ACE Inhibitors and ARB Use in Type 2 Diabetic Patients

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ACO Measures

- ACO 33: Angiotensin-Converting Enzyme (ACE) Inhibitor or Angiotensin Receptor Blocker (ARB) – Diabetes or Left Ventricular Systolic Dysfunction (LVEF < 40%)
- ACO 26: Daily Aspirin or Antiplatelet Medication Use for Patients with Diabetes and Ischemic Vascular Disease

- ACO 33: Angiotensin-Converting Enzyme (ACE) Inhibitor or Angiotensin Receptor Blocker (ARB) – Diabetes or Left Ventricular Systolic Dysfunction (LVEF < 40%)

ACE Inhibitors and ARB's

- Indicated for HTN, CHF, DM nephropathy
- Lower BP - vasodilation, natriuresis
- Decrease albuminuria and stabilize GFR
- Decrease cardiac workload by lowering arteriolar resistance, increase venous capacity, decrease cardiac output, stroke work and stroke volume

ACE Inhibitors

Agent	Initial Dose	Target for CHF
Captopril*	25 mg BID	50 mg TID
Enalapril*	10 mg QD	20 mg BID
Lisinopril*	5 – 10 mg QD	40 mg QD
Ramipril*	2.5 mg QD	5 mg BID
Quinapril*	5 - 10 mg QD	20 mg BID
Fosinopril*	10 mg QD	20 mg BID
Benazepril*	5-10 mg QD	20 mg QD
Trandolapril*†	1 mg QD	4 mg QD

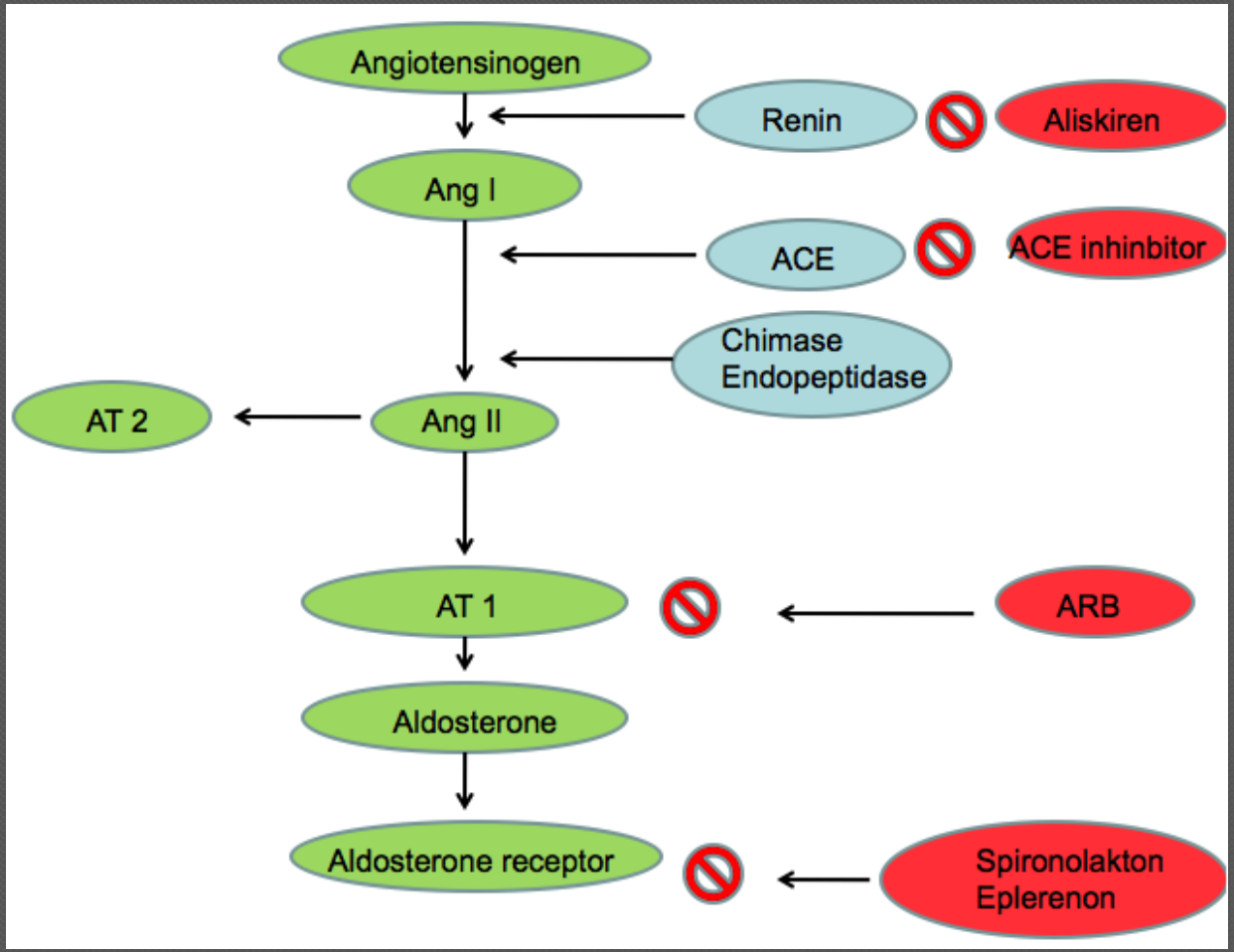
- * FDA-approved for treatment of heart failure.
- † FDA-approved for treatment of post–myocardial infarction heart failure.

Angiotensin Receptor Blockers

Agent	Initial Dose	Maximum Dose
Valsartan*	80 mg	320 mg per day
Candesartan*	4 mg	32 mg per day
Losartan	25 mg	100 mg per day
Irbesartan	75 mg	300 mg per day
Telmisartan	40 mg	80 mg per day
Eprosartan	400 mg	800 mg per day
Olmesartan	20 mg	40 mg per day

* FDA-approved for treatment of heart failure

Renin Angiotensin Pathway



ACE Inhibitor Therapy in CHF

- Initial study published in JAMA in 1995 was retrospective meta-analysis showing decreased mortality and hospital readmission for CHF
- Lancet 2000 May 6;355(9215):1575-81
- 12, 700 patients followed prospectively for 35 months
  - Lower mortality: 23.4% vs 29.1%
  - Readmission for CHF: 11.9% vs 15.5 %
  - Fewer reinfarctions: 10.8% vs 13.2%
- Benefit was more apparent in patients with lower ejection fraction (EF < 40%)

ARB Treatment in CHF

- ELITE Trial (Losartan vs Captopril)
- ELITE II (Losartan Heart Failure Survival)
- CHARM (Candesartan in heart failure)
- RESOLVED Trial (Candesartan)
- Val-HeFT Trial (Valsartan)

ACE Inhibitor Treatment for DM Nephropathy

- Normotensive pt with microalbuminuria
  - 94 patients followed for 7 years. Enalapril Rx:
    - stabilized albuminuria (rose by 40% in controls)
    - stabilized GFR (creatinine rose by 3.3% per year)
    - decreased progression to overt disease (18% vs 60%)
  - 103 pts for 5 years.
    - Enalapril Rx:
    - Reduced progression to overt disease (7.7% vs 23.5%)

ARB Therapy for DM Nephropathy

- 3 studies with similar outcomes
  - Lewis (2001) 1,715 pts over 2.6 yrs
  - Brenner (2001) 1,513 pts over 3.4 yrs
  - Parving (2001) 590 pts over 2 yrs
- Decreased risk of doubling of serum creatinine or developing CKD 5
- Reduced urine albumin levels

Side Effects of ACE / ARB Rx

- Hypotension, Dizziness, Headaches
- Hyperkalemia
- Impaired renal function
- ACE inhibitors : cough or develop angioedema due to effects on bradykinin

Contraindications to ACE/ARB Rx

- Contra-indications:
  - **Pregnancy** – problem in first trimester
  - Prior angioedema or hypersensitivity rxn
- Precautions:
  - Renal artery stenosis
  - Impaired renal function
  - Hypovolemia or dehydration
  - Aortic Valve stenosis

ADA vs ACO Recommendations

- ADA recommends ACE inhibitors and ARB's as first line drug in managing hypertension.
- ADA recommends adding ACE inhibitor and ARB in all diabetic patients with abnormal microalbuminuria.
- But does not recommend ACE inhibitor or ARB in Type 2 diabetics who are normotensive with normal urine microalbumin level.

ACO 26: Daily Aspirin or Antiplatelet Medication Use for Patients with Diabetes and Ischemic Vascular Disease

Rationale for using Aspirin/Antiplatelet Therapy

- Diabetics have 2 to 4 fold higher incidence in cardiovascular disease.
- Diabetics appear to be hypersensitive to platelet aggregating agents (ie Thromboxane).
- Aspirin decreases thromboxane synthesis by acetylating platelet cyclo-oxygenase.

Aspirin Therapy in Diabetics

- Primary prevention
  - US Physicians Health Study:
    - 4% had MI with aspirin Rx compared to 10%
  - HTN Optimal Treatment (HOT) 18790 pts
    - Asa decreased MI by 36% and CV events by 15%
- Secondary prevention
  - Antiplatelet Trialists – meta analysis of 145 prospective articles and found aspirin therapy would prevent 38 events per 1000 diabetics

Contra-indication for Aspirin use

- Contra-indications:
  - h/o aspirin or NSAID induced asthma
  - GI bleeding
  - h/o bleeding disorder
  - Concurrent use of anticoagulant
  - Uncontrolled HTN
- Precautions:
  - patient > 80 y.o
  - h/o PUD or GERD; renal or hepatic impairment, intracranial lesion, thrombocytopenia

Side Effects of Aspirin Therapy

- Side Effects:
  - Anaphylaxis, angioedema, bronchospasm
  - Thrombocytopenia, aplastic anemia
  - Nephrotoxicity, hepatotoxicity
  - Bleeding
  - Rash
  - Dyspepsia, nausea, GERD, abdominal pain

ACO Guidelines

- Recommend ACE Inhibitor or ARB in all patients with diabetes or left ventricular systolic dysfunction (LVEF < 40%)
- Recommend daily aspirin or antiplatelet medication for patients with diabetes and ischemic vascular disease

DM Medications

- Biguanides (metformin)
- Sulfonylureas (glyburide, glipizide, glimepiride)
- Glitinides (nataglinide / repaglinide)
- Alpha- Glucosidase inhibitors (acarbose/ miglitol)
- TZD's (pioglitazone, rosiglitazone)
- DPP-4 inhibitors
  - Januvia, Onglyza, Tradjenta, Nesina
- GLP-1 (Byetta, Bydureon, Victoza)
- SGLT-2 inhibitors (Invokana)
- Others: (Cycloset; Welchol)
- Insulin

Upate on DM Medications

- New concerns / issues
  - Metformin : new dose with reduced GFR
  - Glyburide: use in the elderly
  - Actos: associated with bladder cancer
  - Basal insulin issues
- New medications
  - SGLT-2 inhibitors
  - Cycloset (immediate release bromocriptine)
  - Welchol

ADA Considerations for Dosing Metformin in Renal Disease

- ADA ' s recommends using eGFR rather than serum creatinine for stopping Rx
- eGFR 45 to 60 –
  - Ok to start new patient on Metformin
  - Monitor renal function every 3 to 6 months
- eGFR 30 to 45
  - Lower dose to 50% or 1/2 maximal dose
  - Do not start new patients on Metformin
  - Check renal function every 3 months
- eGFR < 30 : Stop Metformin

Glyburide in the elderly

- American Geriatric Society has "Beers criteria" regarding potentially inappropriate medication in the elderly.
- Added Glyburide to 2012 list of inappropriate medications due to possible hypoglycemia.

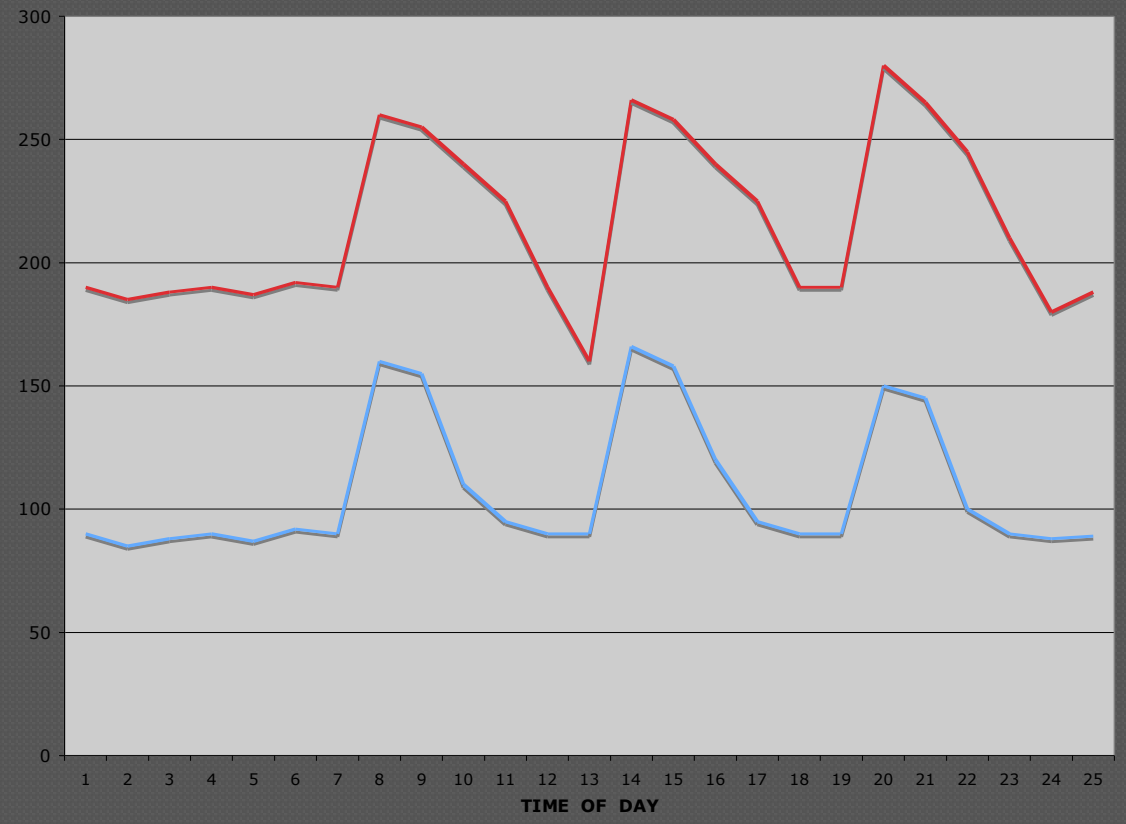
Actos and bladder cancer

- French epidemiology study -1.5 million patients. ~ 30% increase in rate of bladder cancer. Not related to dose or duration of Rx
- FDA requested 5 year analysis of ongoing prospective study by Kaiser ~ 40% increase rate in patients taking over 2 years
- BMJ (May, 2012)
  - 115,700 patients who took Actos between 1988 and 2009.
  - 470 cases vs expected # cases 380 (my calculation)
  - Risk of bladder Ca was related to total cumulative dose ~ 28,000 mg which is equivalent to 30 mg QD for 2.5 years

Issues with Basal Insulin Rx Levemir and Lantus

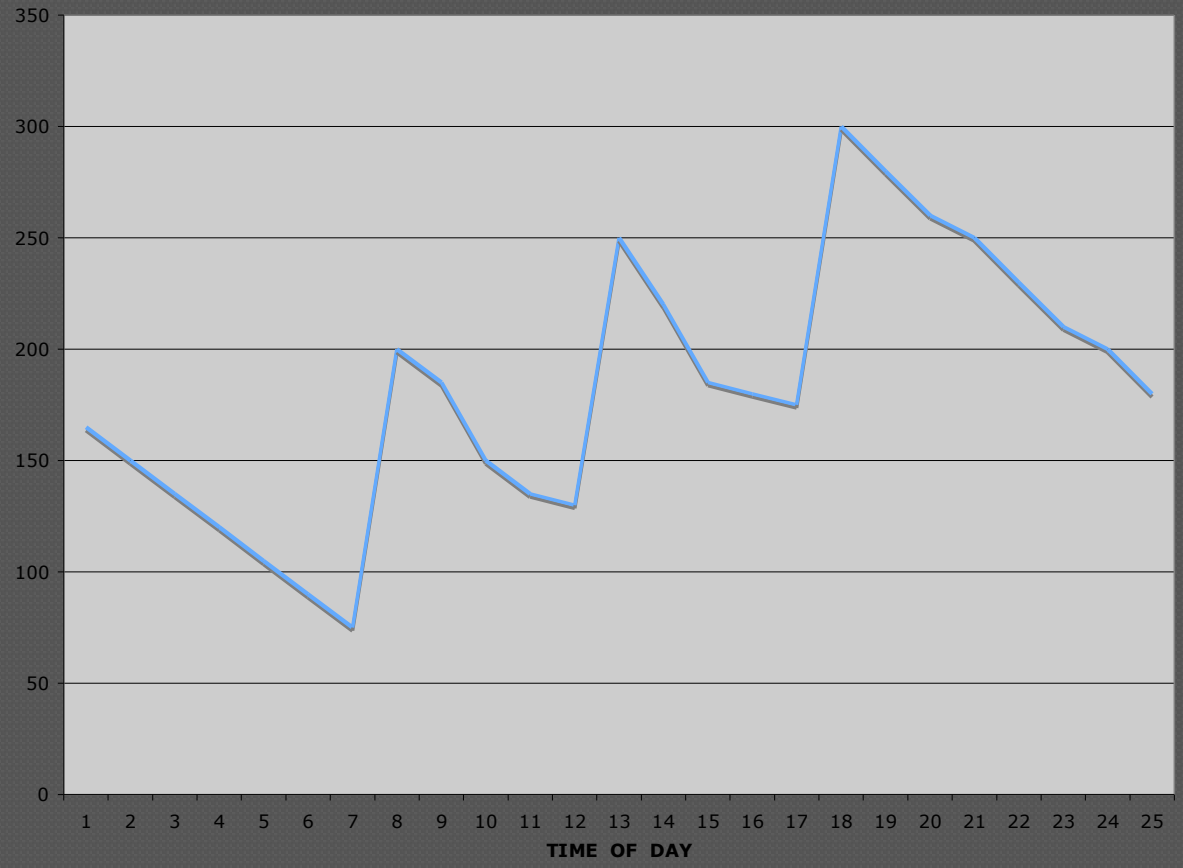
- Decreases glucose for 18 to 24 hours.
- Does not cover meal glucose excursions – **need to continue oral agents**.
- Glucose tends to be high during the day and evening (before lunch, dinner, bedtime) but drop over night resulting in **nocturnal hypoglycemia**.
- Base the dosing on **fasting glucose** (not pre-dinner or bedtime glucose readings).
- DM Center's protocol to start basal insulin.

Ideal Response to Basal Insulin



Possible Effect of Basal Insulin Rx

Fasting hypoglycemia / increasing daytime glucose



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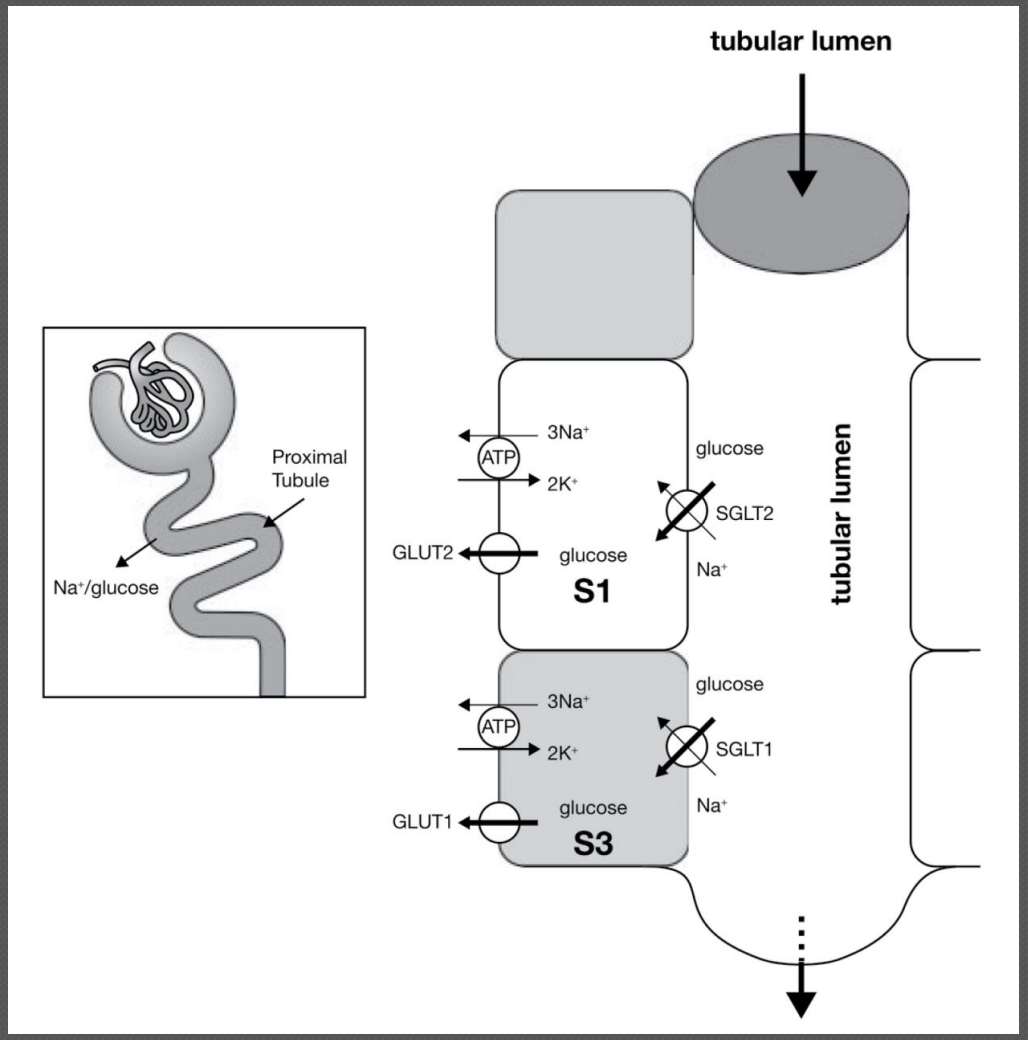
New Diabetes Medications

- SGLT 2 inhibitors
- Cycloset
- Welchol
- Nesina – another DPP4 inhibitor

SGLT-2 Inhibitors

- SGLT2 inhibitors target the kidneys
- Kidneys reabsorb most all of the glucose filtered when plasma glucose < 180
- Mechanisms of re-absorption are through
  - Sodium –glucose cotransporter (SGLT1; SGLT2)
  - Facilitated glucose transporter (GLUT1; GLUT2)
- SGLT 2 inhibitors block re-absorption glucose in the proximal tubule increasing urine glucose excretion

Glucose reabsorption in the kidney.



Valentine V Clin Diabetes 2012;30:151-155

Effects of SGLT 2 inhibitors

- Increase urine glucose levels
- Decrease A1C by about 0.7 to 1.1%
- Decrease weight by about 2 kg
- Decreases systolic BP by 4 to 5 mm Hg

Side Effects of SGLT 2 inhibitors

- Hypotension –
  - from intravascular volume depletion
  - more likely: reduced GFR, diuretics, ACE, ARB
- Hyperkalemia
  - more likely: ACE; ARB; potassium sparing diuretics, reduced GFR
- Renal impairment – may decrease GFR
- Hypoglycemia – if used with other agents
- Dose related increase in LDL cholesterol
- GU infections:
  - Genital mycotic infection, UTI, vulvovaginal pruritis
- Other Sx: polyuria, thirst

SGLT 2 inhibitors

- Canagliflozin (Invokana)– recently FDA approved
  - 100 mg or 300 mg daily – before first meal of the day
  - Adjust dose for impaired renal function
  - Do not start Rx in patients with GFR < 45
- Drug Interactions :
  - Enzyme inducers (Rifampin, Phenytoin, Phenobarbitol, Ritanovir) will decrease efficacy of canagloflozin
  - Digoxin levels increase. Monitor Dig levels
- **Contraindicated** in patients with GFR < 30

- Not yet FDA approved
  - Dapagliflozin, Ipragliflozin, Empragliflozin

Cycloset

- Newly formulated "quick release" preparation of bromocriptine (dopamine agonist)
- Low AM dopamine in the hypothalamus
- Rx increases CNS dopamine levels but does not affect insulin or glucagon, etc
- Take with food within 2 hours of awakening
- 0.8 mg tabs -start with 1 daily (max dose of 6 tabs taken all at once) watch for nausea
- Lowers A1C 0.6 to 0.9 %
- Decreases post prandial glucose levels

Cycloset

- Contraindicated for Type 1 DM, breast feeding, h/o migraine HA, concurrent treatment with ergot derivatives
- Caution if psychosis, concurrent HTN Rx
- Side Effects: severe hypotension, syncope, nausea, flu syndrome, headache, anorexia

Welchol

- Recently FDA approved to manage hyperglycemia
- Primary effect is to decrease LDL levels
- 625 mg tabs (3 tabs BID) or 1 packet BID
- Will lower A1C by 0.5 %
- Side effects: severe rash, intestinal obstruction, pancreatitis, constipation, N/V, dyspepsia
- Contraindicated : GI obstruction, Tg levels > 500, or h/o Tg induced pancreatitis
- Caution: dysphagia, GI motility disorder

DPP-4 Inhibitors

- Januvia - 25 to 100 mg daily.
  - Adjust dose for renal function
- Onglyza - 2.5 to 5 mg daily
  - Adjust dose for renal function
- Tradjenta - 5 mg daily
  - No need to adjust dose
- Nesina – 6.25 to 25 mg daily
  - Adjust dose for renal function

Conclusion

- Recommend ACE Inhibitor or ARB in all patients with diabetes or left ventricular systolic dysfunction (LVEF < 40%)
- Recommend daily aspirin or antiplatelet medication for patients with diabetes and ischemic vascular disease