AMERICAN DIABETES ASSOCIATION UPDATES IN STANDARDS OF MEDICAL CARE IN DIABETES - 2014

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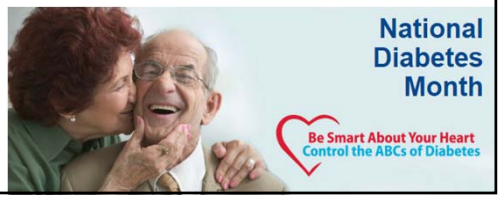


Outline:

- Define current criteria for the diagnosis of diabetes mellitus and prediabetes
- Explain how to prevent/delay type 2 diabetes mellitus
- Provide updates regarding gestational diabetes mellitus (GDM) diagnosis
- Go over glycemic targets for adults with diabetes mellitus
- Highlight upon updates in pharmacological therapy and new medications on the market
- Mention updated methods for glucose monitoring
- Provide updates in the management of high blood pressure, dyslipidemia, antiplatelet therapy, immunization, nephropathy, neuropathy and gastroparesis

International Diabetes Federation 2013

- **1 in 5** people have diabetes in the Persian Gulf region
- **Top 10** nations globally for the highest prevalence of the disease
  - Saudi Arabia
  - Kuwait
  - **Qatar**
- The other seven places are all taken by small islands in the Pacific Ocean
- Bahrain 12, UAE 15 and Egypt 17

IDF Diabetes Atlas 6th Edition

Top 10 countries for prevalence (%) of diabetes (20-79 years) - 2013

COUNTRY/ TERRITORY	2013 (%)
Tokelau	37.5
Federated States of Micronesia	35.0
Marshall Islands	34.9
Kiribati	28.8
Cook Islands	25.7
Vanuatu	24.0
Saudi Arabia	24.0
Nauru	23.3
Kuwait	23.1
Qatar	22.9

IDF Diabetes Atlas 6th Edition

Top 10 countries for prevalence (%) of IGT (20-79 years) - 2013

COUNTRY/ TERRITORY	2013 (%)
Kuwait	17.9
Qatar	17.1
United Arab Emirates	16.6
Poland	16.5
Bahrain	16.3
Malaysia	15.2
Hong Kong SAR	13.3
Nicaragua	12.9
Japan	12.6
Singapore	12.4

IDF Diabetes Atlas 6th Edition

ADA Evidence Grading System for Clinical Practice Recommendations

Level of Evidence	Description
A	Clear or supportive evidence from adequately powered well-conducted, generalizable, randomized controlled trials
B	Supportive evidence from well-conducted cohort studies or case-control study
C	Supportive evidence from poorly controlled or uncontrolled studies
	Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience

American Diabetes Association. ADA. Diabetes Care 2014;37(suppl 1):S15; Table 1

Criteria for Diabetes Diagnosis

A1C ≥6.5%*
Perform in lab using NGSP-certified method and standardized to DCCT assay

OR

FPG ≥126 mg/dL (7.0 mmol/L)*
Fasting defined as no caloric intake for ≥8 hrs

OR

2-hr PG ≥200 mg/dL (11.1 mmol/L) during OGTT (75-g)*

OR

Random PG ≥200 mg/dL (11.1 mmol/L)
In persons with symptoms of hyperglycemia or hyperglycemic crisis

*In absence of unequivocal hyperglycemia, result to be confirmed by repeat testing

FPG=fasting plasma glucose; OGTT=oral glucose tolerance test; PG=plasma glucose

American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37(suppl 1):S14-S80.

Prediabetes

Impaired Fasting Glucose (IFG)
FPG 100 mg/dL-125 mg/dL (5.6 mmol/L-6.9 mmol/L)

OR

Impaired Glucose Tolerance (IGT)
2-hr PG in 75-g OGTT 140 mg/dL-199 mg/dL (7.8 mmol/L-11.0 mmol/L)

OR

A1C 5.7%-6.4%

For all tests	Risk is continuous, extending below lower limit of range and becoming disproportionately greater at higher ends of range
IFG and IGT	View as risk factors for diabetes and CVD

CVD=cardiovascular disease; FPG=fasting plasma glucose; OGTT=oral glucose tolerance test; PG=plasma glucose

American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37(suppl 1):S14-S80.

Prevention/Delay of Type 2 Diabetes

- Patients with IGT, IFG, or an A1c 5.7-6.4%:
  - Target initially weight loss of 7% of body weight, and *maintenance* of weight loss **(A)**
  - Increase physical activity to at least 150 min/week of moderate activity such as *walking* **(A)**
  - Advise all patients not to smoke **(A)** through education and support with counseling and/or pharmacotherapy **(B)**

Prevention/Delay of Type 2 Diabetes *cont'd*

- Medical Nutrition Therapy
  - Recommended for all diabetic patients **(A)**
  - Macronutrient distribution should be based on individualized assessment of current eating patterns, preferences and metabolic goals **(E)**
  - Reduce calories and intake of dietary fat and goals should be individualized **(C)**
    - Fat quality > Fat quantity **(B)**
  - Keep moderation in carbohydrate intake (dietary fiber, foods containing whole grains, vegetables and fruits) **(B)**

Prevention/Delay of Type 2 Diabetes *cont'd*

- **Metformin therapy**
  - Was less effective than lifestyle modification:
  - Finnish **D**iabetes **P**revention **S**tudy: Lifestyle modification ⟶ 43% reduction at 7 years
  - U.S. **D**iabetes **P**revention **P**rogram **O**utcomes **S**tudy: Lifestyle modification ⟶ 34% reduction at 10 years

Metformin therapy *cont'd*

- Was as effective as lifestyle modification **(A)**:
  - BMI ≥ 35 kg/m^2
  - Age < 60 years
  - Women with prior GDM
- Can be considered for all patients with pre-diabetes as *adjunct to* lifestyle modification

Prevention/Delay of Type 2 Diabetes *cont'd*

- Screen for and treat modifiable risk factors for cardiovascular diseases **(B)** :
  - Obesity
  - Hypertension
  - Dyslipidemia
  - Smoking

Gestational Diabetes Screening and Monitoring

- Screen for undiagnosed T2DM at the first prenatal visit in those with risk factors, using standard diagnostic criteria
- No uniform approach for GDM diagnosis

GDM *cont'd*

- Two options for women not previously diagnosed with overt diabetes:

A. "One-Step" (IADPSG and WHO):
  - 75-g OGTT with PG measurement fasting and at 1 h and 2 hrs, at 24-48 weeks of gestation
  - If diagnosis is made, screen for diabetes 6-12 weeks after delivery

GDM *cont'd*

B. "Two-Steps" (NIH and ACOG):
  - 50-g Glucose load test (non-fasting) with PG measurement at 1 hr (**Step 1**), at 24-48 weeks of gestation
  - If PG ≥ 140 mg/dL, proceed to 100-g OGTT (**Step 2**), performed while patient is fasting
  - Measure levels upon fasting, 1 hr, 2 hr and 3 hr post OGTT

GDM *cont'd*

B. "Two-Steps" (NIH and ACOG) *cont'd*:

- GDM diagnosis is made when PG measured 3hrs post-test is ≥ 140 mg/dL (when at least two of the four levels are met or exceeded)

	Carpenter/Coustan	or	NDDG
• Fasting	95 mg/dL (5.3 mmol/L)		105 mg/dL (5.8 mmol/L)
• 1 h	180 mg/dL (10.0 mmol/L)		190 mg/dL (10.6 mmol/L)
• 2 h	155 mg/dL (8.6 mmol/L)		165 mg/dL (9.2 mmol/L)
• 3 h	140 mg/dL (7.8 mmol/L)		145 mg/dL (8.0 mmol/L)

NDDG, National Diabetes Data Group.

GDM *cont'd*

- In 2011, ADA used to recommend the "One-Step" approach in pregnant females not known to have prior GDM
- Prevalence of GDM **increased** from 5–6% to 15–20%), because only one abnormal value, not two, is sufficient to make the diagnosis

GDM *cont'd*

- Different diagnostic criteria will identify different magnitudes of maternal hyperglycemia and maternal/fetal risk
- NIH 2-steps approach:

1. The lack of clinical trial interventions demonstrating the benefits of the "one-step" strategy
2. Large new group of women with GDM
3. Moreover, screening with a 50-g GLT **does not require fasting** and is therefore easier to accomplish for many women

"One-step" or "Two-steps" approach?

- Insufficient data to strongly demonstrate the superiority of one strategy over the other
- The decision based on

1. Cost-benefit estimation
2. Willingness to change practice based on correlation studies rather than clinical intervention trial results and relative role of cost considerations
3. Available infrastructure

Glycemic Targets for Adults with Diabetes

A1C	<7.0%
Preprandial capillary PG	70-130 mg/dL (3.9-7.2 mmol/L)
Peak postprandial capillary PG	<180 mg/dL (<10.0 mmol/L)*
More or less stringent targets may be appropriate for individual patients if achieved without significant hypoglycemia or adverse events	

Individualize targets based on:
- Age/life expectancy
- Comorbid conditions
- Diabetes duration
- Hypoglycemia status
- Individual patient considerations
- Known CVD/advanced microvascular complications

Targets shown are for nonpregnant adults
*Postprandial glucose measurements should be made 1-2 h after the beginning of the meal
CVD=cardiovascular disease; PG=plasma glucose

American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37(suppl 1):S14-S80.

Individualizing Targets

Lowering A1C below or around 7.0% shown to reduce **B**
- Microvascular complications
- Macrovascular disease*

More or less stringent targets may be appropriate for individual patients if achieved without significant hypoglycemia or adverse events

More stringent (<6.5%) **C**
- Short diabetes duration
- Long life expectancy
- No significant CVD

Less stringent (<8%) **B**
- Severe hypoglycemia history
- Limited life expectancy
- Advanced microvascular or macrovascular complications
- Extensive comorbidities
- Long-term diabetes in whom general A1C target difficult to attain†

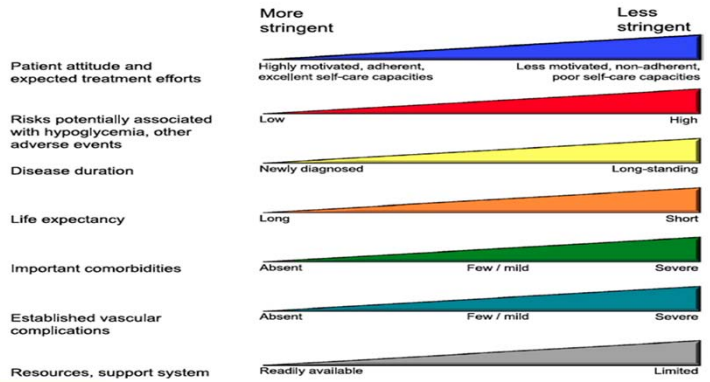
Targets shown are for nonpregnant adults
*If implemented soon after diagnosis; †Despite diabetes self-management, appropriate glucose monitoring, effective doses of antihyperglycemic agents (including insulin)
CVD=cardiovascular disease

American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37(suppl 1):S14-S80.

Examples

- A 42-year-old healthy patient, DM2 since 4 years taking metformin and pioglitazone:
  - Goal A1c ≤ 6.5%
- An 80-year-old patient post–myocardial infarction on insulin therapy:
  - Goal A1c ≤ 8%
- A 49-year-old man with T2DM for 7 years, HTN, and hyperlipidemia on basal/bolus insulin therapy
  - Goal A1c ≤ 7%

Approach to Management of Hyperglycemia

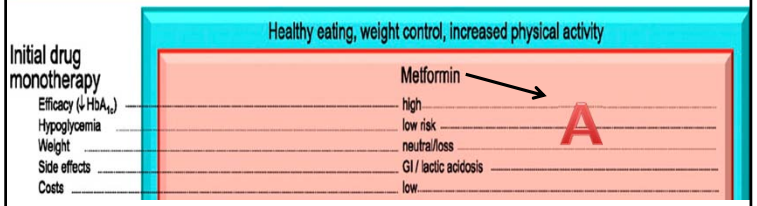


American Diabetes Association (ADA) Professional Practice Committee. Standards of medical care in diabetes - 2014

Pharmacological Therapy: Metformin

- There is a consensus about its use as first-line therapy **(A)**

- **Advantages:**
  - ✓Long standing evidence base for efficacy and safety
  - ✓Inexpensive
  - ✓Reduced risk of cardiovascular events



Pharmacological Therapy *cont'd*

- In patients *intolerant to, or with contraindications for* metformin, select initial drug form **other classes** available and proceed accordingly

- Consider starting with a **2 drug-combination** in patients with very high A1c value (e.g. ≥9%)

Pharmacological Therapy *cont'd*

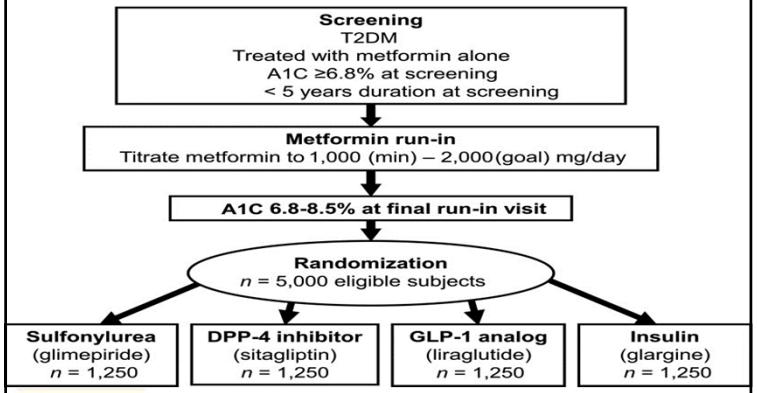
- If non-insulin monotherapy at maximum tolerated dose does not achieve or maintain the A1c target over **3 months**, add a second oral agent, glucagon-like peptide receptor agonist, or insulin **(A)**

Pharmacological Therapy *cont'd*

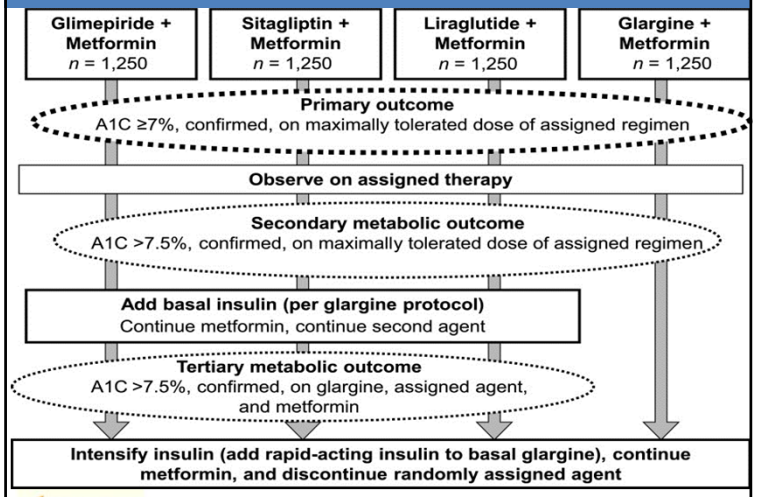
- There exist numerous trials comparing dual therapy to metformin alone, but just few head to head trials compare drugs as add-on therapy
- Even fewer long-term studies exist evaluating durability of medications on glycemic control, especially when added to metformin

American Diabetes Association (ADA) Professional Practice Committee. Standards of medical care in diabetes - 2014

Glycemia Reduction Approaches in Diabetes (GRADE) Study: Comparative Effectiveness



Nathan DM et al. *Diabetes Care* 2013;36(8):2254-61.



Nathan DM et al. *Diabetes Care* 2013;36(8):2254-61.

Add-On Therapy

- Until we have more data, considerations include **(E)**:
  - Efficacy
  - Safety
  - Cost
  - Effect on weight
  - Comorbidities
  - Hypoglycemia risk
  - Patient preferences

American Diabetes Association (ADA) Professional Practice Committee. Standards of medical care in diabetes - 2014

Add-on Therapy *cont'd*

- Choose one of:
  - Sulfonylureas
  - Dipeptidyl-peptidase-4 (DPP-4)inhibitors
  - GLP-1 analogs
  - Thiazolidenediones
  - Basal insulin
  - Sodium glucose cotransporter 2 (SGLT 2) inhibitors (**not yet in the ADA recommendations)**

American Diabetes Association (ADA) Professional Practice Committee. Standards of medical care in diabetes - 2014

Other agents

- Meglitinides
- α-glucosidase inhibitors
- Colesevelam
- Bromocriptine
- Pramlintide

❖Modest efficacy and/or limiting side effects

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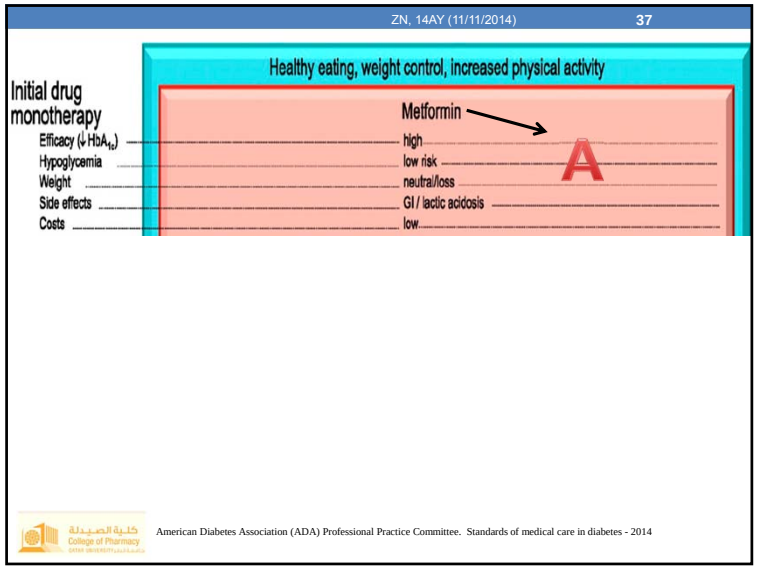
Profiles of Selected Antihyperglycemic Drugs or Drug Classes Used in Type 2 Diabetes

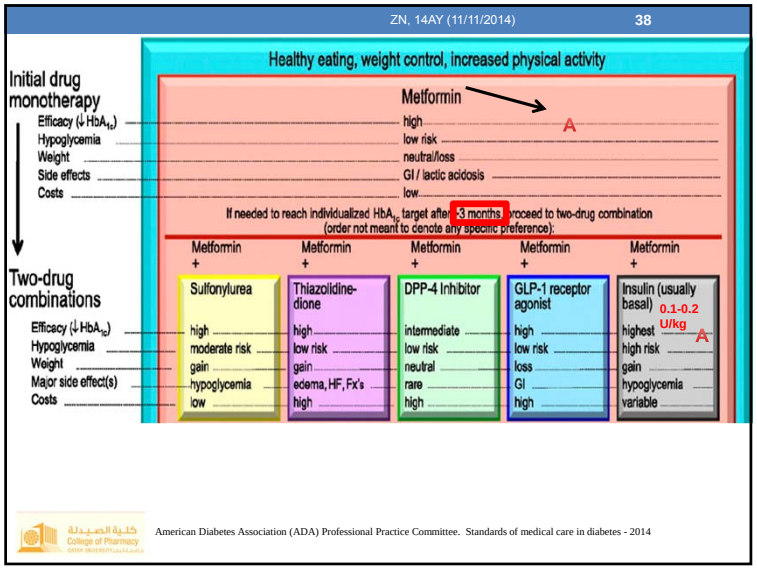
	Considerations				
Drug or Drug Class	Efficacy	Risk of Hypoglycemia	Effect on Weight	Risk of Major Side Effects	Costs
Metformin	High	Low	Neutral or loss	Gastrointestinal effects (frequent), lactic acidosis (rare)	Low
DPP-4 inhibitor	Intermediate	Low	Neutral	Rare	High
GLP-1 receptor	High	Low	Loss	Gastrointestinal effects — nausea, vomiting	High
Insulin (usually basal)	Highest	High	Gain	Hypoglycemia	Variable
Sulfonylurea	High	Moderate	Gain	Hypoglycemia	Low
Thiazolidinedione	High	Low	Gain	Edema, heart failure, bone fracture	High
SGLT2 Inhibitor	High	Low	Loss full safety profile still emerging	Risk appears low;	High

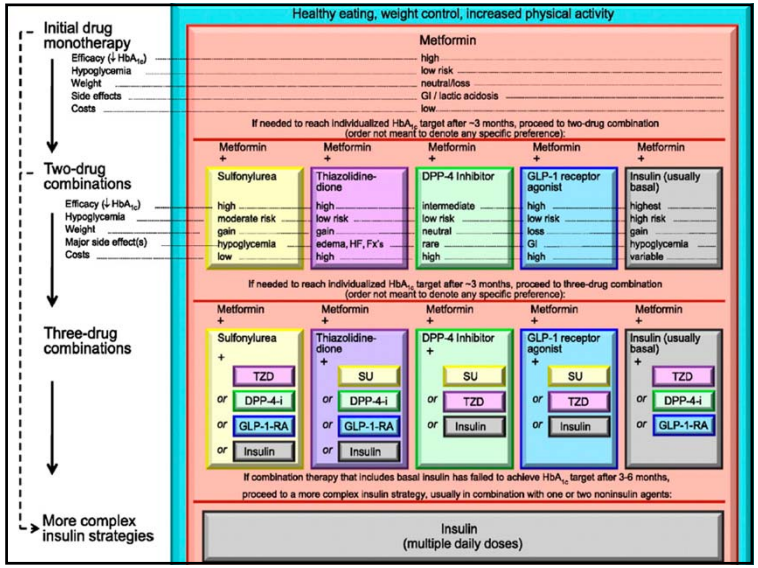
Abbreviations: DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; SGLT2, sodium-glucose cotransporter 2.

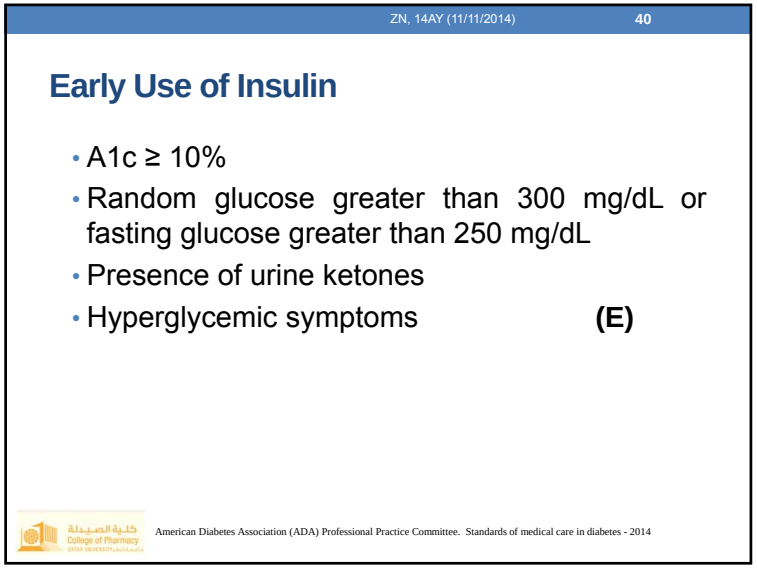
Drugs and Their Primary Glycemic Effects

Fasting Glucose	Mixed Glycemic Effects	Postprandial Glucose
Metformin	Sulfonylurea	Regular insulin
Bile acid sequestrant	Mixed insulin	Aspart/glulisine/lispro insulin
Insulin detemir	SGLT-2 inhibitor	α-Glucosidase inhibitors
Insulin glargine	Liraglutide	Meglitinides
NPH insulin	Weekly exenatide	DPP-4 inhibitors
	TZDs	Twice daily exenatide
		Pramlintide
		Bromocriptine


ZN, 14AY (11/11/2014) 37
Healthy eating, weight control, increased physical activity
Initial drug monotherapy
Metformin
Efficacy (↓ HbA1c)
Hypoglycemia
Weight
Side effects
Costs
high
low risk
neutral/loss
GI / lactic acidosis
low
A
American Diabetes Association (ADA) Professional Practice Committee. Standards of medical care in diabetes - 2014


ZN, 14AY (11/11/2014) 38
Healthy eating, weight control, increased physical activity
Initial drug monotherapy
Metformin
high
low risk
neutral/loss
GI / lactic acidosis
low
A
If needed to reach individualized HbA1c target after ~3 months, proceed to two-drug combination
(order not meant to denote any specific preference):
Two-drug combinations
Metformin + Sulfonylurea
Metformin + Thiazolidine-dione
Metformin + DPP-4 Inhibitor
Metformin + GLP-1 receptor agonist
Metformin + Insulin (usually basal)
Efficacy (↓ HbA1c)
high
high
intermediate
high
highest
Hypoglycemia
moderate risk
low risk
low risk
low risk
high risk
Weight
gain
gain
neutral
loss
gain
Major side effect(s)
hypoglycemia
edema, HF, Fx's
rare
GI
hypoglycemia
Costs
low
high
high
high
variable
0.1-0.2 U/kg
A
American Diabetes Association (ADA) Professional Practice Committee. Standards of medical care in diabetes - 2014


Healthy eating, weight control, increased physical activity
Initial drug monotherapy
Metformin
Two-drug combinations
Three-drug combinations
More complex insulin strategies
If needed to reach individualized HbA1c target after ~3 months, proceed to two-drug combination
(order not meant to denote any specific preference):
Sulfonylurea
Thiazolidine-dione
DPP-4 Inhibitor
GLP-1 receptor agonist
Insulin (usually basal)
If needed to reach individualized HbA1c target after ~3 months, proceed to three-drug combination
(order not meant to denote any specific preference):
TZD
SU
DPP-4-i
GLP-1-RA
Insulin
If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months,
proceed to a more complex insulin strategy, usually in combination with one or two noninsulin agents:
Insulin
(multiple daily doses)


ZN, 14AY (11/11/2014) 40
Early Use of Insulin
• A1c ≥ 10%
• Random glucose greater than 300 mg/dL or fasting glucose greater than 250 mg/dL
• Presence of urine ketones
• Hyperglycemic symptoms (E)
American Diabetes Association (ADA) Professional Practice Committee. Standards of medical care in diabetes - 2014

Early Use of Insulin *cont'd*

- Due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 DM **(B)**

- The total daily insulin requirements in type 2 DM are usually higher than in type 1 DM because of insulin resistance

American Diabetes Association (ADA) Professional Practice Committee. Standards of medical care in diabetes - 2014

Individual Insulins and Their Appropriate Glucose Targets

Target Blood Glucose	Target Insulin
Fasting (prebreakfast)	Bedtime or predinner NPH, detemir, glargine
Prelunch (postbreakfast)	Prebreakfast regular, aspart, glulisine, lispro
Predinner (postlunch)	Prebreakfast NPH, detemir; prelunch regular, aspart, glulisine, lispro
Bedtime (postdinner)	Predinner regular, aspart, glulisine, lispro

NPH = neutral protamine Hagedorn.

Sodium-Glucose Cotransporter 2 (SGLT-2) Inhibitors

- Indication: Treatment of type 2 diabetes mellitus (noninsulin dependent, NIDDM) as an **adjunct to** diet and exercise to improve glycemic control

- They are safe and effective **alone** and with **other medications** including metformin, sulfonylureas, pioglitazone, and insulin

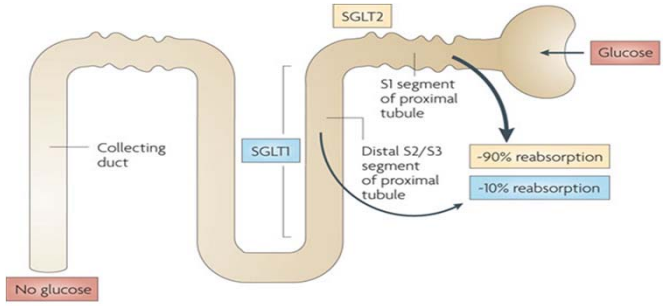
MacEwen A et al. *Br J Cardiol.* 2012;19 (1): 26-29.

SGLT-2 Inhibitors *cont'd*

- In addition to demonstrating significant reductions in A1c, they also provide **reductions in body weight and systolic blood pressure**

MacEwen A et al. *Br J Cardiol.* 2012;19 (1): 26-29.

Mechanism of Action



Nature Reviews | Drug Discovery

FDA Approval

- Canagliflozin (**Invokana**®): May 2013
- Dapagliflozin (**Farxiga**®): January 2014

❖Once daily dosing before 1st meal of the day

http://www.fda.gov/

Combination Products Available:

- Dapagliflozin + Metformin (**Xigduo XR**®): FDA approval as of October 2014
- Canagliflozin + Metformin (**Invokamet**®): FDA approval as of August 2014

http://www.fda.gov/

SGLT-2 Inhibitors *cont'd*

Benefits

- Insulin-independent action
- Associated with caloric loss; could result in weight loss
- Low hypoglycemia
- Complement the action of other anti-diabetic agents
- Can be used regardless of diabetes duration

Adverse Effects

- Repeated urinary tract infections
- Genital infections
- Increased hematocrit
- Decreased blood pressure
- Hyperkalemia
- Dehydration
- Renal monitoring and dose adjustment
- Dose-related increase in LDL

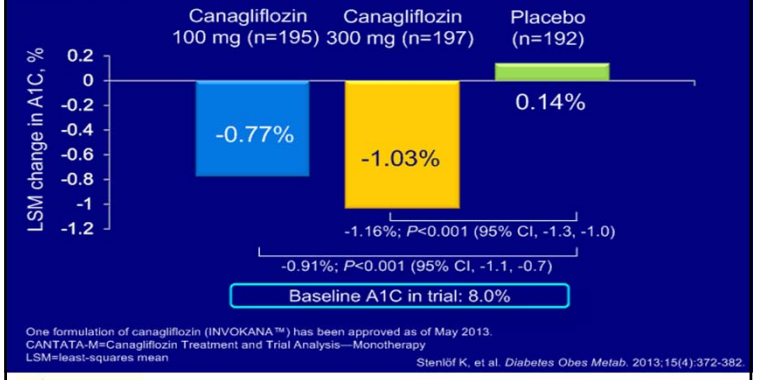
Kim Y et al. *Diabetes Metab Syndr Obes* 2012;5:313-327

CANTATA trials

- Canagliflozin has been studied in the CANTATA trials (CANagliflozin Treatment And Trial Analysis)
- Either as monotherapy or add-on therapy to metformin, metformin and sulfonylureas, or metformin and pioglitazone

Primary Endpoint

CANTATA-M: Significant A1C Reductions with Canagliflozin Vs Placebo at 26 Weeks



One formulation of canagliflozin (INVOKANA™) has been approved as of May 2013.
CANTATA-M=Canagliflozin Treatment and Trial Analysis—Monotherapy
LSM=least-squares mean

Stenlöf K, et al. *Diabetes Obes Metab*. 2013;15(4):372-382.

http://www.ndei.org/

CANTATA-SU: Canagliflozin vs. Glimepiride

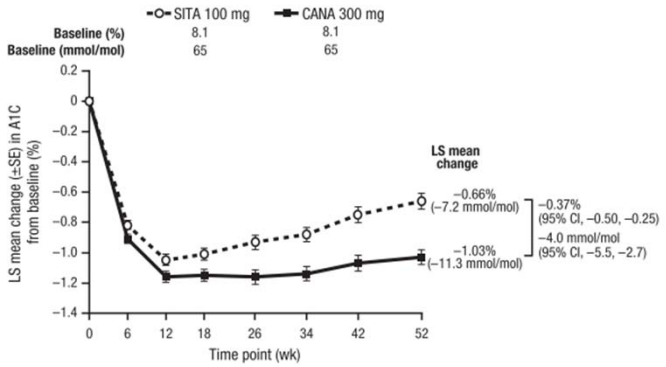
Table. Glycemia, Body Weight, and Blood Pressure Outcomes at 52 Weeks

Outcome at Week 52	Glimepiride (n = 480)	Canagliflozin 100 mg (n = 479)	Canagliflozin 300 mg (n = 480)
Patients achieving HbA1c <7.0%	56%	54%	60%
Patients achieving HbA1c <6.5%	31%	26%	31%
Mean change in fasting plasma glucose	-1.02 mmol/L	-1.35 mol/L	-1.52 mmol/L
Mean change in body weight	0.7 kg	-3.7 kg*	-4.0 kg*
Mean change in systolic blood pressure	0.2 mmHg	-3.3 mmHg	-4.6 mmHg
Mean change in diastolic blood pressure	-0.1 mmHg	-1.8 mmHg	-2.5 mmHg

*<.0001 both canagliflozin doses versus glimepiride. Statistical comparisons for canagliflozin 100 mg and 300 mg versus glimepiride for parameters other than weight were not prespecified and therefore not performed.

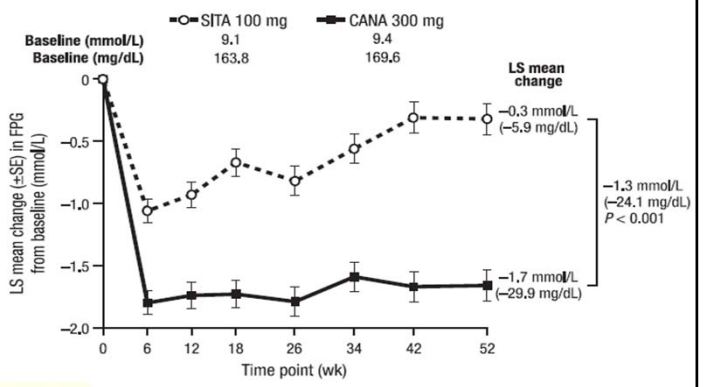
Cefalu W et al. *The Lancet* 2013;382(9896):941-950.

CANTATA-D2: Canagliflozin vs. Sitagliptin as Add on to Metformin and Sulfonylurea



Schernthaner G et al. *Diabetes Care* 2013;36(12):4172.

CANTATA-D2 *cont'd*



Schernthaner G et al. *Diabetes Care* 2013;36(12):4172.

Table 1. Summary of Canagliflozin Trials

Trial	Patient Type	Number of Subjects	Medication Regimen	Duration	Result of Primary Outcome
CANTATA–D	T2DM not controlled with metformin	1,284	Canagliflozin 100 or 300 mg daily compared to placebo for 26 wk, then sitagliptin 100 mg for 26 wk	52 wk	Change in A1C at 26 wk. Significant difference from placebo: 100 mg (-0.62) and 300 mg (-0.77)
CANTATA–SU	T2DM not controlled with metformin	1,450	Canagliflozin 100 or 300 mg daily compared to glimepiride titrated to 6-8 mg/day	104 wk	Change in A1C at 52 wk. Both doses are noninferior to glimepiride. Difference from glimepiride in A1C: 100 mg (-0.01) and 300 mg (-0.12)
CANTATA–D2	T2DM not controlled with sulfonylurea and metformin	755	Canagliflozin 300 mg daily compared to sitagliptin 100 mg/day	52 wk	Change in A1C at 52 wk. Noninferior to sitagliptin when added to metformin and a sulfonylurea. Difference in A1C from sitagliptin (-0.37)
CANTATA–M	T2DM not controlled with diet and exercise	584	Canagliflozin 100 or 300 mg daily compared to placebo for 26 wk, then sitagliptin 100 mg for 26 wk	52 wk	Change in A1C at 26 wk. Significant difference from placebo: 100 mg (-0.91) and 300 mg (-1.16)
CANTATA–MP	T2DM not controlled with metformin and pioglitazone	342	Canagliflozin 100 or 300 mg daily compared to placebo for 26 wk, then sitagliptin 100 mg for 26 wk. Doses of metformin and pioglitazone remained stable	52 wk	Change in A1C at 26 wk. Significant difference from placebo: 100 mg (-0.62) and 300 mg (-0.76)
CANTATA–MSU	T2DM not controlled with metformin and sulfonylurea	469	Canagliflozin 100 or 300 mg daily compared to placebo	52 wk	Change in A1C at 26 wk. Significant difference from placebo: 100 mg (-0.71) and 300 mg (-0.92)
CANVAS–subset	T2DM not adequately controlled with insulin ≥30 U	1,718	Canagliflozin 100 or 300 mg daily compared to placebo. Each in combination with insulin	18 wk	Change in A1C at 18 wk. Significant difference from placebo: 100 mg (-0.65) and 300 mg (-0.73)

A1C: glycated hemoglobin; CANTATA: CANagliflozin Treatment And Trial Analysis; CANVAS: CANagliflozin cardioVascular Assessment Study; T2DM: type 2 diabetes mellitus. Source: References 8, 9.

Willson M and White J. *US Pharm*. 2013;38(10).

CANVAS Study (Canagliflozin Cardiovascular Assessment Study)- Ongoing

- Designed to evaluate to evaluate the effects of canagliflozin on the risk of cardiovascular disease and to assess safety and tolerability in patients with inadequately controlled T2DM and increased cardiovascular risk

Neal B et al. *Am Heart J* 2013;166(2):217-223.

Dapagliflozin Treatment for Type 2 Diabetes

- A recent systematic review and meta-analysis of randomized controlled trials showed that dapagliflozin has beneficial effects on glucose when given as a treatment for Type 2 diabetes with significant reductions in A1c; Pooled A1c weighted mean difference (**WMD:** -0.53%; 95% CI: -0.58% to –0.47%; **p<0.00001**)
- However, further studies are needed to fully explore its safety

Zhang et al. *Diabetes Metab Res Rev* 2014;30:204-221.

Empagliflozin

- Empagliflozin (**Jardiance®**): FDA Approval on August 2014

http://www.fda.gov/

New Medications

- Glucagon-like peptide - 1 receptor agonist: Albiglutide (**Tanzeum®**): FDA approved in April 2014 and Dulaglutide (**Trulicity®**): FDA approved in September 2014 as once weekly injections
- Ultra long-acting insulin: **Insulin Degludec®**
  - Proposed to have > 24 hour activity to give better once daily dose coverage than other products
  - Half-life ~ 42 hours
  - FDA declined approval as of Feb 2013 and requested more long-term cardiovascular safety data
  - Has been **approved** in the European Union by EMA

http://www.fda.gov/

Rosiglitazone (Avandia®) Back on Track

- In June 2013, FDA had an independent analysis of the **RECORD** (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes) trial, and concluded that the trial **didn't show** an elevated risk of heart attack or death associated with rosiglitazone use

http://www.medscape.com/viewarticle/793270

Rosiglitazone (Avandia®) *cont'd*

- In 25th of November 2013, FDA announced it is requiring the **removal** of certain restrictions on prescribing and use of the diabetes drug Avandia®
- Those actions were consistent with the recommendations of expert advisory committees

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm376516.htm

Rosiglitazone (Avandia®) *cont'd*

- The FDA's actions include requiring modifications to labeling about cardiovascular safety, requiring changes to the Risk Evaluation and Mitigation Strategy (REMS) program, and releasing a postmarketing study requirement
- Once the changes are final, rosiglitazone's indication for use will no longer be limited to certain patients

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm376516.htm

Glucose Monitoring

Self-Monitoring of Blood Glucose (SMBG) (B)

Continuous Glucose Monitoring (CGM)

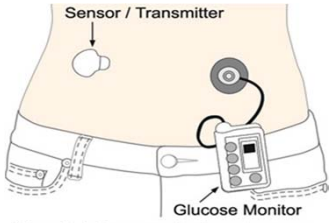


Figure 5. A glucose monitoring system worn at the belt level

Continuous Glucose Monitoring (CGM)

Useful for A1C lowering in select adults (aged ≥25 yrs) with type 1 diabetes requiring intensive insulin regimens (A)	• May be useful among children, teens, and younger adults* (C) • Success related to adherence to ongoing use
May be a useful supplement to SMBG among patients with (E)	• Hypoglycemia unawareness and/or • Frequent hypoglycemic episodes

FDA-approved device that records BG throughout the day and night and has alarms for hypo/hyperglycemic excursions

*Evidence for A1C lowering less strong in these populations
SMBG=self-monitoring of blood glucose

American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37(suppl 1):S14-S80.

SMBG vs. CGM

- A 26-week randomized multi-center trial
- 322 type 1 diabetic patients using intensive insulin therapy (IIT)
- 2 groups: CGM compared to SMBG
- Results favored adults aged ≥ 25 years using the CGM technique with a mean reduction of 0.5% in A1c; from 7.6% to 7.1% (Mean difference in change, −0.53%; 95% [CI], −0.71 to −0.35; **p-value<0.001**)

Tamborlane WV et al. N Engl J Med 2008;359:1464-1476.

Management of High Blood Pressure

Screening	Measure BP at every visit; confirm elevated BP at separate visit (B)
Treatment targets	Diabetes and hypertension: SBP <140 mm Hg (B) •Lower SBP targets (eg, <130 mm Hg) may be appropriate* (C) Diabetes: DBP <80 mm Hg (B)
Treatment	BP >120/80 mm Hg: lifestyle changes (B) •Weight loss (if overweight) • DASH-style diet incl sodium restriction, potassium increase • Moderate alcohol intake • Increased physical activity
	BP >140/80 mm Hg: lifestyle changes + pharmacologic therapy (B) •Diabetes and hypertension: ACEI or ARB† (C) •≥2 agents at max doses usually required to achieve targets (B) •Administer ≥1 agent at bedtime (A) •ACEI, ARB, diuretic: monitor serum creatinine/eGFR and serum potassium (E)
Treatment and targets for pregnant women	Diabetes and hypertension: 110-129/65-79 mm Hg target ACEI, ARB contraindicated (E)

*In certain individuals, if achieved without treatment burden; †If one class not tolerated, substitute other class
ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; BP=blood pressure; DASH=Dietary Approaches to Stop Hypertension; DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate; SBP=systolic blood pressure

American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37(suppl 1):S14-S80.

JNC8 Guidelines

- Blood pressure goal <140 /90 mmHg reduces microvascular and macrovascular complications

Am Fam Physician 2014;90(7):503-4.

Management of Dyslipidemia

Screening	Measure fasting lipids at least annually (B) Every 2 yrs for adults with low-risk lipid values: LDL-C <100 mg/dL (2.6 mmol/L), HDL-C >50 mg/dL (1.3 mmol/L), TG <150 mg/dL (1.7 mmol/L) (E)
Targets	• No overt CVD: LDL-C <100 mg/dL (2.6 mmol/L) (B) • Overt CVD: LDL-C <70 mg/dL (1.8 mmol/L), with high-dose statin* • If targets not achieved on max statin therapy: ~30–40% LDL-C reduction from baseline
Treatment	Lifestyle modification (A) •Reduce saturated fat, trans fat, cholesterol intake •Increase omega-3 fatty acids, viscous fiber, plant stenols/sterols intake •Weight loss (if indicated) •Increase physical activity
	Statin therapy* and lifestyle changes in patients with •Overt CVD (A) •No CVD, aged >40 yrs, ≥1 CVD risk factor† (A) •Consider statins in lower-risk patients (no overt CVD, aged <40 yrs) if LDL-C >100 mg/dL or if multiple CVD risk factors (C)
	Combination therapy not recommended (A)

*Contraindicated in pregnancy; †Hypertension, smoking, dyslipidemia, albuminuria, family history of CVD

American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37(suppl 1):S14-S80.

ACC/AHA 2013 Guidelines

- Suggest lowering LDL by 30-49% in patients with diabetes 40-75 years of age and by at least 50% if the 10 year risk of cardiovascular event is at least 7.5%

http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a.citation

Both Guidelines

- Recognize the high prevalence, morbidity and mortality of cardiovascular disease in patients with diabetes, and the importance of primary and secondary cardiovascular disease risk reduction in this population
- Emphasize the importance to well-being and cardiovascular risk reduction of lifestyle, healthy diet and exercise, and weight management

http://www.diabetes.org/newsroom/press-releases/2013/statement-cholesterol-guidelines.html

Both Guidelines *cont'd*

- Recognize the value of high intensity statin therapy added to lifestyle therapy for patients with diabetes and overt atherosclerotic CVD, regardless of baseline lipid levels
- Recognize risk assessment as a process and that guidelines do not replace clinical judgment and patients' circumstances in setting individualized goals and care for patients

http://www.diabetes.org/newsroom/press-releases/2013/statement-cholesterol-guidelines.html

ADA Statement

- The ADA recognizes the release of the new revised 2013 ACC/AHA guidelines:
- The ADA will consider whether moderate-dose statins should be used for the primary prevention in all patients 40-75 years of age with diabetes, regardless of baseline lipid levels or the presence of other cardiovascular risk factors
- ADA plans to review the changes in the 2013 ACC/AHA guidelines, and will determine if changes are warranted
- However, such a thorough assessment will be addressed in the 2015 Standards of Care

http://www.diabetes.org/newsroom/press-releases/2013/statement-cholesterol-guidelines.html

Antiplatelet Therapy Recommendation

Aspirin: Primary prevention	75-162 mg/day: type 1 and type 2 diabetes at increased CVD risk (10-yr risk >10%)*	(C)
	Low-risk patients (10-yr risk <5%);† not recommended; potential for bleeds likely offsets potential benefits	(C)
	Men <50 yrs, women <60 yrs with multiple other risk factors (10-yr risk 5%-10%): use clinical judgment	(E)
Aspirin: Secondary prevention	75-162 mg/day: diabetes and CVD history	(A)
CVD and aspirin allergy	Clopidogrel 75 mg/day	(B)
Dual antiplatelet therapy	Reasonable for ≤1 year after ACS	(B)

If no PCI, use clopidogrel or ticagrelor; If PCI, use clopidogrel, prassugrel or ticagrelor

*Includes most men aged >50 yrs or women aged >60 yrs with ≥1 add'l major risk factor: family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria
†Men aged <50 yrs and women aged <60 yrs with no major additional CVD risk factors
ACS=acute coronary syndrome; CVD=cardiovascular disease

American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37(suppl 1):S14-S80.

Immunization Recommendations

Influenza vaccine	Annually in all patients with diabetes aged ≥6 mos (C)
Pneumococcal polysaccharide vaccine	• All patients with diabetes aged ≥2 yrs • Aged >65 yrs: one-time revaccination if vaccine administered >5 yrs prior • Repeat vaccination for those with nephrotic syndrome, chronic renal disease, other immunocompromised states (C)
Hepatitis B vaccine New	• Unvaccinated adults with diabetes aged 19-59 yrs • Consider in unvaccinated adults aged ≥60 yrs (C)

American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37(suppl 1):S14-S80.

Nephropathy ADA 2014 Update

- Nephropathy was revised to remove terms "**micro albuminuria**: 30–299 mg/24h " and "**macro albuminuria** >300 mg/24h," and substituted them with: **persistent albuminuria measuring urine albumin excretion**

American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37(suppl 1):S14-S80.

Nephropathy *cont'd*

- Normal albumin excretion is currently defined as: **< 30 mg/24h**
- ACE inhibitors or ARB's for primary prevention of kidney disease are **not recommended** in diabetic patients with **normal** blood pressure and urine albumin excretion **below 30 mg/24h (B)**

American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37(suppl 1):S14-S80.

Neuropathy

- Two drugs have been approved for relief of DPN pain in the U.S.
  - **Pregabalin**
  - **Duloxetine**
- Others may be effective and could be considered
  - Venlafaxine, amitriptyline, gabapentin, valproate, opioids (morphine sulfate, tramadol, and oxycodone controlled-release)

American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37(suppl 1):S14-S80.

Gastroparesis

- Prokinetic agents such as **erythromycin**
- In Europe, metoclopramide use is now restricted to a max. use of **5 days** and is no longer indicated for the long-term treatment of gastroparesis
- FDA decision still pending

American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37(suppl 1):S14-S80.

References

- American Diabetes Association. Standards of Medical Care in Diabetes 2014. *Diabetes Care* 2014; 37(suppl 1):S14-S80.
- Nathan DM et al. Rationale and Design of the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE). *Diabetes Care* 2013;36(8):2254-61.
- MacEwen A et al. Drugs for Diabetes: Part 8 SGLT2 Inhibitors. *Br J Cardiol* 2012;19 (1): 26-29.
- Zhang M et al. Dapagliflozin Treatment for Type 2 Diabetes: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Diabetes Metab Res Rev* 2014;30:204-221.
- Wilson M and White J. SGLT2 Inhibitors: A Review of Canagliflozin. *US Pharm* 2013;38(10):HS13-HS20.
- Kim Y, et al. Clinical Potential of Sodium-Glucose Cotransporter 2 Inhibitors in the Management of Type 2 Diabetes. *Diabetes Metab Syndr Obes* 2012;5:313-327.
- Neal B et al. Rationale, Design, and Baseline Characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS)-A Randomized Placebo-Controlled Trial. *Am Heart J* 2013;166(2):217-223.

References *cont'd*

- Tamborlane WV et al. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous Glucose Monitoring and Intensive Treatment of Type 1 Diabetes. *N Engl J Med* 2008;359:1464–1476.
- JNC 8 Guidelines for the Management of Hypertension in Adults. *Am Fam Physician* 2014;90(7):503-504.
- Stone N et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013.
- Cefalu Wet al. Efficacy and Safety of Canagliflozin Versus Glimepiride in Patients with Type 2 Diabetes Inadequately Controlled with Metformin (CANTATA-SU): 52 week Results from A Randomized, Double-blind, Phase 3 Non-inferiority Trial. *The Lancet* 2013; 382(9896):941-950.
- Schernthaner G et al. Canagliflozin Compared with Sitagliptin for Patients with Type 2 Diabetes Who Do Not Have Adequate Glycemic Control With Metformin Plus Sulfonylurea: A 52-Week Randomized Trial (CANTATA-D2). *Diabetes Care* 2013;36(12):4172.

References *cont'd*

- http://www.idf.org/
- http://www.fda.gov/
- http://www.cdc.gov/
- http://www.medscape.com/
- http://uptodate.com/
- http://diabetes.org/
- http://www.ndei.org