PHARMACOTHERAPY OF TYPE 2 DIABETES – 2015

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OBJECTIVES
• Compare and contrast the mechanism of action of the therapeutic agents used to manage Type 2 Diabetes.
• Discuss the advantages and disadvantages of the agents used to manage Type 2 Diabetes.
• Summarize cardiovascular prevention in a diabetic patient as discussed in the recently updated hypertension and hypercholesterolemia guidelines

RESOURCES
• ADA Standards of Medical Care in DM 2015
  – Diabetes Care 15:38(suppl 1)
• ADA Management of Hyperglycemia in Type2 Diabetes: A Patient-Centered Approach
  – http://care.diabetesjournals.org/content/35/6/1364.full.pdf+
  – Diabetes Care 12:35:1364-79

CASE
• 65 y/o caucasian male
• Smokes 1 ppd, etoh 1-2 drinks 3-4x/wk
• Father had MI at age 52
• No current medications
• BP 150/92 mm Hg, HR 82, exam normal
• Waist 103 cm (40.6 in) – BMI: 32
• FPG 138 mg/dL (last visit, 120 mg/dL), A1C 8
• TC 280; LDL 187; HDL 40; TG 268
• Renal, liver, lytes WNL

RESOURCES
• AACE Comprehensive Diabetes Management Algorithm 2013 Consensus Statement
• Clinical Practice Guidelines Pharmacologic Management of T2DM, Canadian Diabetes Association Clinical Practice Guidelines Expert Committee
  – Can J Diabetes 13:37:561-8

Insulin Resistance Syndrome

Insulin Resistance Syndrome

Cardiometabolic Risk (DM, CVD)

Abnormal Lipid Metabolism

Genetics

Age

Overweight, Obesity

Smoking, Inactivity

HTN

Inflammation, Hypercoagulation

JACC 08;51:1512–24

↑ LDL
↑ ApoB
↑ TG
↓ HDL
Trends in CV Health Metrics & Associations With All-Cause & CVD Mortality

- 44,959 from the NHANES
- Metrics for ideal CV health
  - 2020 AHA strategy – improve CV health in US by 20% & decrease death from CV and CVA by 20%
  - Not smoking; physically active; normal BP (<120/80), blood glucose (<100) and TC (<200) levels, and BMI; healthy diet
- Only 2% met all 7 health metrics
- Lower mortality with increasing number of metrics that were met

Pathogenesis of T2DM

- Insulin resistance (muscle, fat, liver)
  - Decreased glucose uptake
- Increased endogenous glucose production
- Insulin secretory dysfunction
- Deranged adipocyte biology
- Decreased incretin effect
- Increased glucagon secretion (lack of suppression)
- Increased glucose reabsorption by renal tubule
- Neurotransmitter dysfunction

Pathogenesis Type 2 Diabetes

- Peripheral insulin resistance AND relative insulin deficiency
  - Progression to mostly insulin deficiency – initially ↑PPG
  - β-cell secretion of insulin is decreased

Drugs-induced diabetes

- Nicotinic acid
- Glucocorticoids
- Thyroid hormone
- Diazoxide
- β-adrenergic blockers
- Thiazides
- Atypical antipsychotics
- Dilantin
- Interferon
- Statins

Case

- 34 y/o male presents with complaints of a rash
  - Present for 2 wks
  - Started on arms → shoulders and back
- PMH:
  - OCD, Chronic Depression/Anxiety, Mild Intellectual Disability
- Meds:
  - Paroxetine 60 mg qd; Clonazepam 2 mg qhs; Quetiapine (Seroquel) 200 mg qhs
ANTI-DIABETES AGENTS - 2002

- Sulfonylureas
  - 1st generation vs. 2nd generation
- Biguanides (Metformin)
- Alpha-glucosidase inhibitor
  - Acarbose – Precose
  - Miglitol – Glyset
- Meglitinides
  - Nateglinide – Starlix
  - Repaglinide – Prandin
- Thiazolidinediones
  - Pioglitazone – Actos
  - Rosiglitazone – Avandia
- Insulin

JAMA 02;287:360-72

ANTI-DIABETES AGENTS - 2014

- Sulfonylureas
  - Glipizide - Glucotrol, Glucotrol XL, generic
  - Glyburide - Diabeta, Glynase, gen
  - Glimepiride - Amaryl, gen
- Biguanides (Metformin)
  - Generic
  - Glucophage, XR
  - Combinations
- Alpha-glucosidase inhibitor
  - Acarbose – Precose, generic
  - Miglitol – Glyset
- Meglitinides
  - Nateglinide – Starlix, gen
  - Repaglinide – Prandin, gen
- Thiazolidinediones
  - Pioglitazone – Actos, gen
  - Rosiglitazone – Avandia, gen
- Insulin
  - Rapid-acting
  - Regular
  - Intermediate-acting
  - Basal
  - Inhaled?

- GLP-1 receptor agonists
  - Exanatide – Byetta (immediate), Bydureon (ER)
  - Liraglutide – Victoza
  - Albiglutide – Tanzeum
- Dipeptidyl peptidase-4 (DPP-4) inhibitors
  - Linagliptin – Tradjenta
  - Saxagliptin – Onglyza
  - Sitagliptin – Januvia
  - Alogliptin – Nesina
- Amylin analogue
  - Pramlintide – Symlin
- Sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitors)
  - Canagliflozin – Invokana
  - Dapagliflozin – Farxiga
- Bile acid sequestrants
  - Colesevelam – Welchol
- Dopamine receptor agonist
  - Bromocriptine – Cycloset

Class Mechanism

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Activates insulin receptor ↑Glucose disposal, ↓Hepatic glucose production</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amylin mimetics</td>
<td>Activates amylin receptors ↓Glucagon, ↑gastric emptying, ↑satiety</td>
</tr>
<tr>
<td>Sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitors)</td>
<td>↓Renal glucose reabsorption ↑Urine glucose excretion ↓Blood glucose</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Binds bile acids ↓Hepatic glucose production?</td>
</tr>
<tr>
<td>Dopamine-2 agonists</td>
<td>Activates DA receptor alters hypothalamic control of metabolism ↑Insulin sensitivity</td>
</tr>
</tbody>
</table>

EFFECTS OF THERAPY ON ß-CELL FUNCTION

- ß-cell function progressively declines with further deterioration of PG
- SUs induce apoptosis of ß-cell
- Metformin may not inhibit decline on ß-cell function
  -TZDs, GLP-1 agents
- Not known if this improves clinical outcomes

Endocrinol Metab Clin N Am 13:42-94/70
REFERENCES FOR ADVANTAGES & DISADVANTAGES
- Diabetes Care 09;32:193-203 & 10;33:429
- NEJM 12;366:1319-27
- Diabetes Care 12;35:1364-79
- J Amer Medical Direct Assoc 14;15:786-801
- Endocrinol Metab Clin N Am 13;42:947-70
- Treatment Guidelines from The Medical Letter 14;12:17-24
- Med Clin N Am 15;99:131-43
- Med Clin N Am 15;99:87-106
- Am J Kidney Dis 14;63(S2):S22-S38
- Am J Kidney Dis 14;64:510-33

METFORMIN
- Preferred initial agent for T2DM
  - ADA, AACE, Eur Assoc Study Diabetes
- Advantages
  - One of most potent at reducing A1c 1-2%
  - Weight neutral or weight loss of 0.6-2.9 kg
  - Little risk of hypoglycemia with monotherapy
  - Decreases CV events and mortality
    - Meta-analysis showed no CV harm with possible benefit vs. placebo
      Diabetes, Obesity Metabolism 11;13:221-8
  - May be useful for pre-DM

SULFONYLUREAS
- Stimulate insulin secretion – requires residual β-cell function
  - 2nd generation greater potency & efficacy
    - Clin Diab 05;23:64-76
    - Endocrinol Metab Clin N Am 13;42:947-70
  - 66-70% initially respond
    - 5-10%/y failure rate
    - Islet cell “burnout”
    - Noncompliance
    - Disease progression
    - Often need additional agents
      NEJM 96;334:574-70

SULFONYLUREAS
- Advantages
  - One of most potent at lowering A1c 1-2%
  - Many years of use
  - Low GI
  - 1xd dosing
  - Low cost ~$4/month
  - CKD – Glipizide (Glucotrol) no dosage change,
    - Glimepiride (Amaryl) lower dose
- Disadvantages
  - May induce β-cell failure – “tolerance” develops
  - Increases insulin release
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  - Increases insulin release
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  - Increases insulin release
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  - Increases insulin release

SULFONYLUREAS
- Disadvantages (cont.)
  - Hypoglycemia
    - > with elderly & renal/hepatic dysfunction, missed meals
    - > with Glyburide
  - Weight gain of 1.5-2 kg in 1st year is common
    - Due to hyperinsulinemia
    - Contributes to insulin resistance & drug failure
  - Avoid Glyburide (Micronase) in renal dysfunction
  - FDA warning about increased risk of CV death?
  - Hypersensitivity – sulfa
MEGLITINIDES
• Repaglinide (Prandin), Nateglinide (Starlix)
• Reduce A1c 0.5-1.5
• Advantages
  – Rapid onset and duration of insulin release – ↓ PPG
  • Dose with meals – no meal then no dose
  – Safer than some SUs with CKD
  • eGFR < 30 start Repaglinide 0.5 mg or Nateglinide 60 mg
• Disadvantages
  – Hypoglycemia, weight gain
  – Frequent dosing with meals
  – Higher cost than SUs, > $100/month

TZDs/Glitazones Disadvantages
• ↑ weight (~5kg) by activation of adipose tissue
• Fluid retention
  – Edema
  – CHF – contraindicated in NYHA III or IV
Prescribing Information. Actos, Avandia
• Possible increased MI risk with rosiglitazone??
NEJM 07;356:2457-71 Cochran Database of Systematic Reviews 07, Issue 3, Art. No. CD006063
  – See recent FDA statement 11/25/13
Endocrinol Metab Clin N Am 13;42:947-70

FDA Drug Safety Communication: Restrict Access to Rosiglitazone
• Limits use of rosiglitazone to:
  – Already being successfully treated
  – Cannot be controlled with other anti-diabetic medicines
  – Enrollment in Avandia-Rosiglitazone Medicines Access Program is required for providers
• No longer available through pharmacies
  – Only available to enrolled patients by mail order from certified pharmacies

Thiazolidinediones (TZDs, Glitazones)
• Pioglitazone (Actos), Rosiglitazone (Avandia)
• Reduce A1c 0.5-2%
• Advantages
  – Improve insulin sensitivity & preserve β-cell
  • No tolerance?
  – No hypoglycemia
  – Pioglitazone reduces lipids and CV?
  – Pioglitazone CKD – no dose change
  – Used in preDM
  – 1xd dosing

TZDs/Glitazones Disadvantages
• Bladder cancer with pioglitazone
• Negative effect on bone with 2x risk of fractures
• Moderate to high cost
  – Generics ~$45/month

FDA removal of some prescribing and dispensing restrictions for rosiglitazone
• Recent data do not show an increased risk of CV events
• Distribution will no longer be restricted
• May be used to improve control of blood sugar
• No longer required to enroll patients in the rosiglitazone Risk Evaluation & Mitigation Strategy program to prescribe, dispense, or receive rosiglitazone
**α-GLUCOSIDASE INHIBITORS**

- Acarbose (Precose), Miglitol (Glyset)
- Reduce A1c 0.5-1%
- Advantages
  - No weight gain
  - No hypoglycemia
  - Slows glucose absorption & reduces PPG
  - Used for pre-DM
  - May reduce CV events
- Disadvantages
  - GI side effects are common
  - 3x3d dosing
  - Caution with GI diseases
  - Caution in CKD with eGFR <25-30
  - Moderate cost – generic

**INCRETIN-BASED THERAPY**

- Incretins normally released after meals by intestine
  - Rapidly inactivated by dipeptidyl peptidase-4 (DPP-4)
- Incretin mimetics – GLP1 agonists
  - Increases insulin when PG is high (glucose-dependent)
  - Decreases glucagon secretion (glucose-dependent)
  - Slows gastric emptying
  - Promotes satiety with decreased food intake
- DPP-4 inhibitors
  - Inhibits break down of incretins
  - Prolongs incretin survival

### Chart: Glucose-dependent insulin secretion vs. DPP-4 inhibitors

<table>
<thead>
<tr>
<th></th>
<th>GLP-1 agonists</th>
<th>DDP-4 inhib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose-dependent insulin secretion</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Reduce FPG</td>
<td>Weak</td>
<td>Weaker</td>
</tr>
<tr>
<td>Reduce PPG</td>
<td>Yes</td>
<td>Yes – weaker</td>
</tr>
<tr>
<td>Effect on A1c</td>
<td>~0.5-1.8</td>
<td>~0.5-1.8</td>
</tr>
<tr>
<td>Increase (pro)insulin biosynthesis</td>
<td>Yes</td>
<td>Yes – weaker</td>
</tr>
<tr>
<td>Improved β-cell function</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Beneficial CV effects</td>
<td>Probable</td>
<td>Not proven</td>
</tr>
</tbody>
</table>

**INCRETIN-BASED THERAPY**

- GLP-1 receptor agonists – Incretin mimetics
  - “tides”
  - Exenatide (Byetta), Exenatide ER (Bydureon)
  - Liraglutide (Victoza)
  - Albiglutide (Tanzeum)
- Dipeptidyl peptidase-4 inhibitors (DPP-4Is)
  - “gliptins”
  - Linagliptin (Tradjenta)
  - Sitagliptin (Januvia)
  - Saxagliptin (Onglyza)
  - Alogliptin (Nesina)

**Dipeptidyl peptidase-4 inhibitors (DPP-4 Inhibitors)**

- Prolongs duration of endogenous incretin action
- Decrease A1c 0.5-1%
- “apparently are similar with regard to efficacy and tolerability”

- GLP-1 agonists | DDP-4 inhib |
<table>
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<tbody>
<tr>
<td>Route</td>
<td>SC</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>0</td>
</tr>
<tr>
<td>Gastric</td>
<td>Decreased emptying</td>
</tr>
<tr>
<td>Effects on appetite</td>
<td>Decreased</td>
</tr>
<tr>
<td>Weight</td>
<td>Loss</td>
</tr>
<tr>
<td>Use in CKD</td>
<td>Not rec Exen GFR &lt;30; Liraglutide &lt;60</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>GL pancreatitis?, thyroid cancer?</td>
</tr>
</tbody>
</table>
Possible pancreatitis and pre-cancerous findings from incretin mimetics  
- Postmarketing reports of acute pancreatitis associated with incretin mimetics – previously reported  
- Unpublished findings  
  - Increased risk of pancreatitis and pre-cancerous cellular changes (pancreatic duct metaplasia)  
- FDA not reached any conclusions  
  - Will obtain and evaluate new information  
- “patients should continue to take their medicine as directed until they talk to their health care professional, and health care professionals … follow the prescribing recommendations in the drug labels.”  

AMYLIN MIMETICS  
- Pramlintide (Symlin)  
- Reduce A1c by 0.5-1  
- Advantages  
  - Weight loss  
  - No hypoglycemia with monotherapy  
  - Decrease PPG  
- Disadvantages  
  - SC injection  
  - GI  
  - 3xd dosing  
  - Hypoglycemia with insulin FDA warning  
  - Not recommended GFR < 30  
  - High cost

KIDNEYS and GLUCOSE  
- Normal GFR  
  - 180 L filtered/d, 180 g glucose filtered/d, 720 Cal/d  
  - Only ~ 1% excreted in nondiabetics  
- Proximal tubule  
  - SGLT2 responsible for ~90% of renal glucose reabsorption, SGLT1 ~10%  
  - Binds with glucose and Na+  
  - Active transfer Na+ coupled with glucose across luminal surface of epithelial cells  
- Glucose transporter protein (GLUT 1 & 2) transports glucose across to basolateral membrane and into capillary  
- SGLT2 and GLUT2 are upregulated in T2DM

Pancreatic Safety of Incretin-Based Drugs – FDA and EMA Assessment  
- Analysis of database  
  - No compelling evidence of increased risk of pancreatitis or pancreatic cancer  
- Agencies agree  
  - Assertions of causal association for pancreatitis or pancreatic cancer “are inconsistent with the current data.”  
- No final conclusion yet of a causal relationship  
  - Pancreatitis continues to be considered a risk

KIDNEYS and GLUCOSE  
- Involved in glucose control  
- Liver & kidney only organs with significant glucose-6-phosphatase for gluconeogenesis  
  - ~20% of overall endogenous glucose release  
  - ~40% of glucose released by gluconeogenesis  
- Increases in conjunction with hepatic glucose output  
- Renal glucose use about 10% of all use by body  
- Glomerular filtration and reabsorption  
Med Clin N Am 15;99:131-43  

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SGLT2 INHIBITORS

- Canagliflozin (Invokana), Dapagliflozin (Farxiga)
- Novel mechanism of action - inhibits SGLT2
  - Inhibit ~30-50% of filtered glucose
  - Increases urinary glucose excretion to ~ 80 g/d
    - Increasing dose after 50% inhibition does not increase
  - Dose-dependent decrease in FPG and PPG
  - Reduces A1c 0.5-1.5%

Advances Chronic Kidney Dis 14;21:297-303
Diab Res Clin Pract 14;104:297-322
Med Clin N Am 15;99:131-43

SGLT2 INHIBITORS

- Agents dependent on β-cell and/or peripheral insulin resistance
  - May see decreased activity over time as DM progression occurs
- Action not dependent on β-cell or peripheral insulin sensitivity
  - May continue to be effective over time

Advantages
- Weight loss of ~2-4.7 kg
- No hypoglycemia in monotherapy (OR 0.44 vs others)
- Reduces FPG and PPG
  - Decreases total glucose vs. time area under the curve
  - May be as effective as metformin in monotherapy
- Decreases SBP ~2-10 mmHg & DBP ~1.3-1.9
- Canagliflozin 1xd before bkfst; Dapagliflozin 1xd anytime

Disadvantages
- Polyuria, frequency – caution orthostasis in elderly
- Genital yeast infections ~3-8% (OR 3.5-5 vs. comparators)
- UTIs – ~0.3-2% (OR ~1.3 vs. comparators)
- Don’t use: Canagliflozin GFR < 45, Dapagliflozin GFR < 60
- Bladder cancer with dapagliflozin?
- Hyperkalemia – ACEIs/ARBs, K-sparing diuretics
- Hypermagnesemia, hyperphosphatemia
- High cost ~$290/month

CANAGLIFLOZIN AND PPG

- SGLT1 transports glucose in the small intestine
  - Canagliflozin has weak SGLT1 inhibition
- High doses may decrease PPG by transiently inhibiting/prolonging glucose absorption
- 37 inadequately controlled on metformin
  - Crossover study with placebo and canagliflozin
- 300/300 mg > ↓ FPG & PPG vs. 300/placebo or 300/150 mg with similar glucose excretion
- May have a non-renal mechanism in addition to SGLT2 inhibition (major action)
**Canagliflozin in T2DM Inadequately Controlled with Metformin and SU**

- Randomized trial with canagliflozin (or placebo) added to metformin plus SU over 52 weeks
  - Further A1c reduction of ~1%
  - Decrease BP ~3.3/1.3
  - Decrease weight by about 2.8%
  - 4% increased urine frequency, polyuria
    - Volume-related AE ~1.8% with 300 mg dose
  - Mycotic infection 5-13%, UI 0.6%
  - Increased hypoglycemic episodes 18-24%

Int J Clin Pract 13,67:1267-82

**WHAT DOES A NORMAL OR GOAL VALUE MEAN IN THERAPY?**

- This used to be easy to answer based on the normal range given for a particular condition
- Today this is not as simple to answer
- Numerous outcome studies in diabetes, hypertension, hypercholesterolemia, etc. have “tinkered” with what used to be considered normal and goals of therapy
  - ADA 2014, AACE DM guidelines
  - JNC 8 Panel Hypertension 2013
  - AHA/ACC LDL guideline 2013

**DIABETIC COMPLICATIONS**

“Intensive glycemic control reduces the risk of microvascular complications of type 2 diabetes, but the effect of strict glycemic control on the risk of macrovascular disease (especially in well-established type 2 diabetes) is less certain.”

NEJM 12,366:519-27

**BILE ACID SEQUESTRANTS**

- Colesevelam (Welchol)
  - Reduce A1c by ~0.5-1%
  - Advantages
    - Weight neutral
    - No hypoglycemia
    - Decrease LDL
    - May be safe CKD
  - Disadvantages
    - GI
    - Increase TG
    - DDI with adsorption
    - High cost ~$330/month

**GLYCEMIC GOALS – ADA 08**

- HgA1C < 7%
- Clearly reduces microvascular and neuropathic complications
  - Possibly reduces macrovascular disease
- Studies suggest an incremental (in absolute terms, a small) benefit to lowering A1c into the normal range
  - Goal for selected individual patients is as close to normal (<6%) as possible without significant hypoglycemia

**The Action to Control CV Risk in Diabetes (ACCORD) Study Group**

- Sponsored by NHLBI – 77 clinics US/Canada
  - 10,251 patients
- Whether HgA1c < 6% vs. 7-7.9% reduced rate of CV events
- Terminated 17 months early – after 3.5 y
- Safety committee on 1/8/08 – “increased rate of death from any cause in the intensive-therapy group vs. standard-therapy group outweighed any potential benefits”

NEJM 08;358:254-59
Glycemia Management and CV Risk in T2DM: An Evolving Perspective

- Because of ACCORD, ADVANCE, and VADT
- Recently diagnosed DM with no prior CVD events
  - Achieving normal or near-normal A1c appears to be effective in preventing CVD events and mortality
- Diabetes for > 8-10 y with CVD
  - Achieving normal or near-normal A1c does not reduce further CVD events or mortality
- Control risk factors for CVD & microvascular complications
  - Aggressive therapy of HTN, lipids, & PG, use of ASA, & stop smoking is highly beneficial

Endocrine Practice 08;14:639-43

Glycemic Recommendations for Nonpregnant Adults with Diabetes

- Goals should be individualized (patient-centered):
  - Duration of diabetes
  - Age/life expectancy
  - Comorbid conditions
  - Known CVD or advanced microvascular complications
  - Hypoglycemia unawareness
  - Individual patient considerations
- More or less stringent glycemic goals may be appropriate for individual patients
- Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals

ADA Guidelines 2013

Recommendations: Glycemic A1c Goals in Adults

- A1c goal ~7% or less is reasonable
  - Decreases microvascular complications
  - If achieved soon after diagnosis may lead to long-term reduction in macrovascular disease
- A1c < 6.5% is reasonable for individual patients
  - If no significant hypoglycemia or adverse effects
  - Short duration, therapy with lifestyle or metformin only, long life expectancy, and no significant CVD

ADA Guidelines 2015

2011 ADA DIABETIC CONTROL

- A1C < 7% – Primary target
- Preprandial capillary PG
  - 70-130 mg/dl
- Peak PPG
  - < 180 mg/dl
- Goals should be individualized based on:
  - Duration of diabetes; age/life expectancy; comorbid conditions; CVD or advanced microvascular complications, hypoglycemia unawareness; individual patient considerations

ADA Guidelines 2011

PATIENT-CENTEREDNESS

- Recommendations are intended to guide an overall approach to managing a patient population
- “One size does not fit all”
  - Patients may not meet the entry criteria for the studies used to develop recommendations in the guidelines
- Practitioners should use science and the art of medicine to make therapy decisions for individual patients

ADA Guidelines 2015

Recommendations: Glycemic A1c Goals in Adults

- A1c < 8% may be appropriate
  - History of severe hypoglycemia, limited life expectancy, advanced micro- or macro-vascular complications, extensive comorbid conditions, or longstanding DM
  - The general A1c goal may be difficult
    - Despite self-management education, appropriate glucose monitoring, and effective doses of multiple glucose lowering agents including insulin

ADA Guidelines 2015
ADA Guidelines 2015

Adapted with permission from Inzucchi et al. Diabetes Care 12;35:1364-9

AGS Guidelines for Improving Care of Older Adults with DM 2013

- A1c goal generally should be 7.5-8%
- A1c 7-7.5% may be appropriate
  - Safely achieved in healthy & good functional status
- A1c 8-9% may be appropriate
  - Frail and limited life expectancy
  - LTC “an upper limit of 9% is now considered acceptable” J Am Medical Direct Assoc: 14:15786-801
- Potential harm with A1c < 6.5%

JAGS 13:61 2020-26

ADA Recommendations:
Therapy for Type 2 Diabetes

- Therapeutic lifestyle in all
- Metformin preferred initial agent (A)
  - If not contraindicated & if tolerated
- Newly diagnosed & markedly symptomatic &/or elevated PG or A1C
  - Consider insulin, with/without additional agents (E)
- Noninsulin monotherapy at maximal dose fails to achieve/maintain A1C target (B)
  - Add 2nd oral, GLP-1 receptor agonist, basal insulin

ADA Guidelines 2015

ADA Recommendations:
Therapy for Type 2 Diabetes

- A1c ≥ 9%
  - Consider dual combination therapy
  - Consider insulin
    - Severe hyperglycemia
    - Symptomatic
    - Catablic (weight loss, ketosis)

ADA Guidelines 2015

ADA Recommendations:
Therapy for Type 2 Diabetes

- A patient-centered approach should be used to guide choice of agents based on (E):
  - Efficacy, cost, potential side effects, effects on weight, comorbidities, hypoglycemia risk, and patient preferences
- T2DM is progressive
  - Insulin is eventually indicated for many patients (B)

ADA Guidelines 2015
Antihyperglycemic Therapy in T2DM: General Recommendations

ADA Guidelines 2015. Adapted with permission from Inzucchi et al. Diabetes Care 12;35:1364-9

ALGORITHMS

• “easy-to-use decision flow chart based on existing clinical practice guidelines, evidence, and strong expert consensus”

• Evidence- & nuance-based clinical tools
  – From guidelines and new information

• “responsible clinical decision making requires that each patient encounter uses all available evidence; to do otherwise is to abdicate clinical responsibility for patient care”
Letter from AACE. JAMA IM 14:174-827

INSULIN

• “Perhaps because of the reluctance of patients and providers, insulin is generally added much later than medically indicated.”
  NEJM 12;366:1319-27

• Categorized by onset and duration of action
  – Determines timing of dose and frequency of dose

INSULIN CONSIDERATIONS

• Insulin is initially preferred
  – Severely uncontrolled diabetes with catabolism
    • PG > 300-350 mg/dL
    • A1c > 10-12%
    • Presence of ketonuria
    • Symptomatic (polyuria, polydipsia and weight loss)
  – After controlling symptoms and PG
    • Oral agents may eventually be added
    • May be possible to taper insulin off (if preferred)

ADA Guidelines 2015
Cardiovascular Disease and DM

- Major cause of morbidity, mortality in DM
  - Largest contributor to direct/indirect costs
- Common conditions (e.g., HTN, LDL) are clear risk factors for CVD
- DM is an independent risk
- CV benefits when risk factors are controlled
  - Greater benefit the greater multiple risk factors are controlled

ADA Guidelines 2015

JNC 8 PANEL RECOMMENDATIONS

- > 18 y with diabetes, meds at SBP > 140/90
- Goal < 140/90 (Expert Opinion –Grade E)
- RTCs with SBP < 150
  - Better cerebrovascular and CV outcomes, lower mortality
  - No RTCs if better efficacy with SBP < 140
    - Use 140 since consistent with recommendation # 3

ADA Guidelines 2015

Effects of Intensive BP Control in Type 2 DM – ACCORD

- No evidence from RCT to support systolic BP (SBP) < 135-140
- 4733 with T2DM
  - Intensive (SBP <120) vs. standard (SBP <140)
  - Primary outcome
    - Composite CV & mortality outcomes over 4.7 y
- At 1 y mean SBP was 119.3 vs. 133.5
  - 3.4 meds vs. 2.1 meds

NEJM 10;362:1575-85

Oral Agents Plus Insulin

<table>
<thead>
<tr>
<th>Drug</th>
<th>% ↓ A1c</th>
<th>Insulin Hypoglycemia</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>0.74-2.5</td>
<td>0, ↓</td>
<td>↑ 1.1-3.9</td>
</tr>
<tr>
<td>SU</td>
<td>0.3-2</td>
<td>↑ basal</td>
<td>↑ 1.8-3.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓↑ mixed/prandial</td>
<td></td>
</tr>
<tr>
<td>TZD</td>
<td>0.5-1.5</td>
<td>↑</td>
<td>↑ 2.9-5.3</td>
</tr>
<tr>
<td>Incretin Tx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exanatide</td>
<td>0.87</td>
<td>↑</td>
<td>↓ 5.2</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>0.5</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>α-gluc inhib</td>
<td>0.5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Southern Med Assoc 10;103:58-65

JNC 8 PANEL RECOMMENDATIONS

- Common recommendation for SBP < 130 not supported by any RCT
  - ACCORD-BP compared SBP < 120 vs. 140
  - No difference in composite of CV health, nonfatal MI and nonfatal CVA
  - No difference in secondary outcomes except CVA (absolute difference 0.21%/y, NNT ~475)
- No good RCTs comparing DBP < 90 vs. < 80
DM and HTN Goals
ADA Guidelines 2015

- Target of < 140/90 (A)
  - Lower targets such as < 130 (C) and < 80 (B) may be appropriate
  - Younger patients if achieved with few drugs and without side effects. (C)
  - “change in the “default” SBP target is not meant to downplay the importance of treating HTN … or to imply that lower targets than < 140 are generally inappropriate”

Standards of Medical Care in Diabetes 2013. Diabetes Care 36; Suppl 1:S11-S66
http://care.diabetesjournals.org/content/36/Supplement_1/S11.full

<table>
<thead>
<tr>
<th>YEAR</th>
<th>GOAL BP AGE</th>
<th>GOAL BP DM, CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>JNC 7</td>
<td>&lt; 140/90</td>
<td>&lt; 130/80</td>
</tr>
<tr>
<td>JNC 8</td>
<td>≥ 60 y ≤ 150/90</td>
<td>≤ 140/90</td>
</tr>
<tr>
<td>ACC/AHA</td>
<td>&lt; 140/90</td>
<td>Lower may be appropriate</td>
</tr>
<tr>
<td>ADA</td>
<td>2014</td>
<td>&lt; 140/80</td>
</tr>
<tr>
<td>ESH/ESC</td>
<td>2013</td>
<td>DM &lt; 140/85</td>
</tr>
<tr>
<td>ESH/ESC</td>
<td>2013</td>
<td>CKD no protein &lt; 140/90</td>
</tr>
<tr>
<td>ESH/ESC</td>
<td>2013</td>
<td>CKD protein &lt; 130/90</td>
</tr>
<tr>
<td>CHEP</td>
<td>2014</td>
<td>DM &lt; 130/80</td>
</tr>
<tr>
<td>CHEP</td>
<td>2014</td>
<td>CKD &lt; 140/90</td>
</tr>
<tr>
<td>NICE</td>
<td>2011</td>
<td>≥ 80 y &lt; 150/90</td>
</tr>
<tr>
<td>Kidney Dis Improving Global Outcome</td>
<td>2012</td>
<td>No protein &lt; 140/90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Protein ≥ 130/80</td>
</tr>
</tbody>
</table>

Combination Lipid Therapy in Type 2 Diabetes Mellitus – ACCORD

- “do not support the use of combination fibrate-statin therapy … to reduce CV risk in the majority … who are at high risk for CVD.”

NEJM 10.1056/NEJMoa0808678
- “flexible goals should probably be applied to the control of hyperglycemia, BP, and dyslipidemia … taking into account individual clinical factors of importance.”

NEJM 10.1056/NEJMoa0808678 editorial

DM and HTN Goals
ADA Guidelines 2015

- Lifestyle therapy (B)
- Pharmacological therapy should use ACEI or ARB (B)
- Multiple-drug therapy (including a thiazide and ACEI/ARB at maximal doses) is generally required to achieve BP targets (B)

ATP III: Updated LDL-C Goals, Treatment Cutpoints

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal</th>
<th>Initiate TLC</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CHD risk equivalents (10-y risk &gt;20%)</td>
<td>&lt; 100 (optional: &lt; 70)</td>
<td>≥ 100</td>
<td>≥ 100 (consider drug options)</td>
</tr>
<tr>
<td>Moderately high risk: ≥ 2 RFs (10-y risk 10–20%)</td>
<td>≤ 130 (optional: &lt; 100)</td>
<td>≤ 130</td>
<td></td>
</tr>
</tbody>
</table>

DM and STATIN THERAPY

- For each ~38.5 mg/dL decrease in LDL
  - 9% decrease in all cause mortality
  - 13% decrease in vascular mortality

Lancet 08;371:117-25 Meta-analysis
- Decreases in CVD outcomes (CHD death and nonfatal MI) are greatest in high CVD risk
  - Known CVD &/or Very high LDL
- Moderate or high risk for CVD with DM
  - “overall benefits of statin therapy … are convincing.”

ADA Guidelines 2015
STATIN BENEFIT GROUPS

- Potential for an ASCVD risk reduction benefit clearly exceeds potential for adverse effects
  - With ASCVD
  - LDL ≥190 mg/dL
  - 40-75 y with DM (no ASCVD) with LDL 70-189
  - No clinical ASCVD or DM who are 40-75 y with LDL 70-189 & estimated 10-y ASCVD risk of ≥ 7.5%

AHA/ACC Lipid Guidelines 2013

EXAMPLES OF STATIN BENEFIT GROUPS VS. LDL TARGETS

- Type 2 diabetes
  - 40-75 years with risk factors, the potential benefits of LDL lowering with a high-intensity statin are substantial
  - "goal" directed therapy often encourages use of lower statin dose than is supported by the RCTs
  - Nonstatin drugs may be added to address low HDL or high TG, lack of evidence

AHA/ACC Lipid Guidelines 2013

CASE 2

- New ACC/AHA guidelines
  - Moderate- to high intensity statins for primary prevention is recommended for DM 40-75 y
  - Calculated 10-y CVD risk 3%
  - Statins can reduce risk to 2%
  - Patient – benefits seem insufficient
  - Decides against statins & focus on lifestyle

- Conflicted situation prior to new guidelines
  - Preference of patient vs. poor performance on quality measures that are public

DM and STATIN THERAPY

- Should use high-intensity statins (A)
  - All ages with known CVD (A)
  - 40-75 y with additional CVD risk factors (B)
    - Calculated 10-y risk ≥ 7.5%

- Consider moderate- or high-intensity statins
  - < 40 y with additional CVD risk factors (C)
  - > 75 y with additional CVD risk factors (B)

- Consider moderate-intensity statins
  - > 75 y without additional CVD risk factors
  - 40-75 y without additional CVD risk factors (A)
    - Calculated 10-y risk < 7.5%

AHA/ACC Lipid Guidelines 2013  ADA Guidelines 2015  NEJM 14;370:275-8

CASE 2

- 45 y/o woman
  - Moderately obese, T2DM (A1c 6.7%),
  - 135/85, HDL 40, TC 200, LDL 109

- According to ATP III guidelines
  - DM considered CHD risk equivalent
  - Should use statins to LDL < 100
  - Physician held accountable quality measure
  - Patient leaves with a statin
  - She is not sure of benefit/risk or whether she wants to start this form of treatment.

Opinion JAMA 14;311:465-6

Statins – FDA Drug Safety Communication: Labeling Changes

- “Increases in … A1C and fasting serum glucose levels have been reported”
  - Trials suggest >10% increased risk vs. placebo
- “FDA continues to believe that the CV benefits of statins outweigh these small increased risks.”

STATINS & DM RISK
ACC/AHA LDL GUIDELINE 2013
• Modest excess risk of new onset DM in RCTs and meta-analyses
  – 0.1 excess case per 100 treated 1 y with moderate-intensity statin therapy
  – 0.3 excess cases per 100 treated 1 y with high-intensity statin therapy
• Mostly with those with risk factors for DM
  – Usually also at higher risk of ASCVD

CVA Risk Factor Control – Disorders of Glucose Metabolism & Diabetes
• 11.3% U.S. adults have diagnoses or occult DM
• Associated with increased risk for 1st ischemic CVA (RR 1.5-3.7)
• No major trials for secondary prevention have examined interventions for pre-DM or DM
• All at risk for vascular disease benefit from statins regardless of pre-treatment LDL
• Target BP goal < 140/80 mm
AHA/ASA Guidelines for the Prevention of Stroke in Patients With Stroke and TIA [published online ahead of print 5/1/14]. http://stroke.ahajournals.org/content/early/2014/04/30/STR.0000000000000024

AHA/ASA CVA Prevention Glucose Disorders Recommendations
• Screen for DM with testing of FPG, A1c, or OGTT
  – Choice should be guided by clinical judgment
• Optimal A1c < 6% or 6.5% should be for prevention of macrovascular disease
  – May be modestly effective for preventing non-fatal CHD events compared to HbA1c < 7-8%
• Intensive treatment does not appear to ↓ all-cause mortality or CVA & ↑ risk for severe hypoglycemia
AHA/ASA Guidelines for the Prevention of Stroke in Patients With Stroke and TIA [published online ahead of print 5/1/14]. http://stroke.ahajournals.org/content/early/2014/04/30/STR.0000000000000024

STATINS AND DM
ACC/AHA LDL GUIDELINE 2013
• Evaluate for new-onset DM according to current screening guidelines
• DM during statin therapy
  – Encouraged to adhere to heart healthy diet, physical activity, healthy weight, cease tobacco, and continue statins to reduce risk of ASCVD events

AHA/ASA CVA Prevention Glucose Disorders Recommendations
• Optimal A1c < 6% or 6.5% should be for prevention of macrovascular disease
  – May be modestly effective for preventing non-fatal CHD events compared to HbA1c < 7-8%
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