Baptist Health
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Diabetes and New Meds for Cardiovascular Risk Reduction

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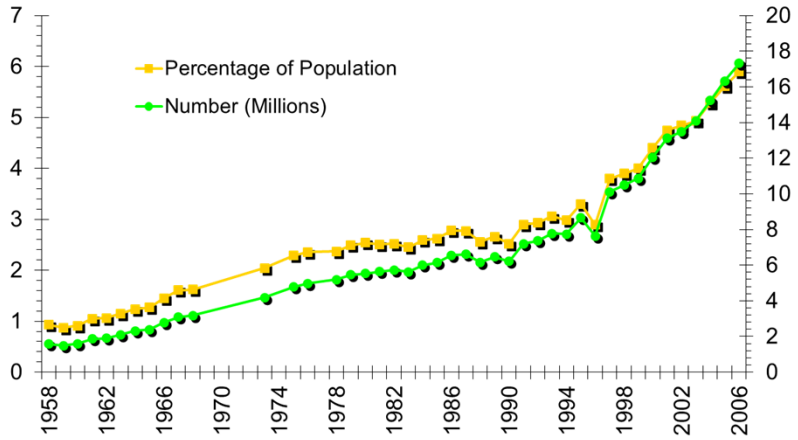
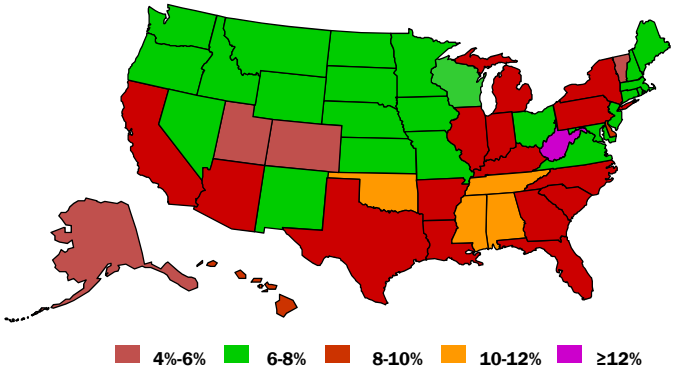
Disclosures:

BI – Boehringer Ingelheim - speaker

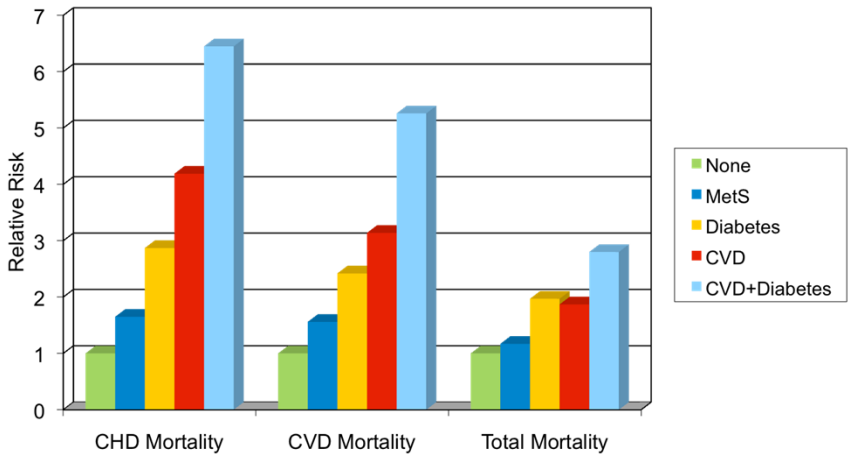
Prevalence of DM



DM – state specific prevalence - 2006



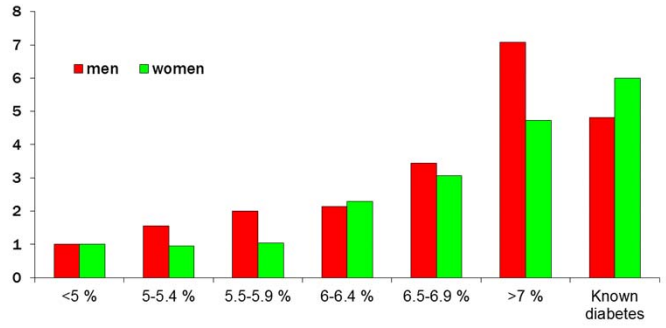
DM and Risk of CV events and death age 30-74



Diabetes CV Risk

Diabetes Mellitus:
Impact of Glycemic Control on CV Risk

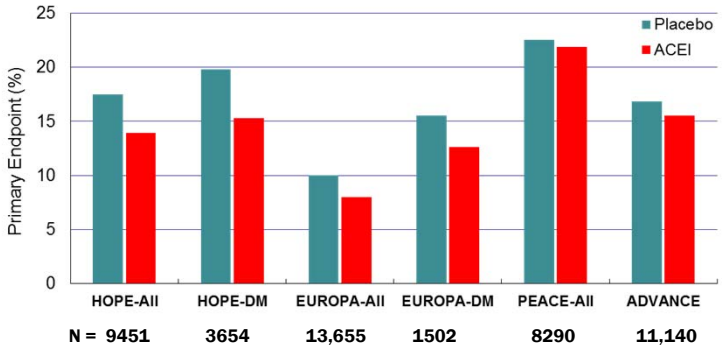
Prospective observational study of 10,232 patients with DM aged 45-79 years
Risk of CV events/disease goes up with Hba1c



Reducing CV Complications

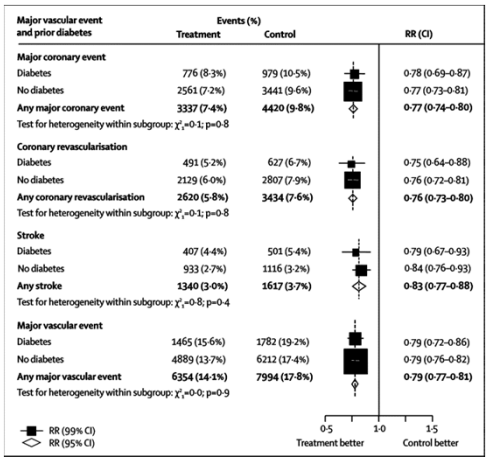
- 4S
- HOPE

DM and Effects of Ace Inhibitor



Diabetes Mellitus: Effect of an HMG-CoA Reductase Inhibitor

Meta-analysis of 18,686 patients with DM randomized to treatment with a HMG-CoA Reductase Inhibitor



Major vascular event and prior diabetes	Events (%) Treatment	Control	RR (CI)
Major coronary event			
Diabetes	776 (8·3%)	979 (10·5%)	0·78 (0·69–0·87)
No diabetes	2561 (7·2%)	3441 (9·6%)	0·77 (0·73–0·81)
Any major coronary event	**3337 (7·4%)**	**4420 (9·8%)**	**0·77 (0·74–0·80)**
Test for heterogeneity within subgroup: χ^2_1=0·1; p=0·8			
Coronary revascularisation			
Diabetes	491 (5·2%)	627 (6·7%)	0·75 (0·64–0·88)
No diabetes	2129 (6·0%)	2807 (7·9%)	0·76 (0·72–0·81)
Any coronary revascularisation	**2620 (5·8%)**	**3434 (7·6%)**	**0·76 (0·73–0·80)**
Test for heterogeneity within subgroup: χ^2_1=0·1; p=0·8			
Stroke			
Diabetes	407 (4·4%)	501 (5·4%)	0·79 (0·67–0·93)
No diabetes	933 (2·7%)	1116 (3·2%)	0·84 (0·76–0·93)
Any stroke	**1340 (3·0%)**	**1617 (3·7%)**	**0·83 (0·77–0·88)**
Test for heterogeneity within subgroup: χ^2_1=0·8; p=0·4			
Major vascular event			
Diabetes	1465 (15·6%)	1782 (19·2%)	0·79 (0·72–0·86)
No diabetes	4889 (13·7%)	6212 (17·4%)	0·79 (0·76–0·82)
Any major vascular event	**6354 (14·1%)**	**7994 (17·8%)**	**0·79 (0·77–0·81)**
Test for heterogeneity within subgroup: χ^2_1=0·0; p=0·9			

ADA/AHA/ACCF Primary Prevention of CV Disease Antiplatelet Agent Recommendations Primary Prevention

- Low-dose aspirin therapy (75-162 mg/day) is reasonable for adults with DM and no previous history of vascular disease who are at increased CVD risk (10-year risk >10%) and who are not at increased risk for bleeding (based on a history of previous GI bleeding or peptic ulcer disease or concurrent use of other medications that increase bleeding risk such as NSAIDs or warfarin). Those adults with DM at increased CVD risk include most men >50 years of age or women >60 years of age who have at least one additional major risk factor.*†

AHA Primary Prevention of CV Disease in DM Cholesterol Recommendations (Continued)
Primary Prevention

- In those >40 years of age without overt CVD, but with ≥1 major CVD risk factor*, the primary goal is an LDL-C level <100 mg/dL.
- In those <40 years of age use clinical judgement

ADA Cholesterol Recommendations for Patients with Diabetes Mellitus (Continued)
Primary and Secondary Prevention

- In individuals without overt CV disease, the primary goal is an LDL-C <100 mg/dL (2.6 mmol/L).
- In individuals with overt CV disease, a lower LDL-C goal of <70 mg/dL (1.8 mmol/L), using a high dose of statin is an option.
- Triglyceride levels <150 mg/dL and HDL-C >40 mg/dL in men and >50 mg/dL in women, are desirable. However, LDL-C targeted statin therapy remains the preferred strategy.

ADA Cholesterol Recommendations for Patients with Diabetes Mellitus (Continued)
Primary Prevention

- Triglyceride levels <150 mg/dL and HDL-C >40 mg/dL in men and >50 mg/dL in women, are desirable. However, LDL-C targeted statin therapy remains the preferred strategy.

FDA Guidance 2008

- Guidance to Industry
  - Mandating – demonstration of CV safety in any new glucose lowering therapy
  - Led to series of large CV outcome trials initially set up to rule out undue CV risk
  - Initially considered futile

Summary

- T2DM
  - Effect of glycemic control itself on CVD outcomes in clinical trials is little to non-existent
  - Glucophage may have CV benefits but data weak
  - SU, insulin and DPP4 inhibitors are likely neutral for CV outcomes
  - 4 large RCTs
    - Demonstrated CV benefits from TZD, SGLT2, GLP-1 RA

Summary of MACE and HF

	MACE	HF
Insulin	Neutral	Neutral
SU	Neutral	Neutral
Glucophage	Decrease	Neutral
TZD's – Pioglitazone	Neutral to Decrease	Increase
DDD-4 – Sitagliptin	Neutral	Neutral to Increase
GLP-1 RA – Dulaglutide	?	?
SGLT2-I	?	?

SGLT2 Inhibitors

- Help kidneys remove more glucose
  - Prevent glucose reabsorption
    - Inhibit a form of proteins that help reabsorption
      - Sodium-glucose transport proteins (SGLT2)
      - Excess glucose passed out to the urine
- Approved since 2013
  - Dapagliflozin
  - Canagliflozin
  - Empagliflozin

SGLT2-I

- Benefits
  - Decrease A1C
  - Decrease weight
  - Decrease BP
  - Decrease TG and increase HDL

  - Class Risks : infection, UTI, dehydration, increase LDL

Drug Specifics

- Dapagliflozin
  - Incidence of liver damage and breast/bladder CA
  - Not to high enough degree to indicate clear risk
- Canagliflozin/Empagliflozin
  - Increase in LDL and HDL cholesterol

Canagliflozin Effects

- Low BP
- Ketoacidosis
- Kidney problems
- Hyperkalemia
- UTI
- Yeast infection
- Bone breaks
- Increased cholesterol
- Amputation risk

CANVAS

	Placebo N-1,441	Canagliflozin 100mg N=1,445	Canagliflozin 300mg N=1,441	Canagliflozin (pooled) N=2,886
With an amputation	22 (1.5%)	50 (3.5%)	43 (3.1%)	95 (3.3%)
Total amputations	33	83	79	162
Amputations per 1000 patient-years	2.8	6.2	5.5	5.9
Hazard Ratio	-	2.24	2.01	2.12

CANVAS-R

	Placebo N=2,903	Canagliflozin 100mg N=2,904
Patients with amputation	25 (0.9%)	45 (1.5%)
Total amputations	36	59
Amputation incidence rate Per 1000 patient-years	4.2	7.5
Hazard Ratio	-	1.80

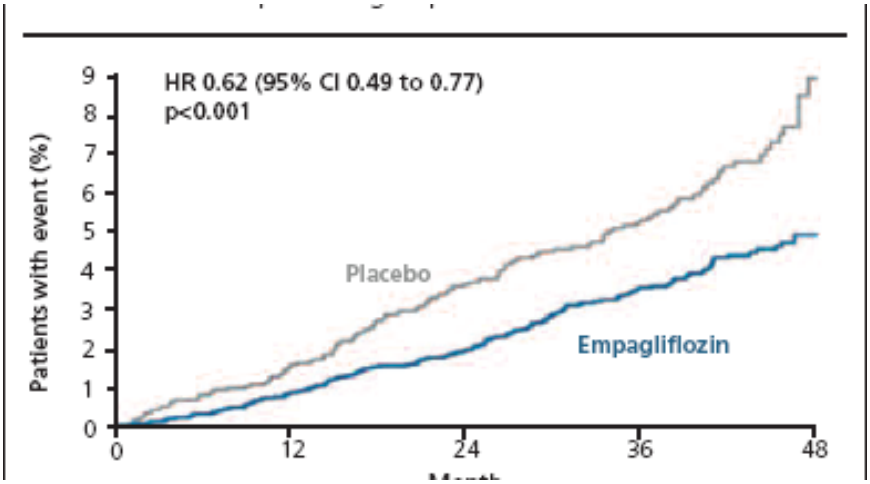
FDA Communication

- Increased risk of leg and foot amputations with canagliflozin – 5/16/17
  - Based on new data from two clinical trials
  - Boxed warning added
  - Consider factors that may predispose to the need for amputations
    - Prior amputations
    - PVD
    - Neuropathy
    - Diabetes foot ulcers

FDA Communication cont.

- Sodium-glucose cotransporter-2 (SGLT2) inhibitor
- CANVAS and CANVAS-R
  - Leg and foot amputations occurred @ twice as often compared to placebo
    - CANVAS – 5.9/1000 versus 2.8/1000
    - CANVAS-R – 7.5/1000 versus 4.2/1000
    - Toe and middle of the foot most common
    - No evidence to suggest a class effect

EMPA-REG Outcome



Empagliflozin Stroke Outcomes

	Placebo N=2333	Empagliflozin N=4687	Hazard Ratio	P-value
Stroke	3%	3.5%	1.18	0.26
Fatal Stroke	0.5%	0.3%	0.72	0.40
Non-fatal Stroke	2.6%	3.2%	1.24	0.16
TIA	1.0%	0.8%	0.85	0.54
Fatal or non-fatal CVA/TIA	3.9%	4.1%	1.05	0.67
Non-fatal or fatal CVA	0.7%	0.6%	0.81	0.50
CV death or non-fatal CVA	8.3%	6.6%	0.79	0.009

Empagliflozin Adverse Events

	Placebo N=2.333`	Empagliflozin 10mg N=2.345	Empagliflozin 25mg N=2,342
DKA	<0.1%	0.1%	<0.1%
Urosepsis	0.1%	0.3%	0.5%
Pyelonephritis	0.9%	0.6%	0.7%
Bone Fractures	3.9%	3.9%	3.7%
Acute Kidney Injury	1.6%	1.1%	0.8%
Lower Limb Amputation	1.8%	1.8%	2.0%

Why was Empagliflozin studied in established CV disease?

- Resulted from 2008 FDA mandate
  - Industry demonstrate glucose lowering therapies not increase CV risk
  - Stipulated include higher risk patients

Long Term Impact of Empagliflozin on Renal Function

- Therapy results in initial increases in serum CR
- Therapy results in initial decreases in eGFR
- Reversed after treatment discontinuation
- Suggests hemodynamic factors play a role
- Assess renal function prior to starting
- Assess renal function periodically
- Discontinue if eGFR consistently <45ml/min/1.73m2

Empagliflozin -Increase in LDL

- >80% on lipid lowering agents at baseline
- Placebo (2.3%), 10mg (4.6%), 25mg (6.5%)
- Phase 3 safety data
  - Incidence similar to placebo
  - Ratio of LDL and HDL remained neutral

Body Weight and Blood Pressure Impact

- Body weight
  - 4.9 lbs
- Systolic blood pressure
  - Systolic blood pressure – 3.7mmHg

Heart Failure Hospitalization

- Empagliflozin
  - 1.4% absolute reduction in the risk for HF hospitalization
  - FDA did not add to label

SGLT2-I Mechanism of Action to Reduce CV Risk

- Unknown

Apply Your Knowledge and Hang On but remember…

Be Careful…You Might Not Know Everything

Thank You

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