130/80 mmHg

d) It depends on the patient's age, with a goal of <150/95 mmHg in patients older than 65 years

# 1) BP GOALS IN CKD

A 52 year old Chinese man with T2DM complicated by retinopathy, neuropathy and stage 3 CKD (eGFR 40ml/min) from diabetic nephropathy comes to your office for routine follow-up care.

He is currently treated with basal insulin glargine 12 units at bedtime, linagliptin 5mg OM and glipizide 5mg OM.

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Key laboratory values include: serum potassium 4.7 mmol/L, serum creatinine 1.5mg/dL (132umol/L), urine albumin:creatinine ratio 90mg/mmol/ (severe albuminuria), HbA1c 7.1%.

**What should the BP goal be for this patient ?**

a) Although lower BP decreases cardiovascular events, it has no impact on clinically meaningful renal outcomes

b) 140/90 mmHg

c) 130/80 mmHg

d) It depends on the patie[illegible] ents older than 65 years

Hence BP goal of 130/80 mmHg or less

2)

# ANTI-HYPERTENSIVES OF CHOICE

## IN DIABETIC KIDNEY DISEASE

# 2) ANTI-HYPERTENSIVES OF CHOICE FOR DKD

52 year old Chinese man with T2DM complicated by retinopathy, neuropathy and stage 3 CKD from diabetic nephropathy comes to your office for routine follow-up care.

He is currently treated with basal insulin glargine 12 units at bedtime, linagliptin 5mg OM and glipizide 5mg OM.

His BP is 150/95mmHg.

Key laboratory values include: serum potassium 4.7 mmol/L, serum creatinine 1.5mg/dL (132umol/L), urine albumin:creatinine ratio 90mg/mmol/ (severe albuminuria), HbA1c 7.1%.

**What anti-hypertensive should be started to slow the progression of diabetic nephropathy?**

a) Add an ARB with the goal of decreasing proteinuria
b) Add an ACE-inhibitor with the goal of decreasing proteinuria
c) Add both an ARB and an ACE-inhibitor, with the goal of decreasing proteinuria
d) Add a calcium channel blocker with the goal of targeting an optimal blood pressure

# 2) ANTI-HYPERTENSIVES OF CHOICE FOR DKD

**What anti-hypertensive should be started to slow the progression of diabetic nephropathy?**

**T2DM + Hypertension + eGFR <60ml/min + severe albuminuria** ☐ ACEi or ARBs prevent CKD progression

**T2DM + Hypertension + mild/mod albuminuria** ☐ ACEi or ARBs reduce progression to more advanced albuminuria and CV events (but not progression to ESRD)

**T2DM + Hypertension (no albuminuria/CKD)** ☐ no convincing evidence that ACEi/ARB prevents development of CKD, treat with any effective anti-hypt

**T2DM + albuminuria (no Hypertension)** ☐ no clinical trials to determined whether ACEi/ABR improves renal outcomes, but often prescribed

American Diabetes Association Standards of Medical Care in Diabetes 2019

# 2) ANTI-HYPERTENSIVES OF CHOICE FOR DKD

52 year old Chinese man with T2DM complicated by retinopathy, neuropathy and stage 3 CKD from diabetic nephropathy comes to your office for routine follow-up care.

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a) Add an ARB with the goal of decreasing proteinuria
b) Add an ACE-inhibitor with the goal of decreasing proteinuria
c) Add both an ARB and an ACE-inhibitor, with the goal of decreasing proteinuria
d) Add a calcium channel blocker with the goal of targeting an optimal blood pressure

# 3) GLYCEMIC TARGETS IN DIABETIC KIDNEY DISEASE

You are seeing a 56 year old Chinese lady with T2DM for 10 years, complicated by stage 3b CKD (eGFR 40ml/min) and proliferative diabetic retinopathy. She is treated with metformin XR 1000mg OM and mixtard 34 units pre-breakfast and 28 units pre-dinner.

Her HbA1c is 9.2%.

**Are you happy with her current glycemic control?**

a) Yes, she has already developed multiple DM complications & is at risk of hypoglycaemia if I increase her insulin further. I will not uptitrate her medications any further.
b) No, I will try to get her HbA1c down to 7-8.5% instead.
c) No, I will try to get her HbA1c down to 6.5-7% instead.

3)

# GLYCAEMIC GOALS

## IN DIABETIC KIDNEY DISEASE

# GLYCEMIC GOALS IN CKD

| KDOQI Diabetes Guideline: 2012 Update | NDT (Nephrology Dialysis Transplantation) 2015 |
| --- | --- |
| HbA1c ~ 7% | |

# GLYCEMIC GOALS IN CKD

| KDOQI Diabetes Guideline: 2012 Update | NDT (Nephrology Dialysis Transplantation) 2015 |
| --- | --- |
| HbA1c ~ 7%<br><br>HbA1c > 7% for patients with diabetes who are at<br>i) at risk for hypoglycaemia or<br>ii) clinically significant co-morbidities or<br>iii) limited life expectancy | |

# GLYCEMIC GOALS IN CKD

| KDOQI Diabetes Guideline: 2012 Update | NDT (Nephrology Dialysis Transplantation) 2015 |
| --- | --- |
| HbA1c ~ 7%<br><br>HbA1c > 7% for patients with diabetes who are at<br>i) at risk for hypoglycaemia or<br>ii) clinically significant co-morbidities or<br>iii) limited life expectancy<br><br>Examples given for risk for hypoglycaemia:<br>Advanced CKD eg. stage 4 and 5<br>Treated with insulin or sulphonylureas | |

# GLYCEMIC GOALS IN CKD

| KDOQI Diabetes Guideline: 2012 Update | NDT (Nephrology Dialysis Transplantation) 2015 |
| --- | --- |
| HbA1c ~ 7%<br><br>Based on ADVANCE/ACCORD/VADT conventional group HbA1c 7.3-8.4%<br><br>HbA1c > 7% for patients with diabetes who are at<br>i) at risk for hypoglycaemia or<br>ii) clinically significant co-morbidities or<br>iii) limited life expectancy<br><br>Examples given for risk for hypoglycaemia:<br>Advanced CKD eg. stage 4 and 5<br>Treated with insulin or sulphonylureas | |

# GLYCEMIC GOALS IN CKD

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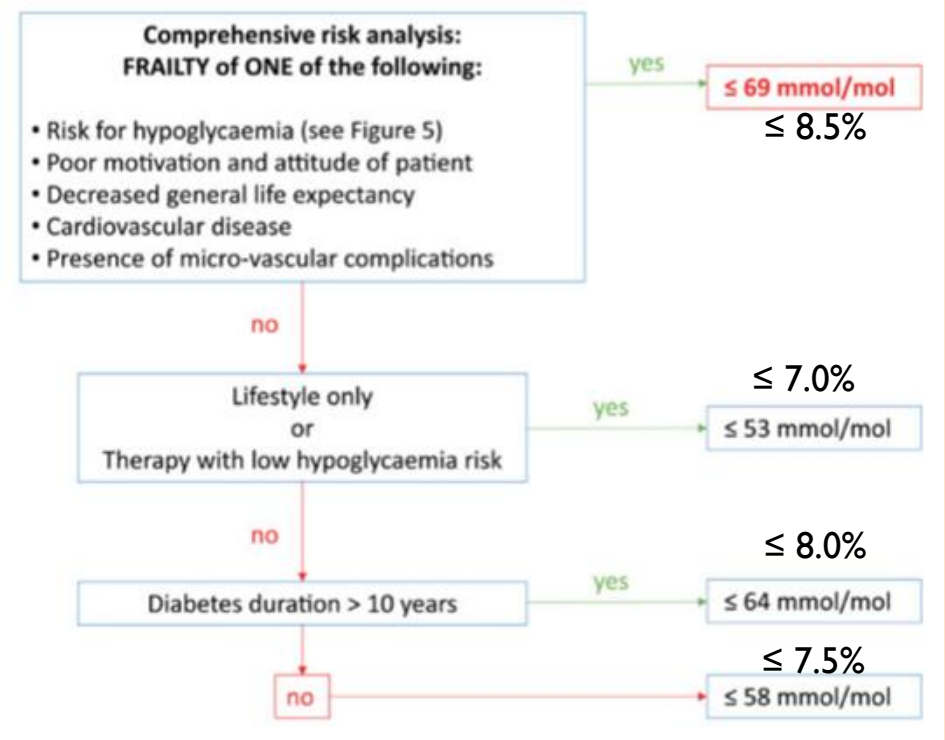
|---|---|
| HbA1c ~ 7%<br><br>Based on ADVANCE/ACCORD/VADT conventional group HbA1c 7.3-8.4%<br><br>HbA1c > 7% for patients with diabetes who are at<br>i) at risk for hypoglycaemia or<br>ii) clinically significant co-morbidities or<br>iii) limited life expectancy<br><br>Examples given for risk for hypoglycaemia:<br>Advanced CKD eg. stage 4 and 5<br>Treated with insulin or sulphonylureas |  |

# GLYCEMIC GOALS IN CKD

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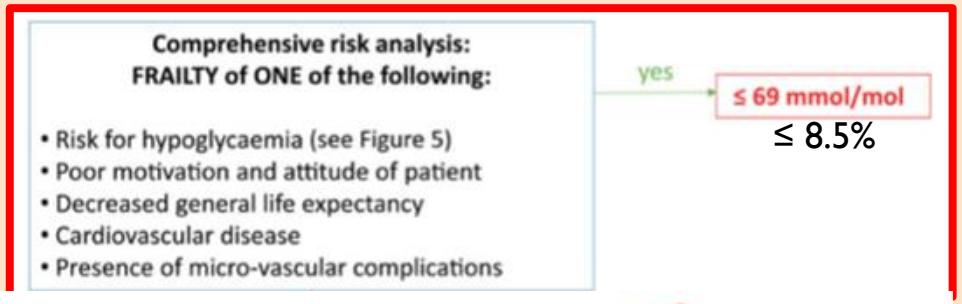
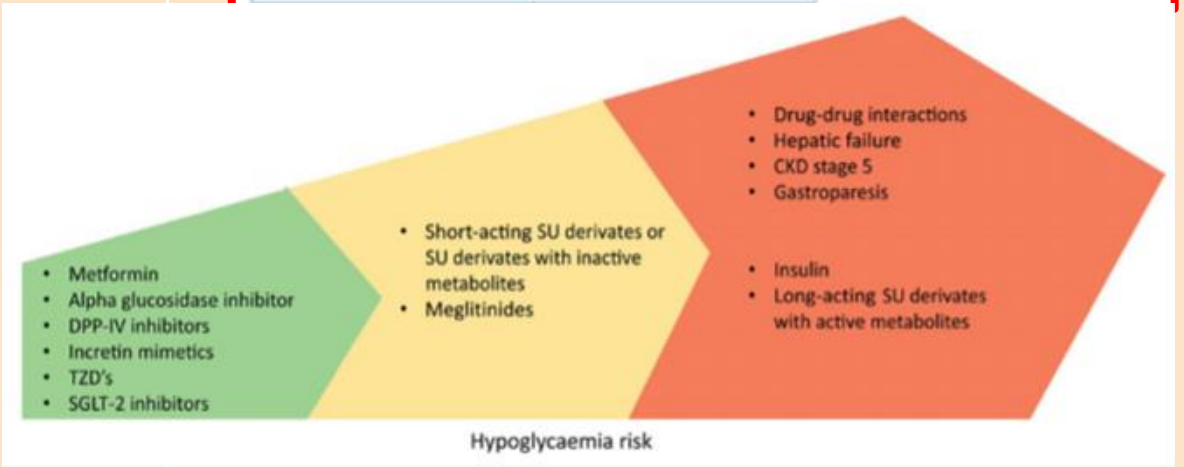
|---|---|
| HbA1c ~ 7%<br>Based on ADVANCE/ACCORD/VAD T conventional group HbA1c 7.3-8.4%<br><br>HbA1c > 7% for patients with diabetes who are at<br>i) at risk for hypoglycaemia or<br>ii) clinically significant co-morbidities or<br>iii) limited life expectancy<br><br>Examples given for risk for hypoglycaemia:<br>Advanced CKD eg. stage 4 and 5<br>Treated with insulin or sulphonylureas |  <br>  |

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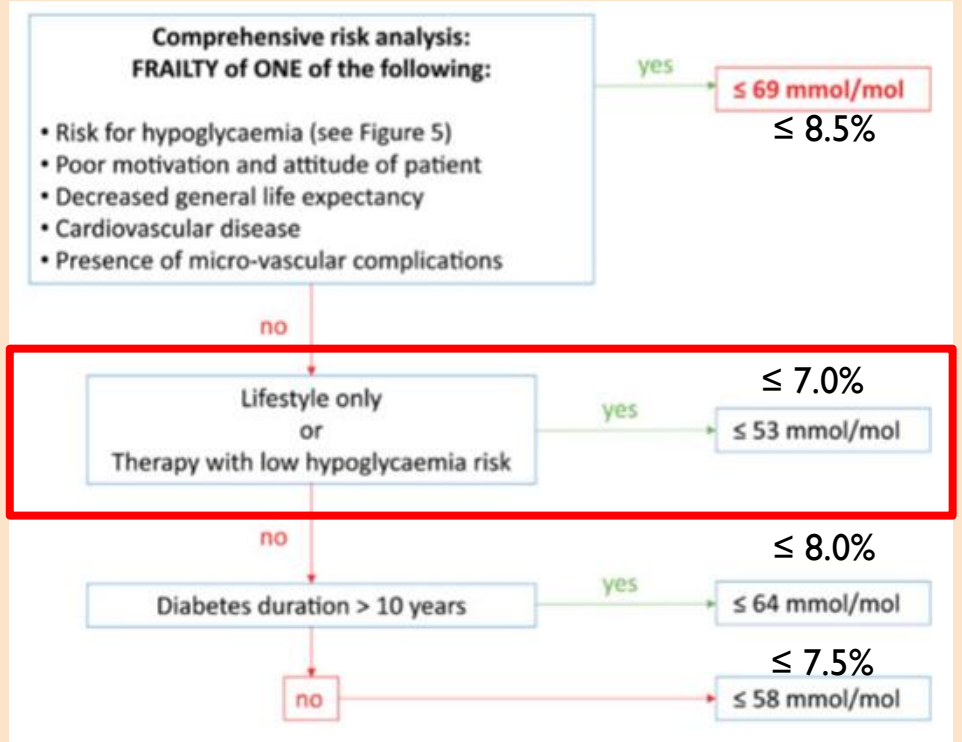
| KDOQI Diabetes Guideline: 2012 Update | NDT (Nephrology Dialysis Transplantation) 2015 |
|---|---|
| HbA1c ~ 7%<br><br>Based on ADVANCE/ACCORD/VADT conventional group HbA1c 7.3-8.4%<br><br>HbA1c > 7% for patients with diabetes who are at<br>i) at risk for hypoglycaemia or<br>ii) clinically significant co-morbidities or<br>iii) limited life expectancy<br><br>Examples given for risk for hypoglycaemia:<br>Advanced CKD eg. stage 4 and 5<br>Treated with insulin or sulphonylureas |  |

# GLYCEMIC GOALS IN CKD STAGE 5

| KDOQI Diabetes Guideline: 2012 Update | NDT (Nephrology Dialysis Transplantation) 2015 |
|---|---|
| HbA1c > 7% (Based on ADVANCE/ACCORD/VADT conventional group HbA1c 7.3-8.4%) | HbA1c ≤ 8.5% |

HbA1c levels of ~7-9% are associated with better outcomes for survival, hospitalisation and CVD in patients on hemodialysis in some but not all observational studies, but this relationship has not been tested in prospective, randomized studies

# GLYCEM TAGE 5

**KDOQI Diabetes ogy Dialysis Transplantation)**

HbA1c > 7%

HbA1c levels of ~7-9 hospitalisation and CVD in patients on hemodial is relationship has not been tested in prospective, rando

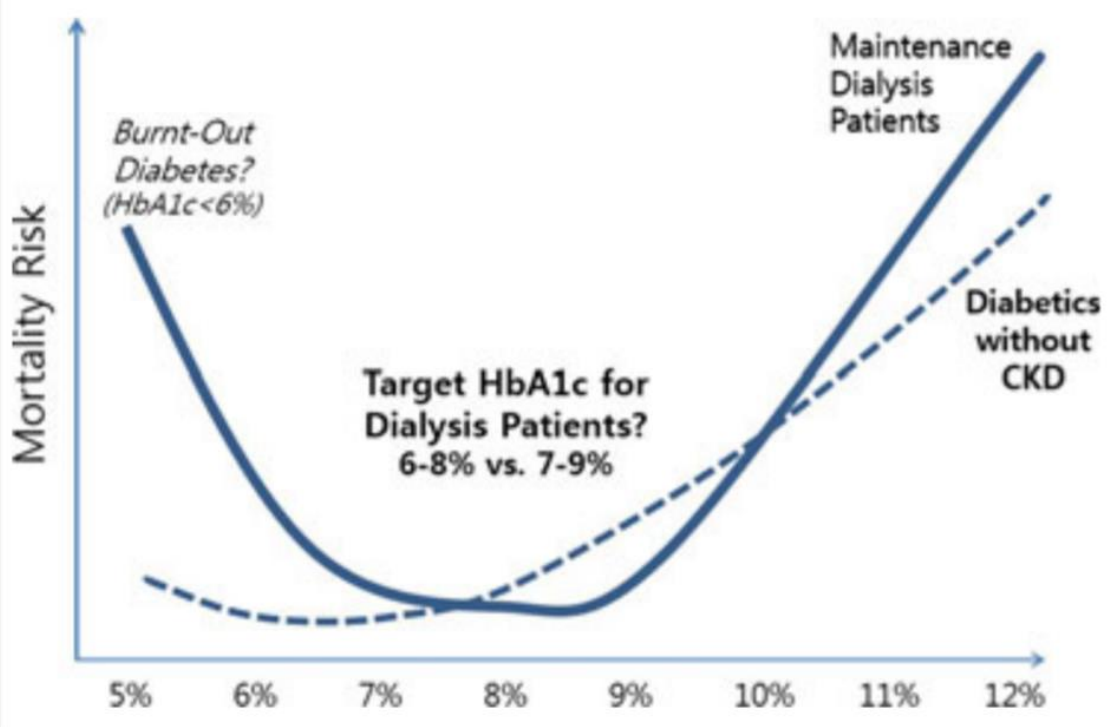


**TABLE 2. Observational studies of glycemic control and mortality in dialysis patients**

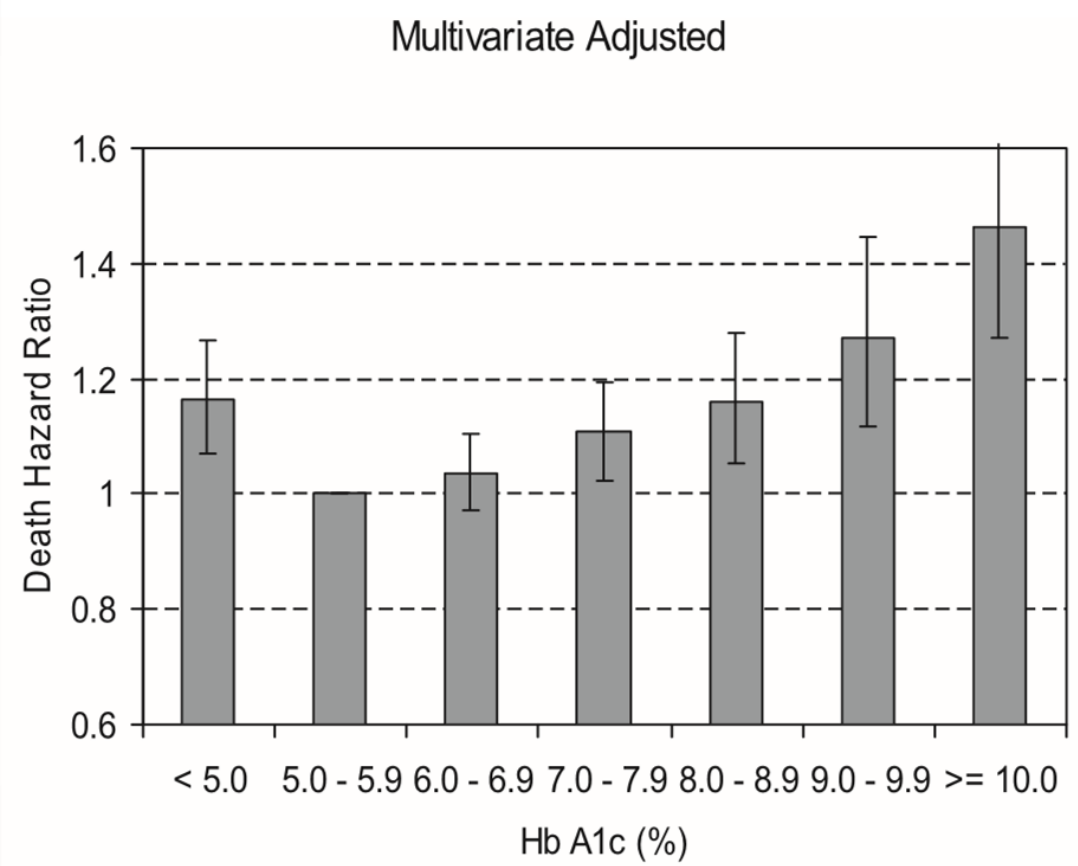
| Author | Study cohort (Country) | Exposure definition | Results |
|---|---|---|---|
| Tzamaloukas et al. (47) | 226 dialysis (PD and HD) patients with type 1 and 2 DM (USA) | Glycemic control during the 1st 6 months of study | Good glycemic control (50% of glucose measurements within acceptable range, or HbA1c 5–10%) associated with lower mortality vs. poor glycemic control (HbA1c <10%) Study limitations included lack of adjustment for confounders |
| Wu et al. (56) | 137 HD patients with type 2 DM (Taiwan) | Predialysis glycemic control within six months prior to starting HD | Good glycemic control (HbA1c 5–10%) associated with lower all-cause mortality vs. poor glycemic control (A1c >10%) |
| Yu et al. (58) | 60 PD patients with type 2 DM (Taiwan) | Predialysis glycemic control within 6 months before starting HD (measured monthly) | Good glycemic control (A1c all 5–10%) associated with lower all-cause mortality vs. poor glycemic control (A1c >10% at least once) |
| Morioka et al. (50) | 150 incident HD patients with type 1 and 2 DM (Japan) | HbA1c before HD initiation | Higher HbA1c associated with increased mortality |
| McMurray et al. (97) | 83 dialysis (HD and PD) patients with type 1 and 2 DM (USA) | Nonrandomized interventional trial of intensive education/care vs. control | Study group with decline in HbA1c from 6.9% to 6.3%; no change in HbA1c in control group Tight control improved QOL, but no improvement in survival |
| Oomichi et al. (51) | 114 HD patients with type 1 and 2 DM (Japan) | Mean HbA1c during the 3-month period prior to study entry | Higher Hb A1c (>8%) associated with increased mortality vs. HbA1c <6.5% |
| Williams et al. (68) | 24,875 HD patients with type 1 and 2 DM (USA—Fresenius) | Baseline HbA1c during the 3-month period prior to study entry | No association between HbA1c and survival Study limitations included short-term follow-up, lack of repeated measured for HbA1c, and residual confounding by malnutrition, inflammation, and anemia |
| Kalantar-Zadeh et al. (16) | 23,618 HD patients with DM (USA—DaVita) | Time-dependent HbA1c | Higher HbA1c incrementally associated with increased mortality |
| Okada et al. (98) | 78 HD patients with type 2 DM (Japan) | Mean HbA1c during 1 year period after HD initiation AND Mean HbA1c over 3 months prior to study entry | No association between HbA1c and all-cause mortality |
| Ishimura et al. (49) | 122 HD patients with type 1 and 2 DM (Japan) | Mean HbA1c of 3 values measured during 3 months prior to study entry | Higher HbA1c associated with increased mortality |
| Dreschsler et al. (48) | 1255 HD patients with type 2 DM (Germany) | Baseline HbA1c | HbA1c >8% and >6.8% associated with increased sudden cardiac death and all-cause mortality vs. ≤6% |
| Williams et al. (55) | 24,875 HD patients with type 1 and 2 DM (USA—Fresenius) | Time-dependent HbA1c | Time-dependent HbA1c <6.5% and >11% associated with increased mortality risk |
| Shurraw et al. (99) | 1454 HD patients type 1 and 2 DM (Canada) | Monthly HbA1c averaged over 3 months pre- and post-HD initiation | No association between HbA1c and mortality risk |
| Shima et al. (100) | 245 HD patients with type 1 and 2 DM (Japan) | Time-averaged HbA1c (measured monthly) | No association between HbA1c and mortality risk |
| Duong et al. (14) | 2798 PD patients with DM (USA—DaVita) | Baseline and time-averaged HbA1c | Time-averaged HbA1c levels >8% incrementally associated with increased mortality risk |
| Sturm et al. (54) | 78 dialysis (PD and HD) patients with type 1 and 2 DM | Time-varying HbA1c (measured every 3 months) | Lower HbA1c levels <7% associated with decreased mortality risk |
| Ricks et al. (53) | 54,757 HD patients with DM (USA—DaVita) | Baseline and time-averaged HbA1c | Time-averaged HbA1c >8% and <6% associated with increased mortality risk |
| Ramirez et al. (52) | 9201 HD patients with type 1 and 2 DM (USA DOPPS only) | Mean HbA1c during 1st 8 months after study entry | HbA1c <6% and ≥9% associated with increased all-cause mortality risk |
| Yoo et al. (57) | 140 PD patients with DM (Korea) | Averaged monthly or quarterly HbA1c levels during 1st year after PD initiation | All-cause and CV mortality higher in highest vs. lowest HbA1c tertile |
| Kim et al. (101) | 347 HD patients with DM (USA) | Baseline HbA1c | HbA1c <6% associated with increased all-cause mortality risk |

PD, peritoneal dialysis; HD, hemodialysis; DM, diabetes; HbA1c, hemoglobin A1c; QOL, quality of life; DOPPS, Dialysis Outcomes and Practice Patterns Study; CV, cardiovascular.

# GLYCEMIC GOALS IN CKD STAGE 5




Ricks J et al. Diabetes 61(3):708-715, 2012.
54,757 patients with DM on dialysis.
"Time averaged HbA1c >8% and <6% associated with increased mortality risk"




Kalantar-Zadeh K et al. Diabetes Care 30:1049-1055, 2007.
23,618 patients with DM on dialysis.
"Higher HbA1c is incrementally associated with mortality"

# 3) GLYCEMIC TARGETS IN DIABETIC KIDNEY DISEASE

You are seeing a 56 year old Chinese lady with T2DM for 10 years, complicated by stage 3b CKD (eGFR 40ml/min) and proliferative diabetic retinopathy. She is treated with metformin XR 1000mg OM and mixtard 34 units pre-breakfast and 28 units pre-dinner.

Her HbA1c is 9.2%.

**Are you happy with her current glycemic control?**

a) Yes, she has already developed multiple DM complications & is at risk of hypoglycaemia if I increase her insulin further. I will not uptitrate her medications any further.

b) No, I will try to get her HbA1c down to 7-8.5% instead.

c) No, I will try to get her HbA1c down to 6.5-7% instead.

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4)

# UPDATE: ROLES OF NEW DM AGENTS

## IN DIABETIC KIDNEY DISEASE

# 4) ROLES OF NEWER DM AGENTS IN DM DIABETIC KIDNEY DISEASE

56 year old Chinese lady with T2DM for 6 years, complicated by mild albuminuria and non-proliferative diabet retinopathy comes to your office for routine follow-up care.

She is currently treated with metformin 850mg TDS, glipizide 5mg BD and enalapril 10mg BD.

Her BP is 132/85mmHg. BMI is 24.6kg/m2.

Key laboratory values include: serum potassium 4.1 mmol/L, serum creatinine 0.75mg/dL (67umol/L), urine albumin:creatinine ratio 26mg/mmol/ (mild albuminuria), HbA1c 7.8%.

Her diabetes control is not optimal despite compliance to diet and her efforts in brisk walking 30 min 4 times a week. **How would you optimise her diabetes medication to confer the <u>most</u> benefit to her?**

a) Increase glipizide to 10mg BD
b) Add a thiazolinedione
c) Add a DPP-4 inhibitor
d) Add an SGLT-2 inhibitor
e) Add a GLP-1 agonist

# 4) ROLES OF NEWER DM AGENTS IN DM & DIABETIC KIDNEY DISEASE

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# 4) ROLES OF NEWER DM AGENTS IN DM & DIABETIC KIDNEY DISEASE

Are there now preferred DM agents that can alter the course of development of diabetic kidney disease?

# 4) ROLES OF NEWER DM AGENTS IN DM & DIABETIC KIDNEY DISEASE

*In the good old days….*

Good glycemic control reduces the risk of development of diabetic kidney disease – did not matter what DM medication was used to attain glycemic control.

# ROSIGLITAZONE

- 2007: Publication of a meta-analysis of 42 trials showing that rosiglitazone was associated with a significant increase in the risk of MI and increase in the risk of death from CV causes (that had borderline significance)

# ROSIGLITAZONE

- 2009, RECORD: the only prospective randomized trial designed to assess the CV efficacy & safety of rosiglitazone
- Results: inconclusive about any possible harmful effect on MI, did not increase risk of overall CV morbidity or mortality compared to standard glucose-lowering drugs

# ROSIGLITAZONE

- CV safety concern of rosiglitazone persisted
- Consequently, use was not recommended anymore in the ADA guidelines in 2009, withdrawn from the market in many countries in 2010
- In 2013, FDA lifted restrictions over the prescribing & use of rosiglitazone based on data including data from the RECORD trial
- However, rosiglitazone remains hardly used after it has been removed from the market by most other countries

# POST-ROSIGLITAZONE

- US FDA: Guidance for Industry; Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes (December 2008)

**III. RECOMMENDATIONS**

To establish the safety of a new antidiabetic therapy to treat type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk. To ensure that a new therapy does not increase cardiovascular risk to an unacceptable extent, the development program for a new type 2 antidiabetic therapy should include the following.

# RATIONALE & LIMITATIONS OF CV SAFETY TRIALS

1. To prove that therapy does not result in unacceptable increase in CV risk (Market and regulatory driven )
2. Performed on patients with high CV risks (cannot be extrapolated to patients without vascular damage)
3. Limited primary end-points – MI, stroke (not microvascular cxs, heart failure, PVD, UAP)
4. Short periods of follow-up – CV outcomes need longer-term F/U
5. Lack of head-to-head comparison between different types of drugs

# CV SAFETY TRIALS COMPLETED SINCE 2008

Since 2008, every newly approved glucose lowering drug has undergone a CVOT to evaluate its CV safety.
4 main classes:

## DPP-4 Inhibitors

- SAVOR – DPP IV inhibitor Saxagliptin (2013)
- EXAMINE – DPP IV inhibitor Alogliptin (2015)
- TECOS – DPP IV inhibitor Sitagliptin (2015)
- CARMELINA – Linagliptin (2018)

## GLP-1 Receptor Agonists

- ELIXA – Lixisenatide (2015)
- LEADER – Liraglutide (2016)
- SUSTAIN-6 – Semiglutide (2016)
- EXSCEL – exenatide (2017)
- Harmony – Albiglutide (2018)

## SGLT-2 inhibitors

- EMPA-REG – SGLT-2 inhibitor Empagliflozin (2015)
- CANVAS – canagliflozin (2017)
- DECLARE-TIMI 58 – Dapagliflozin (2018)

## Insulins

- ORIGIN—insulin glargine (2012)
- DEVOTE—insulin degludec (2017)

# CV SAFETY TRIALS COMPLETED SINCE 2008

A number of large CVOTs in T2DM with existing CVD/at high risk of CVD examined kidney effects as secondary outcomes, including large numbers of participants with renal disease.

## DPP-4 Inhibitors

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## Insulins

- ORIGIN—insulin glargine (2012)
- DEVOTE—insulin degludec (2017)

# 4) ROLES OF NEWER DM AGENTS IN DM & DIABETIC KIDNEY DISEASE

1. EMPA-REG: compared to placebo, empagliflozin reduced the risk of incident or worsening nephropathy (composite of progression to urine ACR >300mg/g Cr, doubling of serum creatinine, ESRD or death from ESRD) by 39% (HR 0.54)
2. CANVAS: Canagliflozin reduced the risk of progression of albuminuria by 27% and risk of reduction in eGFR, ESRD or death from ESRD by 40% (HR 0.47-0.77)
3. DECLARE-TIMI 58: compared to placebo, dapagliflozin reduced the risk of reduction in eGFR, ESRD, kidney transplantation, renal/CV death (HR 0.53)
4. LEADER: liraglutide reduced the risk of new or worsening nephropathy by 22%
5. SUSTAIN-6: Semaglutide reduced the risk of new or worsening nephropathy by 36%

# 4) ROLES OF NEWER DM AGENTS IN DM & DIABETIC KIDNEY DISEASE

- Following that, several large clinical trials of SGLT-2 inhibitors focused on patients with CKD, with assessment of primary renal outcomes: some completed, some ongoing
  - CREDENCE: placebo controlled trial of canagliflozin among 4,401 adults with T2DM, urine ACR >=300 mg/g, eGFR 30-90ml/min had a primary composite end point of ESRD, doubling of serum creatinine or renal/CV death
  - Stopped early due to positive efficacy
  - **Reduced renal endpoints by 34% compared to placebo (HR 0.66, 0.53-0.81)**
  - **Reduced CV endpoints (CV death HR 0.78, nonfatal MI HR 0.81, nonfatal stroke HR 0.80)**
  - No increased risk of lower limb amputations, fractures, AKI or hyperkalemia
  - Increased risk for DKA (2.2 and 0.2 events per 1000 patient-years in canagliflozin and placebo groups respectively)
- Ongoing:
  - DAPA-CKD trial (NCT03036150), results expected in 2021 (recruiting pts with eGFR down to 25ml/min)
  - EMPA- KIDNEY (NCT03594110), results expected in 2022 (recruiting pts with eGFR down to 20ml/min)

Circulation, 2019 Jul 11. Epub ahead of print

# 4) ROLES OF NEWER DM AGENTS IN DM & DIABETIC KIDNEY DISEASE

ADA recommendations updated with recent studies:

American Diabetes Association *Living* Standards of Medical Care in Diabetes 2019

# 4) ROLES OF NEWER DM AGENTS IN DM & DIABETIC KIDNEY DISEASE

ADA recommendations updated with recent studies:

| | Efficacy | Hypoglycemia | Weight change | CV effects | | Cost | Oral/SQ | Renal effects | | Additional considerations |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | ASCVD | CHF | | | Progression of DKD | Dosing/use considerations* | |
| **SGLT-2 Inhibitors** | Intermediate | No | Loss | Benefit: empagliflozin†, canagliflozin | Benefit: empagliflozin†, canagliflozin<br>dapagliflozin | High | Oral | Benefit: canagliflozin, empagliflozin<br>dapagliflozin | ▪ Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin) | ▪ **FDA Black Box:** Risk of amputation (**canagliflozin**)<br>▪ Risk of bone fractures (canagliflozin)<br>▪ DKA risk (all agents, rare in T2DM)<br>▪ Genitourinary infections<br>▪ Risk of volume depletion, hypotension<br>▪ ↑LDL cholesterol<br>▪ Risk of Fournier's gangrene |
| **GLP-1 RAs** | High | No | Loss | Neutral: lixisenatide<br>Benefit: liraglutide† > sema-glutide > exenatide extended release | Neutral | High | SQ | Benefit: liraglutide | ▪ Renal dose adjustment required (exenatide, lixisenatide)<br>▪ Caution when initiating or increasing dose due to potential risk of acute kidney injury | ▪ **FDA Black Box:** Risk of thyroid C-cell tumors (**liraglutide, albiglutide, dulaglutide, exenatide extended release**)<br>▪ Gastrointestinal side effects common (nausea, vomiting, diarrhea)<br>▪ Injection site reactions<br>▪ ?Acute pancreatitis risk |
| **DPP-4 inhibitors** | Intermediate | No | Neutral | Neutral | Potential risk: saxagliptin, alogliptin | High | Oral | Neutral | ▪ Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment<br>▪ No dose adjustment required for linagliptin | ▪ Potential risk of acute pancreatitis<br>▪ Joint pain |

American Diabetes Association *Living* Standards of Medical Care in Diabetes 2019

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| DPP-4 inhibitors | Intermediate | No | Neutral | Neutral | Potential risk: saxagliptin, alogliptin | High | Oral | Neutral | ▪ Renal dose adjustment required (sitagliptin, saxagliptin, alogliptin); can be used in renal impairment<br>▪ No dose adjustment required for linagliptin | ▪ Potential risk of acute pancreatitis<br>▪ Joint pain |

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| SGLT-2 inhibitors | Intermediate | No | Loss | Benefit: empagliflozin†, canagliflozin | Benefit: empagliflozin†, canagliflozin dapagliflozin | High | Oral | Benefit: canagliflozin, empagliflozin dapagliflozin | ▪ Renal dose adjustment required (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin) | ▪ **FDA Black Box:** Risk of amputation (**canagliflozin**)<br>▪ Risk of bone fractures (canagliflozin)<br>▪ DKA risk (all agents, rare in T2DM)<br>▪ Genitourinary infections<br>▪ Risk of volume depletion, hypotension<br>▪ ↑LDL cholesterol<br>▪ Risk of Fournier's gangrene |
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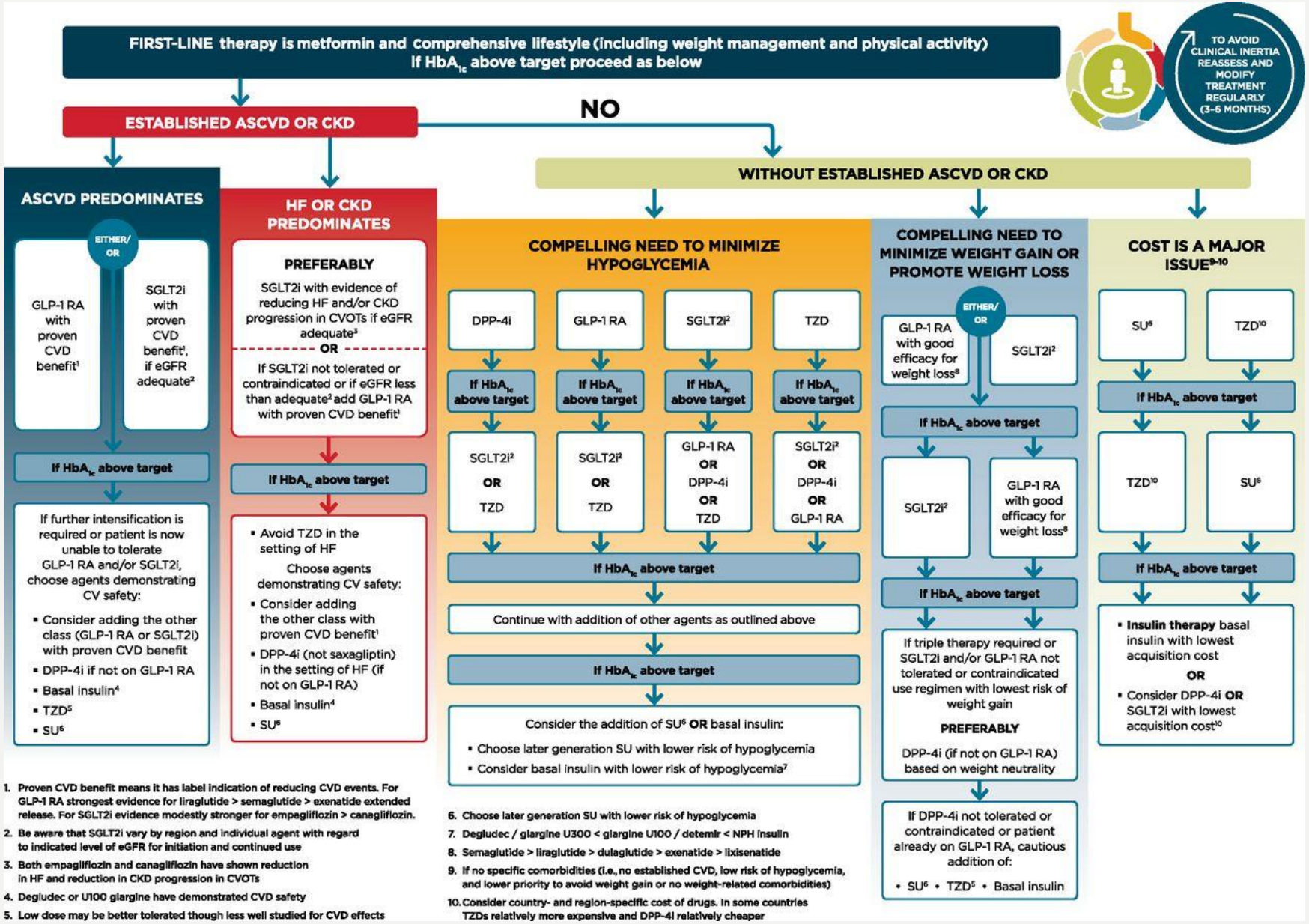
American Diabetes Association *Living* Standards of Medical Care in Diabetes 2019

# Glucose-lowering medication in type 2 diabetes: overall approach.




American Diabetes Association Dia Care 2019;42:S90-S102

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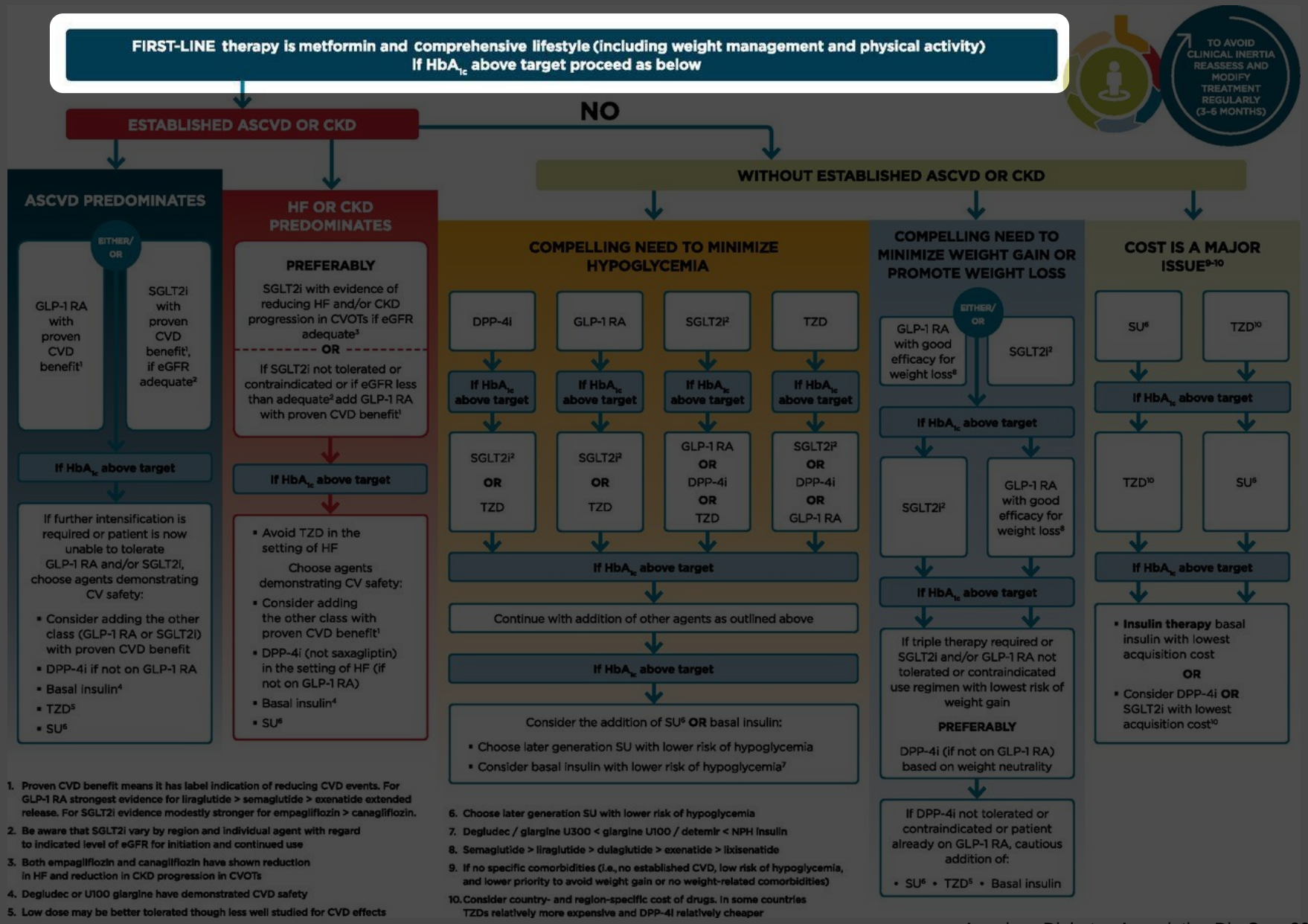


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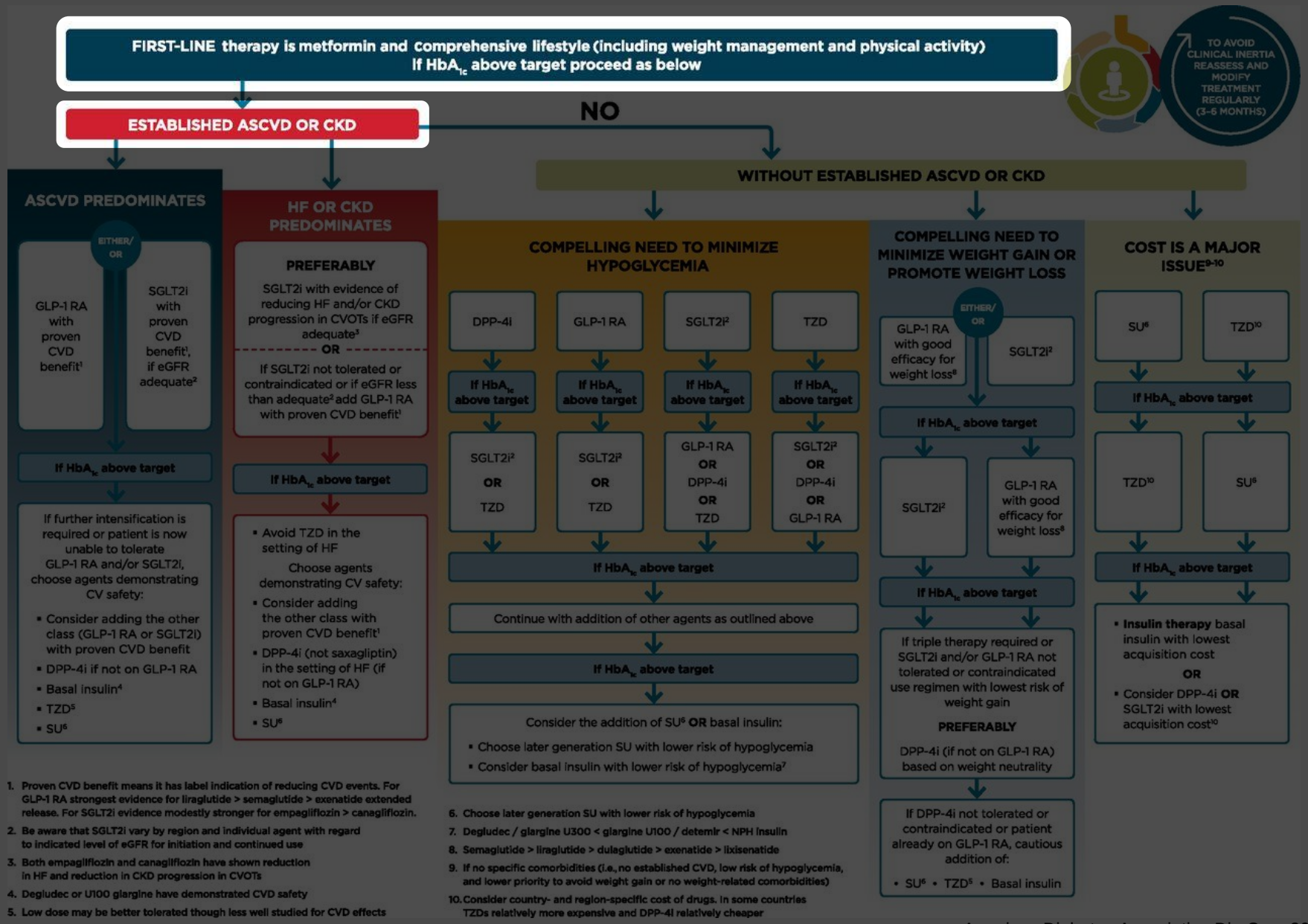


1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

American Diabetes Association Dia Care 2019;42:S90-S102

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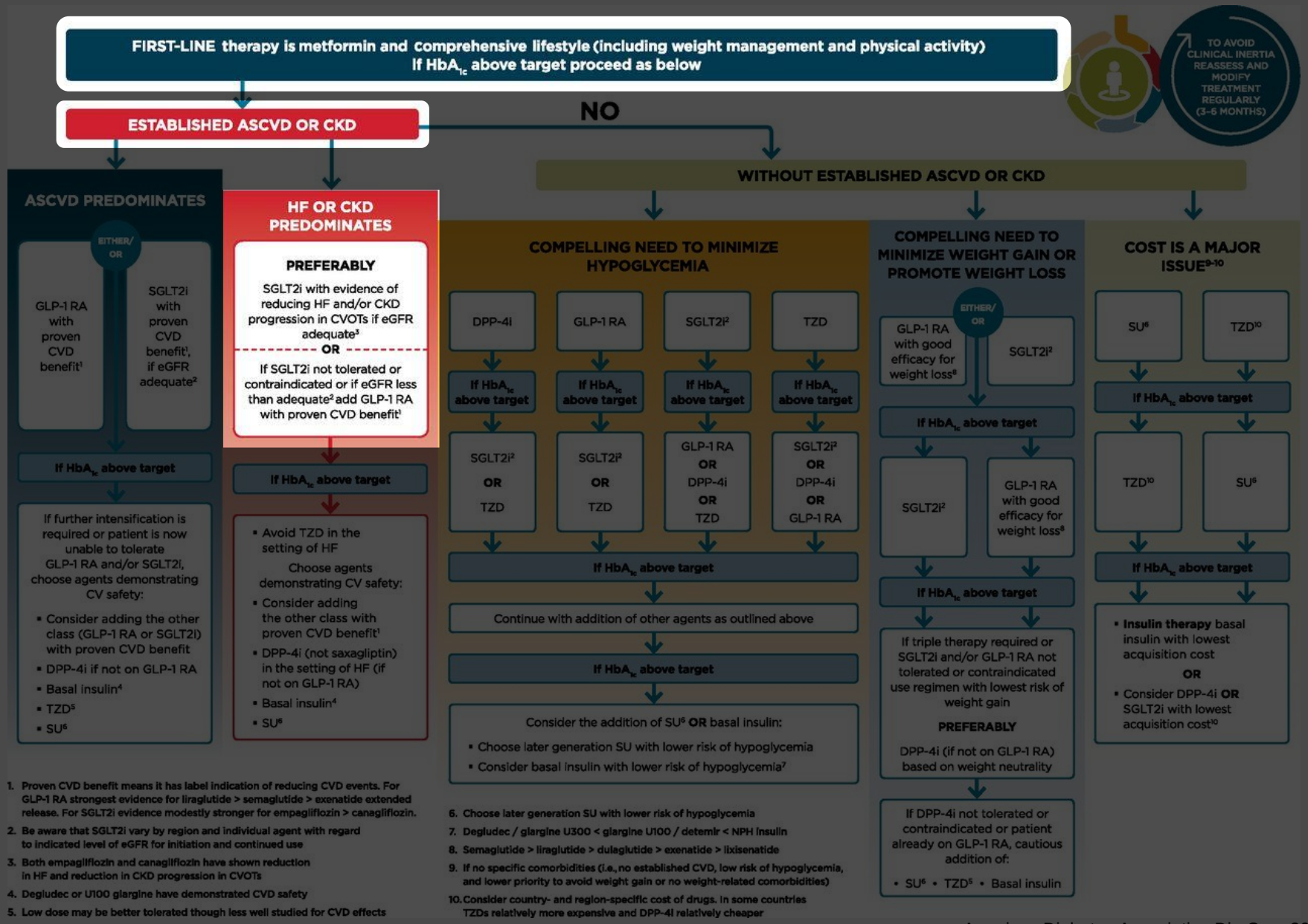


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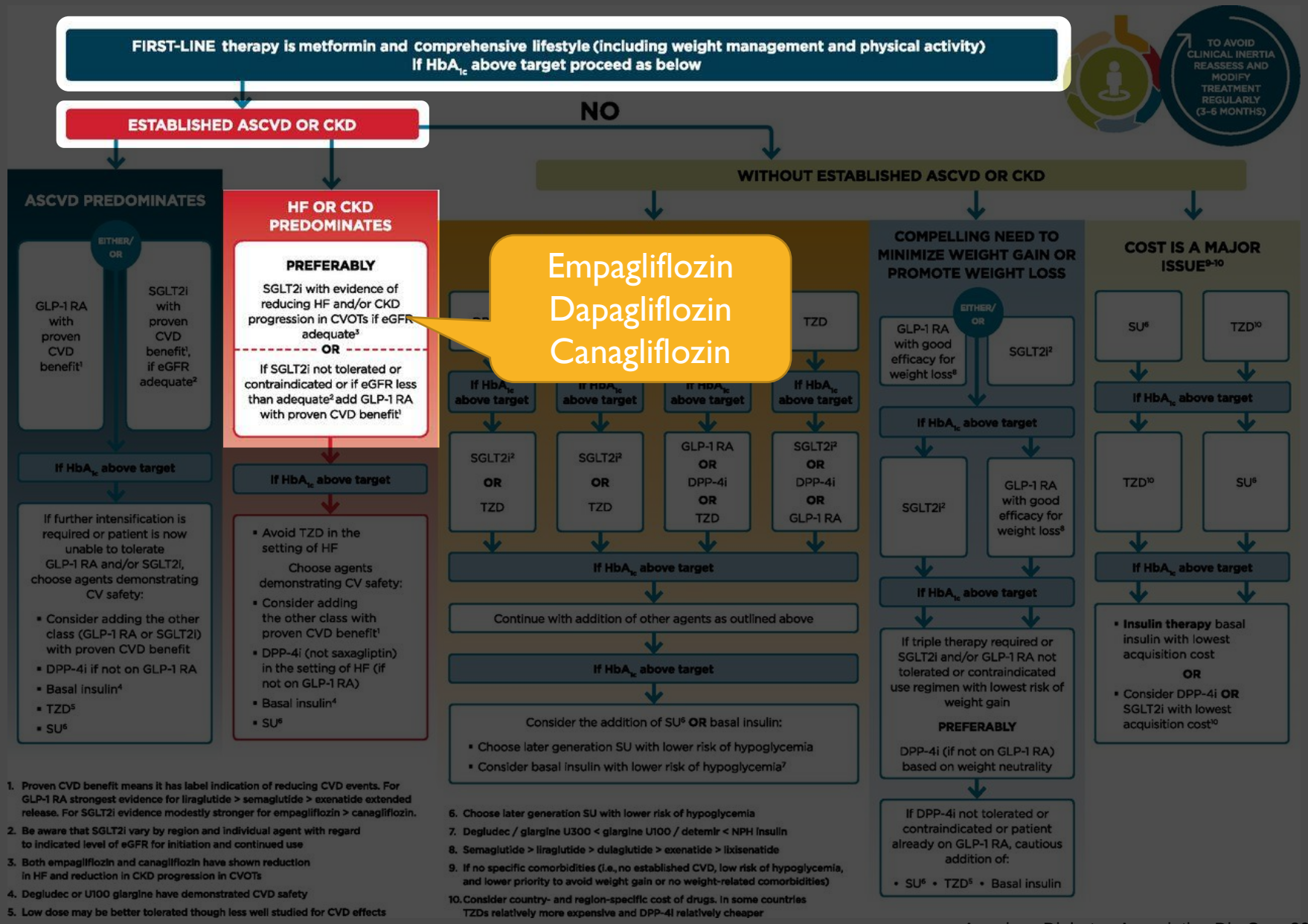


American Diabetes Association Dia Care 2019;42:S90-S102

# 4) ROLES OF NEWER DM AGENTS IN DM & DIABETIC KIDNEY DISEASE

## Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

✓ Dapagliflozin 5 mg and 10 mg tablets, and empagliflozin 10 mg and 25 mg tablets for managing type 2 diabetes mellitus, in the following circumstances:

- as a dual therapy in combination with metformin for patients with HbA1c measurement greater than 7% despite treatment with metformin monotherapy and when sulfonylureas are contraindicated or not tolerated, or the person is at significant risk of hypoglycaemia or its consequences; or
- as a dual therapy in combination with a sulfonylurea for patients with HbA1c measurement greater than 7% despite treatment with sulfonylurea monotherapy and when metformin is contraindicated or not tolerated; or
- as a triple therapy in combination with metformin and a sulfonylurea for patients with HbA1c measurement greater than 7% despite treatment with optimal doses of dual therapy; or
- in combination with insulin, with or without metformin.

### Subsidy status

Dapagliflozin 5 mg and 10 mg tablets, and empagliflozin 10 mg and 25 mg tablets are recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indications.

MAF assistance **does not** apply to canagliflozin.

*Update published on 1 October 2018*

Agency for Care Effectiveness (ACE) Singapore, 1 October 2018

# 4) ROLES OF NEWER DM AGENTS IN DM & DIABETIC KIDNEY DISEASE

For patients in whom ASCVD, HF or CKD predominates, the best choice for a second agent is a GLP-1 receptor agonist or SGLT2 inhibitor with demonstrated renal and/or cardiovascular risk reduction, after consideration of drug-specific and patient factors.

For patients without established ASCVD or CKD, the choice of a second agent to add to metformin is not yet guided by empiric evidence. Rather, drug choice is based on avoidance of side effects, particularly hypoglycemia and weight gain, cost, and patient preferences.

# 4) ROLES OF NEWER DM AGENTS IN DM DIABETIC KIDNEY DISEASE

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She is currently treated with metformin 850mg TDS, glipizide 5mg BD and enalapril 10mg BD.

Her BP is 132/85mmHg. BMI is 24.6kg/m2.

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Her diabetes control is not optimal despite compliance to diet and her efforts in brisk walking 30 min 4 times a week. How would you optimise her diabetes medication to confer the most benefit to her?

a) Increase glipizide to 10mg BD
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c) Add a DPP-4 inhibitor
d) Add an SGLT-2 inhibitor
e) Add a GLP-1 agonist

5)

# DOSE ADJUSTMENTS OF DM MEDICATIONS

## IN CHRONIC KIDNEY DISEASE

# 5) WORSENING CKD AND DM DRUG ADJUSTMENTS NEEDED

Mr A has T2DM for more than 20 years, complicated by CKD and ischemic heart disease.

During his appointment with you, his eGFR is 38ml/min.

For his T2DM, he is currently treated with metformin 850mg TDS, glipizide 5mg BD, linagliptin 5mg OM and empagliflozin 10mg OM.

**What medication needs to be stopped/reduced in view of his reduced eGFR?**

1) Stop both metformin and empagliflozin
2) Reduce the dose of metformin and stop empagliflozin
3) Keep current dose of metformin but stop empagliflozin

# SPECIAL CONSIDERATIONS IN CKD

1. Risk of hypoglycemia is increased in CKD, especially in stage 4 & 5 CKD (eGFR<30ml/min & <15ml/min)
   - Choose therapy with less hypoglycemic risks
   - Importance of asking for hypoglycemia during clinic consults & encouraging & reviewing home blood glucose monitoring

2. Some DM medications are not recommended in advanced CKD, some need dose adjustments in CKD stage 3
   - Higher risk for lactic acidosis, hypoglycemia, AKI, fluid overload
   - No available usage & safety data sometimes
   - Not effective at lower eGFR (SGLT-2 inhibitors, but await studies to prove safety & utility at lower eGFR)
3. Hemodialysis & peritoneal dialysis
   - Fluctuation of glycemia due to the process of hemodialysis & peritoneal dialysis
   - Most PD patients need insulin for good glycemic control (due to carb-containing PD fluids)
   - Dosages & timing of insulin may need to be changed for hemodialysis days to overcome these "iatrogenic hypos & hypers" & attain normoglycemia as much as possible

# BIGUANIDES: METFORMIN

| eGFR | | | 60 | 45 | 30 | 15 | |
|---|---|---|---|---|---|---|---|
| Metformin | CKD-1 | CKD-2 | CKD-3a | **CKD-3b** | **CKD-4** | **CKD-5ND** | **CKD-5D** |
| EU/UK | No adjustments | | 850-1500mg/d | | 500mg/d | Consider carefully/Awaiting further data | |
| US | | | | Dose adjust | To be avoided | | |

First-line treatment for diabetes mellitus due to low risk for hypoglycaemia, beneficial impact on all-cause and CV mortality and low risk for hypoglycaemia.

Renal clearance of metformin decreases by about 75% when GFR <60, and serum concentrations of metformin at GFR of 30-60 are about 2-fold higher than in normal kidney function.

KDOQI 2012 & US FDA (mandated black-box warning): metformin should not be used in men with SCr of ≥1.5 mg/dL or in women with SCr of ≥1.4 mg/dL (evidence from pharmacokinetic studies)

US FDA 2016: Assess benefits & risks & reduce dose (no specifics) if eGFR 30-45, do not start if eGFR <45. To be avoided if eGFR <30.

Serum concentrations of metformin when GFR 30 are only about 3% found in patients with true metformin-associated lactic acidosis

Subsequent clinical and postmarketing data and outcomes from unrestricted use outside the US do not support this constraint

A recent systematic review of 65 studies found no clinically worrisome lactic acidosis in patients with mild-to-moderate CKD (eGFR 30-60ml/min) and very limited data suggest a more substantial excess risk of 6-7 fold for DM patients with severe CKD

Nephrology Dialysis Transplantation (2015) 30: ii211-ii142
US FDA 2016
Inzucchi SE et al. JAMA 2014 Dec

# SULPHONYLUREAS

# SULPHONYLUREAS

| eGFR | 45 | 30 | 15 | |
|---|---|---|---|---|
| | **CKD-3b** | **CKD-4** | **CKD-5ND** | **CKD-5D** |
| Chlorpropramide | To avoid use | | | |
| Tolazamide | To avoid use | | | |
| Tolbutamide | To avoid use (US. See note below for EU/UK.) | | | |
| Glyburide | To avoid use | | | |
| Glipizide | No dose adjustment | | | |
| Gliclazide | No dose adjustment | | | |
| Glimipiride | Start conservatively at 1mg/day | | | |

1st generation SUs (eg. Chlorpropramide, tolazamide, tolbutamide) should be avoided: rely on kidneys to eliminate both the parent drug and its active metabolites ☐ increased T1/2 & hypoglycaemia

Note: tolbutamide is metabolised by the liver & kidneys into inactive metabolites. EU/UK: 250mg 1-3 times/day for CKD 3b & 4, avoid in CKD 5ND & 5D

2nd generation SUs: glipizide & gliclazide are metabolized by the liver into renally excreted, inactive metabolites. The others have active metabolites, which are dependent on renal elimination & hence should not be used in ESRD.

KDOQI Diabetes Guideline: 2012 Update

# MEGLITINIDES

| eGFR | 45 | 30 | 15 | |
|---|---|---|---|---|
| | **CKD-3b** | **CKD-4** | **CKD-5ND** | **CKD-5D** |
| Repaglinide | No dose adjustment | Start conservatively at 0.5mg with meals | | |
| Nateglinide | No dose adjustment | Start conservatively at 60mg with meals | | |

Similar to SUs: Insulin secretagogues, act at ATP-dependent K channels on pancreatic beta cells to stimulate insulin secretion
Unlike SUs: Shorter acting, targeted at controlling postprandial glucose levels, peak insulin within 30 min, insulin levels fall to basal within 2 hours

Repaglinide is almost entirely metabolised by the liver to inactive metabolites (<10% metabolites excreted in the urine)

Nateglinide is metabolised by the liver but has active metabolites that are 80% excreted in the urine

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# THIAZOLIDINEDIONES

| eGFR | 45 | 30 | 15 | |
|---|---|---|---|---|
| | **CKD-3b** | **CKD-4** | **CKD-5ND** | **CKD-5D** |
| Pioglitazone | No dose adjustment | | To be avoided | |
| Rosiglitazone | No dose adjustment | | To be avoided | |

Do not lead to hypoglycaemia, are metablised by the liver, thus can be used without dose adjustment in CKD.

However, fluid retention is a major limiting side effect due to activation of epithelial Na channels along the luminal membrane of the collecting tubule: DO NOT USE IN ADVANCED HEART FAILURE AND ADVANCED CKD.

Linked with increased fracture rates and bone loss. Do not use in patients with underlying bone disease eg. Renal osteodystrophy.

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# ALPHA-GLUCOSIDASE INHIBITORS

| eGFR | 45 | 30 | 15 | |
|---|---|---|---|---|
| | **CKD-3b** | **CKD-4** | **CKD-5ND** | **CKD-5D** |
| Acarbose | No dose adjustment | To be avoided | | |

Metabolised by intestinal flora with minimal absorption.

However, with reduced kidney function, serum levels and metabolites increase significantly (consequences unestablished)

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# DPP-IV INHIBITORS

| eGFR | 45 | 30 | 15 | |
|---|---|---|---|---|
| | **CKD-3b** | **CKD-4** | **CKD-5ND** | **CKD-5D** |
| Sitagliptin | 50mg daily | 25mg daily | | |
| Saxagliptin | 2.5mg daily | | | |
| Linagliptin | No dose adjustment | | | |
| Vildagliptin | 50mg daily | | | |
| Alogliptin | 12.5mg daily | | | |

All except linagliptin are excreted by the kidney and must be dose-adjusted. Linagliptin is hepatically metabolised (<10% renal metabolism) and predominantly excreted by the fecal route and does not need to be dose-adjusted for GFR.

Low risk of hypoglycaemia as GLP-1 enhancement largely occurs during meal ingestion.

Timing with regards to HD:

Sitagliptin can be given without regard to timing of HD (<15% removed by HD)
Linagliptin can be given without regard to timing of HD (likely not removed by HD)
Vildagliptin can be given without regard to timing of HD (3% removed by HD)
Saxagliptin should be given after dialysis (25% removed by HD)

KDOQI Diabetes Guideline: 2012 Update

# INCRETIN MIMETIC

| eGFR | 45 | 30 | 15 | |
|---|---|---|---|---|
| | **CKD-3b** | **CKD-4** | **CKD-5ND** | **CKD-5D** |
| Exenatide | 5mcg 1-2x/day | Not recommended | | |
| Liraglutide | 0.6-1.8mg daily | Limited clinical experience. Use with caution. | | |
| Dulaglutide | 0.75-1.5mg weekly | Limited clinical experience. Use with caution. | | |
| Lixisenatide | 0.25-1mg weekly | Limited clinical experience. Use with caution. | Not recommended | |

Exenatide:

Excreted by the kidneys
Clearance is reduced by 36% with GFR <45: use at ¼ to ½ dose
Clearance is reduced by 64% with GFR <30
Poorly tolerated in the HD patients (nausea, diarrhea, headache)
Associated with AKI/acceleration of CKD progression in case reports
Not recommended for use in GFR <30

The rest:

Kidneys are not a major organ of elimination but limited clinical experience in GFR <30
Use with caution if GFR<30, watch for GI SEs that can lead to AKI

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# SGLT-2 INHIBITORS

| eGFR | 45 | 30 | 15 | |
|---|---|---|---|---|
| | **CKD-3b** | **CKD-4** | **CKD-5ND** | **CKD-5D** |
| Dapagliflozin | Not recommended for GFR<45. Trials undergoing for pts with eGFR as low as 25ml/min. | | | |
| Empagliflozin | Not recommended for GFR<45. Trials undergoing for pts with eGFR as low as 20ml/min. | | | |
| Canagliflozin | Not recommended for GFR<45. | | | |

MOA:

SGLT-2 is found in the renal proximal tubule & is responsible for approximately 90% of glucose reabsorption.
Inhibiting SGLT-2 causes glucosuria & a mild natriuresis.
Glucose-lowering action & elimination of SGLT-2 inhibitors require intact kidney function: not expected to be effective (for lowering blood glucose) if kidney function is compromised.

CREDENCE (Canagliflozin in CKD) has patients with eGFR as low as 30ml/min being treated with canagliflozin 100mg OM, but at the moment, prescribing information has not changed regarding recommendation for a minimum eGFR of 45ml/min.

Manufacturer information.

# INSULIN

| eGFR | 45 | 30 | 15 | |
|---|---|---|---|---|
| | **CKD-3b** | **CKD-4** | **CKD-5ND** | **CKD-5D** |
| Glargine | No advised dose adjustment (adjust based on patient response) | | | |
| Detemir | No advised dose adjustment (adjust based on patient response) | | | |
| NPH | No advised dose adjustment (adjust based on patient response) | | | |
| Regular | No advised dose adjustment (adjust based on patient response) | | | |
| Aspart | No advised dose adjustment (adjust based on patient response) | | | |
| Lispro | No advised dose adjustment (adjust based on patient response) | | | |
| Glulisine | No advised dose adjustment (adjust based on patient response) | | | |

KDOQI Diabetes Guideline: 2012 Update

# INSULIN

The kidney plays an important role in insulin clearance. Insulin clearance decreases with renal failure.

Specific information about dose adjustment and differences in insulin profiles in CKD is still missing.

Certain authors have suggested an insulin reduction by 25% when the GFR is between 10 and 50 mL/min and by 50% for a GFR of <10 mL/min, as a rough rule of thumb. Interestingly, dosages of long-acting human insulin (NPH) and aspart (novorapid) do not seem to be related to eGFR, mechanism still unknown.

KDOQI Diabetes Guideline: 2012 Update

# ANTI-GLYCEMIC TREATMENT IN CKD

| DOSE ADJUSTMENTS IN CHRONIC KIDNEY DISEASE: SUMMARY | |
|---|---|
| Metformin | Reduce dose if GFR30-60, stop if GFR<30 |
| Sulphonylureas | No dose adjustment for glipizide, gliclazide, start glimepiride conservatively at 1mg/day, avoid the rest |
| Meglitinides | Dose adjust if GFR <30 |
| Thiazolinediones | Avoid in advanced CKD |
| DPP-4 inhibitors | Dose adjustment needed for all DPP-4 inhibitors except linagliptin |
| SGLT-2 inhibitors | Not recommended for eGFR<45 currently |
| GLP-1 agonists | No dose adjustment down to GFR 30. Use with caution if GFR<30. |
| Insulin | No advised dose adjustment (adjust based on patient response) |

# 5) WORSENING CKD AND DM DRUG ADJUSTMENTS NEEDED

Mr A has T2DM for more than 20 years, complicated by CKD and ischemic heart disease.

During his appointment with you, his eGFR is 38ml/min.

For his T2DM, he is currently treated with metformin 850mg TDS, glipizide 5mg BD, linagliptin 5mg OM and empagliflozin 10mg OM.

**What medication needs to be stopped/reduced in view of his reduced eGFR?**

1) Stop both metformin and empagliflozin
2) Reduce the dose of metformin and stop empagliflozin
3) Keep current dose of metformin but stop empagliflozin

# 5) WORSENING CKD AND DM DRUG ADJUSTMENTS NEEDED

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During his appointment with you, his eGFR is 38ml/min.

For his T2DM, he is currently treated with metformin 850mg TDS, glipizide 5mg BD, linagliptin 5mg OM and empagliflozin 10mg OM.

**What medication needs to be stopped/reduced in view of his reduced eGFR?**

1) Stop both metformin and empagliflozin
2) Reduce the dose of metformin and stop empagliflozin
3) Keep current dose of metformin but stop empagliflozin

6)

# DOSE ADJUSTMENTS OF DM MEDICATIONS

## IN THE OLDER ADULT

# 6) DM IN THE OLDER ADULT

Mdm N, 70 years of age, has had T2DM for more than 25 years, complicated by CKD, ischemic heart disease, and ischemic stroke. She is chairbound, ADL dependent and but is able to be fed a soft diet for all 3 meals.

Her eGFR is 42ml/min. Her latest HbA1c 6.4%.

She is currently treated with SC mixtard 24 units OM and 12 units ON, glipizide 5mg BD, and linagliptin 5mg OM.

**What would you do?**

1) DM control is excellent so I would continue her current DM medications
2) I am worried about hypoglycemia at this HbA1c and drug regime so I would stop glipizide and continue with mixtard and linagliptin
3) I am worried about hypoglycemia at this HbA1c and drug regime so I would continue with glipizide and linagliptin but change insulin to a basal insulin

# 6) DM IN THE OLDER ADULT

**Overtreatment of diabetes is common in older adults and should be avoided**

| Patient characteristics/ health status | Rationale | Reasonable A1C goal‡ |
|---|---|---|
| Healthy (few coexisting chronic illnesses, intact cognitive and functional status) | Longer remaining life expectancy | <7.5% (58 mmol/mol) |
| Complex/intermediate (multiple coexisting chronic illnesses* or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment) | Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk | <8.0% (64 mmol/mol) |
| Very complex/poor health (LTC or end-stage chronic illnesses** or moderate-to-severe cognitive impairment or 2+ ADL dependencies) | Limited remaining life expectancy makes benefit uncertain | <8.5%† (69 mmol/mol) |

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# 6) DM IN THE OLDER ADULT

In older adults at increased risk of hypoglycemia (CKD, unpredictable/poor feeding, on SU/insulin), medication classes with low risk of hypoglycaemia are preferred

Deintensification or simplification of complex regimens is recommended to reduce the risk of hypoglycemia, if it can be achieved within the individualised A1c target

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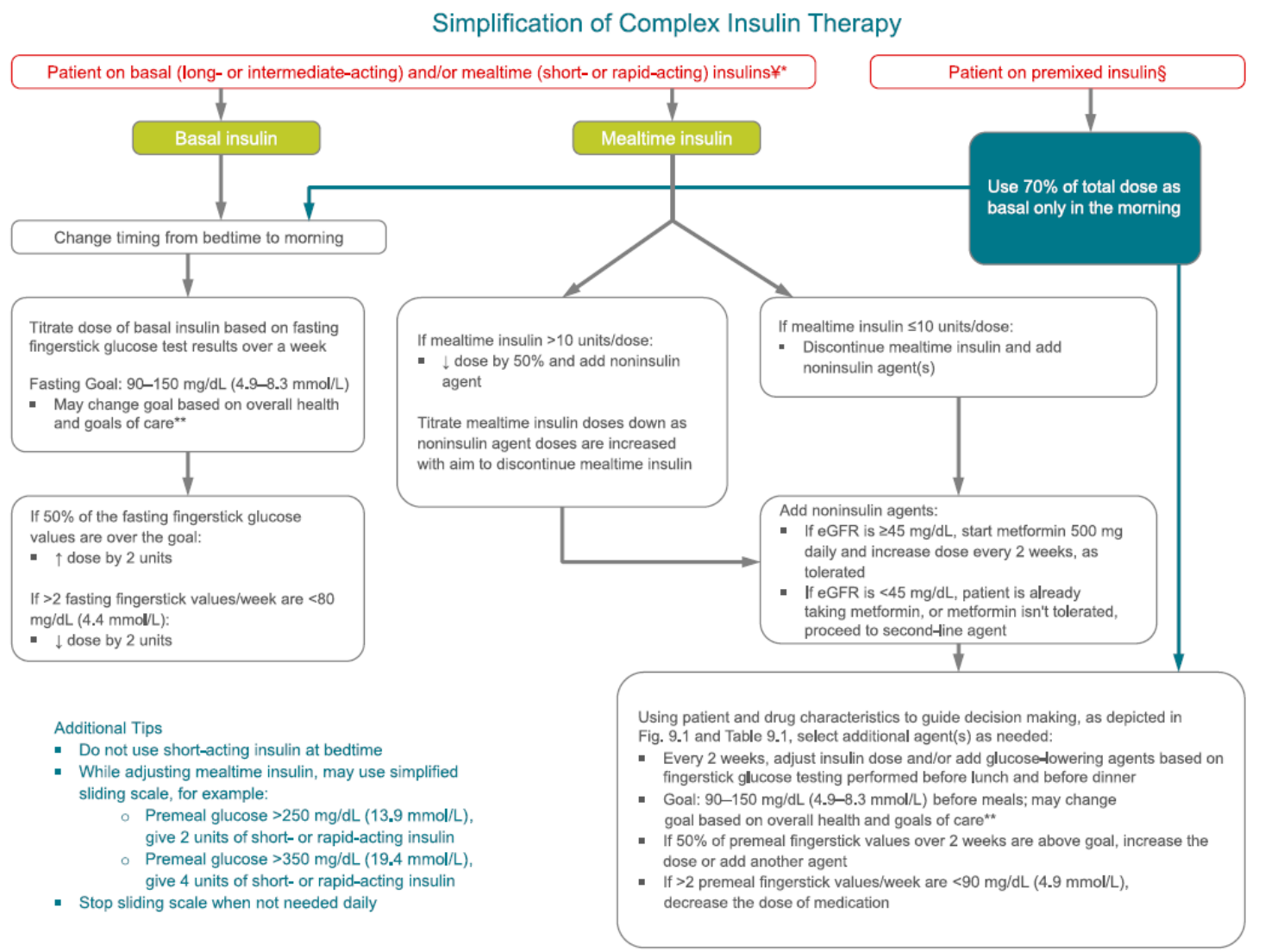
# 6) SIMPLIFYING INSULIN

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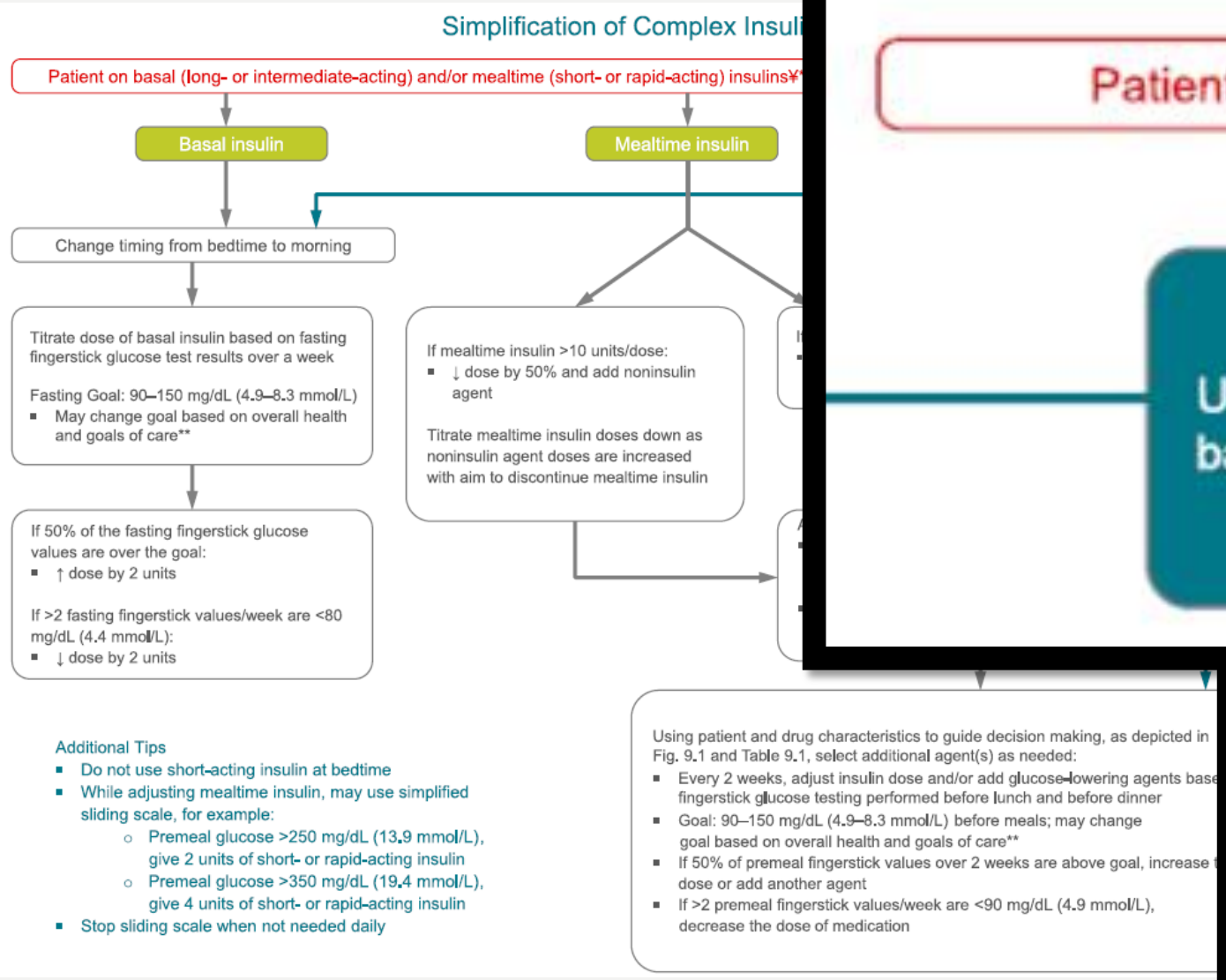
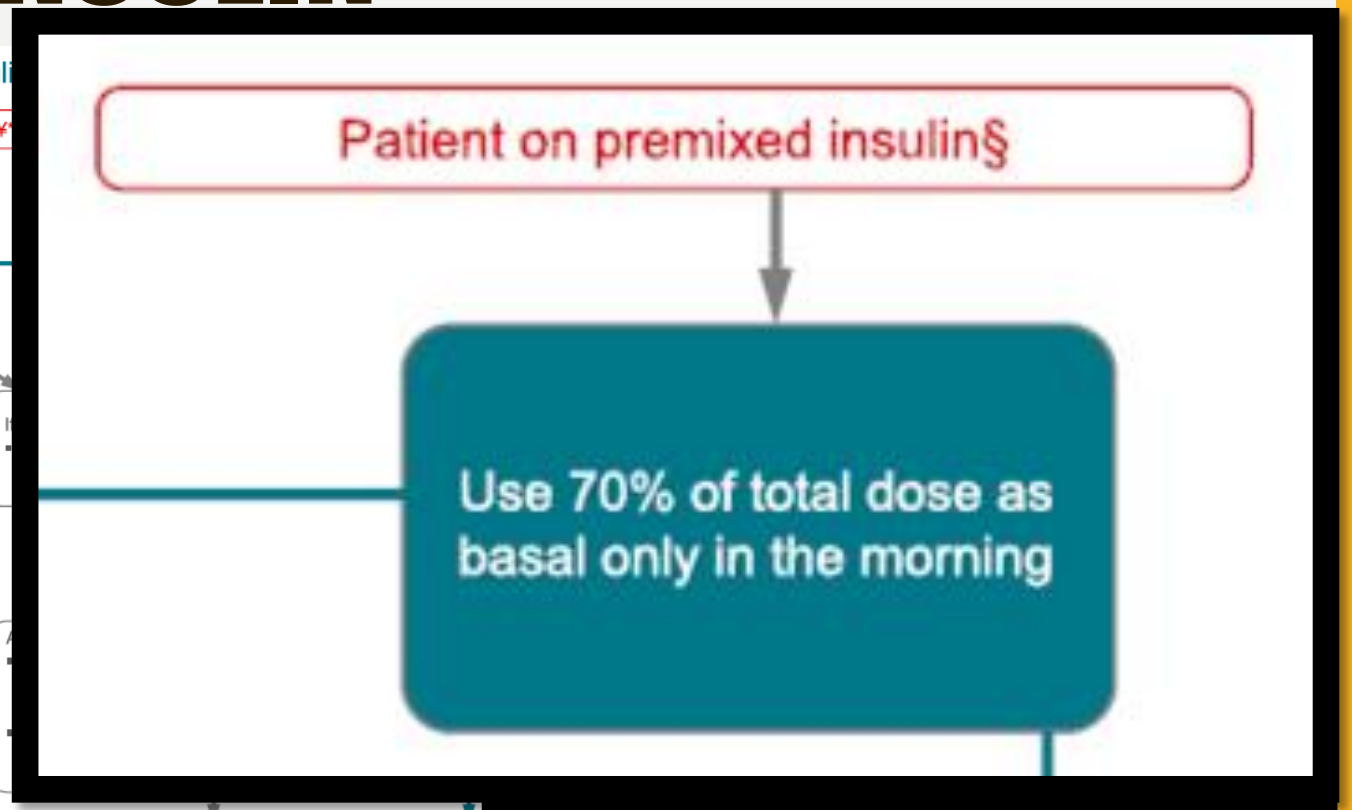
# 6) SIMPLIFYING INSULIN

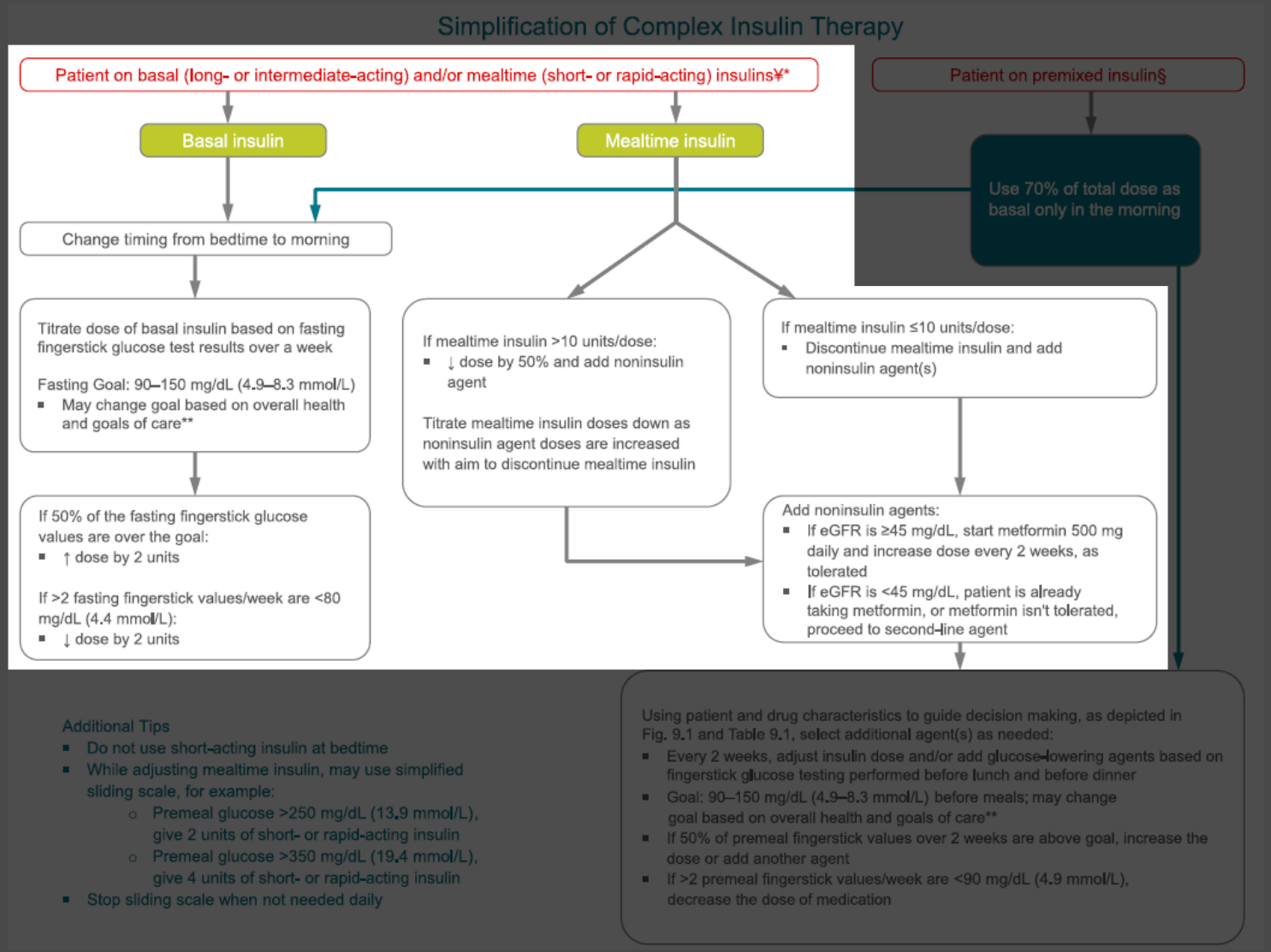



- Every 2 weeks, adjust insulin dose and/or add glucose-lowering agents based on CBG pre-lunch and pre-dinner
- Goal: 4.9-8.3 mmol/L before meals (depending on overall health and goals of care)

American Diabetes Association Standards of Medical Care in Diabetes 2019

# 6) DM IN THE OLDER ADULT

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# 6) SIMPLIFYING INSULIN

Basal insulin: change timing from bedtime to morning, titrate according to fasting CBG (may want to aim 5-8.5mmol/L according to goals of care)

Mealtime insulin <10units/dose: stop mealtime insulin, add non-insulin agent (non-SU, since preventing hypoglycaemia is of priority), adjust or add non-insulin agent according to CBG monitoring and goals of care

If mealtime insulin >10units/dose: reduce mealtime insulin dose by 50%, add non-insulin agent and gradually increase dose of non-insulin agent and reduce mealtime insulin, aiming to stop mealtime insulin

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# 6) DM IN THE OLDER ADULT

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Her eGFR is 42ml/min. Her latest HbA1c 6.4%.

Too tight?

She is currently treated with SC mixtard 24 units OM and 12 units ON, glipizide 5mg BD, and linagliptin 5mg OM.

What would you do?

1) DM control is excellent so I
2) I am worried about hypog
   glipizide and continue with mi
3) I am worried about hypoglycemia at this HbA1c and drug regime so I would continue with glipizide and linagliptin but change insulin to a basal insulin

She is at high risk of hypoglycemia. Her current regime of mixtard and glipizide is a recipe for hypoglycemia (disaster).

# 6) DM IN THE OLDER ADULT

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She is currently treated with SC mixtard 24 units OM and 12 units ON, glipizide 5mg BD, and linagliptin 5mg OM.

What would you do?

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3) I am worried about hypoglycemia at this HbA1c and drug regime so I would continue with glipizide and linagliptin but change insulin to a morning basal insulin

6)

# CHOOSING NON-INSULIN AGENTS

## IN THE OLDER ADULT

# 7) CHOOSING NON-INSULIN AGENTS IN THE OLDER ADULT

Older adults usually at increased risk of hypoglycaemia, therefore, choose oral medication classes with low risk of hypoglycaemia, including:

1. **Metformin** (note: not for GFR<30)
2. **Thiazolidinediones** (note: avoid in those with/at risk of CHF or falls/fractures)
3. **Shorter duration sulphonylureas** e.g. glipizide (note: use with caution due to risk of hypoglycaemia)
4. Incretin-based therapies e.g. **DPP-4 inhibitors** (note: higher cost), **GLP-1 agonists** (note: costly, injectable, nausea/vomiting/diarrhoea, weight loss not desirable in old patients)
5. **SGLT-2 inhibitors** (note: no long-term experience in this population but seems safe and efficacious and with CV benefits, not for GFR <45)

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7)

# DM IN THE ADOLESCENT

## CLINICAL POINTS

# 8) DM IN THE ADOLESCENT

You are seeing SBH, an18 year old Malay girl, who has had osmotic symptoms over the last 2 weeks. Her mother has T2DM and hence used her own glucometer to check SBH's CBG, which revealed readings ranging 9-18mmol/L. She is at your clinic for the first time today. Her BMI is 24kg/m2.

You do an OGTT and HbA1c for her which reveals a 0 hour glucose of 8.8mmol/L and 2 hour glucose of 17.8mmol/L. Her HbA1c is 10.6%.

**What would you do?**

1) Start metformin as it is T2DM (+ve fhx of T2DM, obese) and hence there is no need to check her GAD and islet cell antibodies
2) Start insulin because the diagnosis is T1DM because she is young
3) Start insulin because of severe, symptomatic hyperglycemia. I will check her GAD and islet cell antibodies and if it is negative, it is T2DM, if it is positive, the diagnosis is T1DM
4) Start insulin because of severe, symptomatic hyperglycemia. I will check her GAD and islet cell antibodies but it can be negative even if the diagnosis is T1DM.

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# 9) DM IN THE ADOLESCENT – MEDICATIONS OF CHOICE

Her GAD and islet cell antibodies came back negative. She did not have DKA at diagnosis.

Whilst waiting for the results, you had started her on basal insulin glargine 25 units once a day (about 0.5units/kg/day).

Her C-peptide and insulin levels are high, reflecting intact pancreatic function and high insulin resistance ie.T2DM. You have followed treatment guidelines and also started metformin, now at a dose of 850mg TDS. She has lost some weight with regular exercise and compliance to diet control.

HbA1c is 8.5% after 3-4 months of the above efforts.

**Which of the following is true:**

1) HbA1c goal is <8.5%
2) Changing insulin to mixed insulin or adding on meal-time insulin is a therapeutic option if basal insulin has been optimised or increased to 1.5units/kg/day.
3) Apart from metformin and insulin, rosiglitazone has been licenced and can be used to treat adolescents with T2DM

# 9) DM IN THE ADOLESCENT: SUMMARY

1. A reasonable **HbA1c goal is <7%** for most children & adolescents with T2DM *on oral agents.*
2. HbA1c targets for youth *on insulin* should be individualized, taking into account the relatively low rate of hypoglycaemia in youth-onset type 2 diabetes.
3. Only metformin and insulin have been approved for use in youth with T2DM
4. No other medications have been approved, but Liraglutide (GLP-1 receptor agonist) has recently been shown in the ELLIPSE trial to be safe, tolerated and efficacious in improving glycemic control in 10-16 year olds over the course of 1 year
5. Medication titration: Metformin +/- basal insulin up to 1.5 units/kg/day ☐ add premeal bolus insulins if HbA1c target not met/insulin pump
6. Similar lifestyle modifications as in adults.
7. Consider metabolic surgery if BMI >35kg/m2 (Asian 32.5kg/m2) with uncontrolled glycemia and/or serious comorbidities despite lifestyle and pharmacologic intervention
8. Screen & treat for complications as in adults

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# 9) DM IN THE ADOLESCENT: SUMMARY

9. Psychiatric care may be need for certain patients e.g.depression, disordered eating behaviours
10. Starting at puberty, preconception counselling should be incorporated into routine diabetes clinic visits for all females of childbearing potential
11. Evaluate for PCOS in female adolescents with T2DM +/- refer for lab studies, OCPs not contraindicated, metformin & lifestyle modification likely to improve menstrual cyclicity & hyperandrogenism
12. Cholesterol goals: LDL <2.6mmol/L (<100mg/dL), TG <1.7mmol/L (<150mg/dL), start treatment aiming LDL <2.6 and TG <4.7 (<400) if still remains high after diet and glycemic control (>10 years old)

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HbA1c is 8.5% after 3-4 months of the above efforts

Needs to be individualized, but <7% would be a reasonable target instead

**Which of the following is th**

1) HbA1c goal is <8.5%
2) Changing insulin to mixed insulin or adding on meal-time insulin is a therapeutic option if basal insulin has been optimised or increased to 1.5units/kg/day.
3) Apart from metformin and insulin, rosiglitazone has been licenced and can be used to treat adolescents with T2DM

# 9) DM IN THE ADOLESCENT – MEDICATIONS OF CHOICE

Her GAD and islet cell antibodies came back negative. She did not have DKA at diagnosis.

Whilst waiting for the results, you had started her on basal insulin glargine 25 units once a day (about 0.5units/kg/day).

Her C-peptide and insulin levels are high, reflecting intact pancreatic function and high insulin resistance ie.T2DM. You have followed treatment guidelines and also started metformin, now at a dose of 850mg TDS. She has lost some weight with regular exercise and compliance to diet control.

HbA1c is 8.5% after 3-4 months of the above efforts.

**Which of the following is true:**

1) HbA1c goal is <8.5%

Correct.

2) Changing insulin to mixed insulin or adding on meal-time insulin is a therapeutic option if basal insulin has been optimised or increased to 1.5units/kg/day.
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No. Only metformin and insulin have been approved for the treatment of T2DM in youths.

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# TAKE HOME POINTS

- DM in patients with DKD
  - BP targets 140/90 vs 130/80
  - ACEi or ARBs preferred if DKD and hypertension present
  - HbA1c goal ranges from ~7% to up to 8.5%, depending on risks of hypoglycaemia and complications already present/lifespan
  - SGLT-2 inhibitors and GLP-1 agonists and their role in DKD
  - Adjusting DM medications in CKD
- DM in the older adult
  - Looser HbA1c goals
  - Simplifying insulin treatment
  - Preferred non-insulin DM drugs
- DM in the adolescent
  - Latest clinical guidelines

THANK YOU!