Heart to Heart: Diabetes Medications and Cardiovascular Outcomes

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Objectives

Review the available medication options used to treat Type 2 Diabetes
Examine the cardiovascular outcomes trial data for the above medications
Discuss considerations for appropriate Type 2 Diabetes medication selection given cardiovascular safety information

The Lingo
The Lingo

Primary outcome
- Specific key measurement of the effect of a variable

Secondary outcome
- Information on events of secondary importance
  - E.g. side effects, tolerability, or therapeutic effects

Major Adverse Cardiovascular Event (MACE)
- 3-Point MACE: Cardiovascular (CV) death, non-fatal myocardial infarction (MI), or non-fatal stroke (CVA)
- 4-Point MACE: 3-P MACE + first occurrence of hospitalization for unstable angina

Superiority vs. Non-inferiority

The Risk

ACCORD

BACKGROUND
Patients with established cardiovascular disease (CVD) or high risk for CVD
Primary outcome: 3P MACE
Compared treatment targets of standard of care vs intensive therapy

RESULTS
Intensive therapy arms
- Systolic blood pressure <120mmHg
- No change in outcome
- Adding fibrate to statin therapy
- No change in outcome
- Normoglycemia
- Increased risk of CV death and all-cause mortality in intensive treatment arm
  - This portion of the trial was stopped 18 months early due to the increased rate of death
**ADVANCE**

**BACKGROUND**
Patients with a history of a microvascular/macrovascular complication or a risk factor of vascular disease. Compared standard of care to intensive glucose and blood pressure control in the reduction of micro- and macrovascular disease (3P MACE).

**RESULTS**
- Glucose arm: Reduction in primary outcome driven primarily by reduction in nephropathy, increase in severe hypoglycemia and hospitalizations, no difference in death.
- Blood pressure arm: Reduction in primary outcome.


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**HEART2D**

**BACKGROUND**
Patients with history of MI. Comparing fasting vs postprandial blood glucose control on rates of 3P MACE, coronary revascularization, or hospitalization for acute coronary syndrome (ACS).

**RESULT**
No difference in outcome between the arms for the primary outcome.


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**The Precedence**
The Precedence

2007: FDA concludes that rosiglitazone increases the risk of myocardial ischemia (meta-analyses)
2008: FDA issues a guidance for new antidiabetic agents to demonstrate that there is not an unacceptable increase in the CV risk
  • HbA1c as primary endpoint is not sufficient
2010: FDA significantly restricts rosiglitazone use to patients who are unable to control blood glucose by any other means
2013: After reanalysis of the data including the RECORD trial, FDA votes to remove restrictions on rosiglitazone

Case #1: Irma

56 year old Hispanic female presents to endocrine clinic for Type 2 DM follow-up
Past medical history:
  • Type 2 DM
  • Hypertension
  • Systemic Lupus Erythematous
  • Congestive Heart Failure Class II
  • Osteoporosis
Current medications:
  • Glimepiride 1mg QD
  • Rosuvastatin 10mg OHS
  • Lisinopril 40mg QD
  • Lasix 20mg QD
  • KCl 10mEq QD

Vital signs:
  • BP 130/78
  • Pulse 76
  • Height: 70”, weight 230 pounds, BMI 33 kg/m²
Lab evaluation:
  • HbA1c 7.6%
  • Total cholesterol 196mg/dL, Triglycerides 179mg/dL, HDL 32mg/dL, LDL 76mg/dL
  • Microalbumin <30mcg/mg creatinine
  • CMP normal
Patient concerns: Does not want to gain weight
Case #2: Harvey

45 year old Caucasian male presents to the endocrine clinic for Type 2 DM follow up

Past medical history:
- Type 2 Diabetes
- Hypertension
- Hyperlipidemia
- 3 vessel CABG age 43

Current medications:
- Metformin 1,000mg BID
- Atorvastatin 20mg QHS
- Lisinopril 20mg QD
- Metoprolol 100mg QD
- ASA 81mg QD

Case #2: Harvey

Vital signs:
- BP 138/86
- Pulse 82
- Height: 74”, weight 350 pounds, BMI 44 kg/m²

Lab evaluation:
- HbA1c 7.9%
- Total cholesterol 204mg/dL, Triglycerides 135mg/dL, HDL 43mg/dL, LDL 66mg/dL
- Microalbumin <30mcg/mg creatinine
- CMP normal

Patient concerns: Does not want to add more pills

The Agents
Thiazolidinediones

Generic
Mechanism of action:
- Insulin sensitizer in peripheral tissue
Considerations
- Early DM and high insulin resistance
- Concomitant non-alcoholic fatty liver disease
- Loss of bone mineral density

Cautions
- Risk of heart failure (HF)
- Hepatic impairment
- Rosiglitazone

Contraindications
- NYHA Class III or IV HF
- Active bladder cancer (CA)
- Pioglitazone

Rosiglitazone: RECORD

PRO
- Included both normal and high risk CV patients
- Non-inferiority for 3P MACE
  - Cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke

CON
- Increased
  - HF hospital admission or death
  - Upper and distal lower limb fracture, mainly in women

Pioglitazone: PROACTIVE

PRO
- Pts with history of CVD
- Non-significant reduction in primary outcome:
  - All-cause mortality
  - Non-fatal MI and stroke
  - ACS
  - Endovascular or surgical intervention in the coronary or leg arteries
  - Amputation above the ankle
- Reduction in secondary outcome:
  - Composite of all-cause mortality, non-fatal myocardial infarction, and stroke

CON
- Increased hospitalizations for HF
- HF mortality rates did not differ
Pioglitazone: TOSCA IT

**PRO**
- Pts with low risk of CVD
- Comparing pioglitazone vs sulfonylurea (glibenclamide, glimepiride, gliclazide) as add on to metformin
- Non-inferiority for primary outcome:
  - All-cause mortality
  - Non-fatal MI and stroke
  - Coronary revascularization
- No difference in heart failure, bladder cancer, and fractures
- Significantly lower rates of hypoglycemia

**CON**
- Average of 2kg weight gain in both groups

Metformin (Biguanide)

**Generic**
- Mechanism of action:
  - Increase hepatic insulin sensitivity
  - Decrease gluconeogenesis
  - Decrease glucagon secretion

**Considerations**
- First line
- Vitamin B12
- Slow titration

**Contraindications**
- Acute or unstable HF
- Severe CKD (eGFR <30mL/minute per 1.73 m²)

**Caution**
- Hepatic impairment

Metformin: SPREAD-DIMCAD

**PRO**
- Patients with coronary artery disease (CAD)
- **Significantly reduced** primary outcome vs glipizide: composite of 3P MACE, death from any cause, or arterial revascularization
- No significant difference in adverse events

**CON**
- None
### Sulfonylureas (SU)

#### Generic
- **Mechanism of action**
  - Stimulates beta cell insulin release

#### Cautions
- Hypoglycemia
- Full risk/bone density
- Hypoglycemic unawareness
- CAD/Arythmia
- Seizure disorder
- Sulfur allergy
- Hepatic and renal impairment

#### Considerations
- Potential for slight weight gain (2kg)
- Cost

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### Glimepiride

2001: prior to CVOT guidance

**Glimepiride compared to glibenclamide**

**Effect of ischemic preconditioning (IP) in rat hearts**

**Results:**
- Glibenclamide removes the protective effects of IP
- Glimepiride does not interfere with IP

### Agent Primary Outcome Considerations

<table>
<thead>
<tr>
<th>Agent</th>
<th>Primary Outcome</th>
<th>Result</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosiglitazone</td>
<td>CV death, non-fatal MI, or non-fatal stroke</td>
<td>Non-inferiority</td>
<td>HF hospital admission/death</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Upper/distal lower limb fracture</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Women</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Non-fatal MI and stroke</td>
<td>Non-inferiority</td>
<td>HF hospital admission</td>
</tr>
<tr>
<td></td>
<td>All-cause mortality, ACS, endovascular/surgical intervention in coronary/leg arteries, amputation</td>
<td></td>
<td>No change in mortality</td>
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<tr>
<td>Metformin</td>
<td>CV death, non-fatal MI, or non-fatal stroke</td>
<td>Superiority</td>
<td></td>
</tr>
</tbody>
</table>
Dipeptidyl Peptidase 4 Inhibitors

Brand-only
- Exception: alogliptin

Mechanism of action
- Slows GLP-1 metabolism, restoring insulin and glucagon to physiologic levels
- Increases insulin synthesis/release
- Decreases glucagon levels

Consideration
- Modest decrease in HbA1c
- Postprandial hyperglycemia

Excretion
- Renal: sitagliptin, saxagliptin, alogliptin
- Feces: linagliptin

Contraindications
- Dose adjustment in renal impairment (not linagliptin)
- History of pancreatitis

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Sitagliptin: TECOS

<table>
<thead>
<tr>
<th>PRO</th>
<th>CON</th>
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<tbody>
<tr>
<td>Established CVD</td>
<td>Non-significant increase in acute pancreatitis</td>
</tr>
<tr>
<td>Non-inferiority for 4P MACE</td>
<td>No increased hospitalization for HF</td>
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</table>


Alogliptin: EXAMINE

<table>
<thead>
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<th>CON</th>
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<tbody>
<tr>
<td>Patients with ACS 15-90 days prior to randomization</td>
<td>None</td>
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<tr>
<td>Non-inferiority primary outcome: 3P MACE</td>
<td>FDA warning issued for increase in HF hospitalizations with alogliptin and saxagliptin</td>
</tr>
<tr>
<td>No statistical difference in HF hospitalizations</td>
<td>Non-significant decrease in HF deaths in alogliptin arm</td>
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</table>

Saxagliptin: SAVOR-TIMI 53

<table>
<thead>
<tr>
<th>PRO</th>
<th>CON</th>
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</thead>
<tbody>
<tr>
<td>History of established CVD or multiple risk factors for vascular disease</td>
<td>Non-significant increase in hospitalization for HF</td>
</tr>
<tr>
<td><strong>Non-inferiority: 3P MACE</strong></td>
<td>Significant increase in hypoglycemia in patients on SU and with HbA1c &lt;7%</td>
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Linagliptin: CAROLINA

<table>
<thead>
<tr>
<th>PRO</th>
<th>CON</th>
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<tbody>
<tr>
<td>Patients with established CVD</td>
<td>Non-significant increase in HF</td>
</tr>
<tr>
<td><strong>Non-inferiority vs glimepiride and voglibose for composite of 4P-MACE</strong></td>
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<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Result</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>CV death, non-fatal MI, nonfatal stroke, or hospitalization for unstable angina</td>
<td>Non-inferiority</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>CV death, non-fatal MI, or non-fatal stroke</td>
<td>Non-inferiority</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>CV death, non-fatal MI, or non-fatal stroke</td>
<td>Non-inferiority</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>CV death, non-fatal MI infarction, non-fatal stroke, and hospitalization for unstable angina</td>
<td>Non-inferiority</td>
</tr>
</tbody>
</table>
Glucagon-like Peptide-1 Receptor Agonists

- **Brand-only**
- **Mechanism of action**
  - Augment glucose-dependent insulin secretion and decreases glucagon levels
  - Slow gastric emptying and increase satiety which may promote weight loss
  - May increase beta cell mass and function
- **Contraindications**
  - Gastroparesis
  - History of pancreatitis
  - Fam Hx or PMH medullary thyroid CA or MEN 2
- **Considerations**
  - Weight loss/Appetite control
  - Poor medication adherence (weekly preparations)
  - Titrination (except exenatide weekly)
  - Caution in renal impairment (exenatide)

*Multiple endocrine neoplasia type 2

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Liraglutide: LEADER

**PRO**
- Patients at high risk of or established CVD
- Primary outcome: superiority
- Composite of 3P MACE
- Decrease in all cause mortality
- Nonsignificant decrease in HF hospitalizations and acute pancreatitis
- No difference in medullary thyroid cancer

**CON**
- Decrease in non-fatal MI and stroke were not significant
- Increase in cholelithiasis
- Non-significant increase in pancreatic CA

FDA indication 8/25/17: Reduce the risk of MACE, MI, CVA, or CV death in DM2 and established CVD


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Exenatide Weekly: EXSCEL

**PRO**
- Wide range of risk for CVD
- Non-inferiority: 3P MACE
- Non-significant reduction in CV events
- No difference in acute pancreatitis, pancreatic CA, or medullary thyroid CA

**CON**
- Non-significant increased rate of papillary thyroid CA

Lixisenatide: ELIXA

**PRO**
- Patients with recent ACS
- Non-inferiority for 4P MACE

**CON**
- None

Other Glucagon-like Peptide-1 Receptor Agonists

Dulaglutide: REWIND
- Ongoing
- Evaluating reduction in 3P MACE

Semaglutide: SUSTAIN-6
- Significant reduction in composite of 3P MACE
  - Driven by non-fatal MI/stroke
  - No difference in CV death

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<tbody>
<tr>
<td>Liraglutide</td>
<td>Composite of CV death, non-fatal MI, or non-fatal stroke</td>
<td>Superiority</td>
<td>- Non-significant decrease in non-fatal MI and stroke</td>
</tr>
<tr>
<td></td>
<td>CV death, non-fatal MI, or non-fatal stroke</td>
<td>Non-inferiority</td>
<td>- Non-significant decrease in HF hospitalizations</td>
</tr>
<tr>
<td>Exenatide Weekly</td>
<td>CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina</td>
<td>Non-inferiority</td>
<td>- No difference in acute pancreatitis, pancreatic CA, or medullary thyroid CA</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>Composite of CV death, non-fatal MI, or non-fatal stroke</td>
<td>Non-inferiority</td>
<td>- Non-significant increased rate of papillary thyroid CA</td>
</tr>
</tbody>
</table>

Eli Lilly and Company

Marso, Steven P, MD, et al
### Sodium-glucose Co-transporter-2 Inhibitors

**Brand-only**

- **Mechanism of action**
  - Reduce renal glucose reabsorption and increase urinary glucose excretion

- **Contraindications**
  - GFR <30 mL/min/1.73 m²

- **Warnings**
  - GFR <45 mL/min/1.73 m²
  - canagliflozin: dose adjustment
  - empagliflozin
  - GFR <60 mL/min/1.73 m²

**Considerations**

- Monitor hydration
- Monitor for hyperkalemia (canagliflozin)
- Caution for genitourinary/mycotic infections
- Weight loss
- Moderate HbA1c reduction

### Empagliflozin: EMPA-REG

**12/2/2016 Label update:** reduction in CV death in pts with DM2 and CVD

<table>
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<th>CON</th>
</tr>
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<tbody>
<tr>
<td>Pts with established CVD</td>
<td>No difference in reduction of MI or stroke</td>
</tr>
<tr>
<td>Superiority for composite primary outcome of 3P MACE</td>
<td></td>
</tr>
</tbody>
</table>
  - Primarily due to reduction in CV death |
| Significantly lower risk of: | |
  - Death from cardiovascular causes |
  - Death from any cause |
  - Hospitalization for heart failure |
| Lower rate of acute renal failure | |

**CON**
Non-significant increase in fractures (falls)

**Label update September 2015**

- FDA safety alert May 16, 2017


### Canagliflozin: CANVAS

**PRO**

- Included patients with both high risk for CVD and with a history of CVD

- **Superiority in composite of primary outcome: 3P MACE**

- Significant reduction in HF hospitalization

**CON**

- Twice the risk of amputation
  - Particularly at the toe or metatarsal

- FDA safety alert May 16, 2017

- Non-significant increase in fractures (falls)

- **Label update September 2015**

Canagliflozin: CANVAS-R

<table>
<thead>
<tr>
<th>PRO</th>
<th>CON</th>
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<tbody>
<tr>
<td>Non-significant</td>
<td>Exploratory analysis</td>
</tr>
<tr>
<td>• Reduction in progression of albuminuria</td>
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<tr>
<td>• Increased regression of albuminuria</td>
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<tr>
<td>• Helps maintain eGFR</td>
<td></td>
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<tr>
<td>• Reduced progression of end stage kidney disease, and renal death</td>
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<tr>
<td>• No increased risk of fractures</td>
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</tbody>
</table>

Dapagliflozin, Canagliflozin, Empagliflozin: CVD-REAL

Spurred by EMPA-REG

Observational study of patients with and without CVD

Compared hospitalization for HF with the SGLT2 inhibitors vs standard of care with other glucose lowering drugs (oGLD)

- Lower risk of hospitalization for HF and all-cause mortality
- Suggests class effect

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<tr>
<td>Empagliflozin</td>
<td>Composite of CV death, non-fatal MI, or non-fatal stroke</td>
<td>Superiority</td>
<td>Patients with established CVD</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>No difference in reduction of MI or stroke</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Lower risk of HF hospitalization</td>
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<td>Composite of CV death, non-fatal MI, or non-fatal stroke</td>
<td>Superiority</td>
<td>Amputation</td>
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<tr>
<td></td>
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<td>Particularly toe or metatarsal</td>
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<td></td>
<td></td>
<td>Fractures</td>
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<td></td>
<td></td>
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<td>Fewer HF hospitalizations</td>
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<td></td>
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<td>Renal benefits</td>
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<tr>
<td>Dapagliflozin, Canagliflozin, and Empagliflozin</td>
<td>Hospitalization for HF and all-cause mortality</td>
<td>Superiority</td>
<td>Observational study</td>
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<td>Consider class effect</td>
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</table>
The New Paradigm?

Irma: Clinical application

56 year old Hispanic female

Past medical history:
- Type 2 Diabetes
- Hypertension
- Systemic Lupus Erythematosus
- Congestive Heart Failure Class II
- Osteoporosis

Current medications:
- Glimepiride 1mg QD
- Rosuvastatin 10mg QHS
- Lisinopril 40mg QD
- Lasix 20mg QD
- KCl 10mEq QD

Vital signs:
- BP 130/78
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- Height: 70", weight 230 pounds, BMI 33 kg/m²

Lab evaluation:
- HbA1c 7.6%
- Total cholesterol 196mg/dL, Triglycerides 179mg/dL, HDL 32mg/dL, LDL 76mg/dL
- Microalbumin <30mcg/mg creatinine
- CMP normal

Patient concerns: Does not want to gain weight

Clinician concerns?
Irma: Minimizing Risk

HF class—which medications should be avoided?
- Rosiglitazone, pioglitazone, saxagliptin, alogliptin
- Metformin ok (unstable)

Patient has osteoporosis
- Hypoglycemia/fall risk/bone risk:
  - Consider discontinuing glimepiride
  - Avoid canagliflozin, pioglitazone, rosiglitazone

HbA1c reduction—What is Irma’s goal?

Weight concerns
- Weight neutral: select DPP4i
- Possible weight loss: GLP-1 agonist or select SGLT2i

Irma: Improving Clinical Outcome

<table>
<thead>
<tr>
<th>Agent</th>
<th>HF risk reduction</th>
<th>Cardiovascular protection/prevention</th>
<th>HbA1c reduction</th>
<th>Weight loss</th>
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<tr>
<td>Liraglutide</td>
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<td>Empagliflozin</td>
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Increased Awareness of the Impact on HF

<table>
<thead>
<tr>
<th>Heart Failure</th>
<th>Agent</th>
<th>Rosiglitazone</th>
<th>Pioglitazone</th>
<th>Saxagliptin</th>
<th>Alogliptin</th>
<th>Metformin</th>
<th>Sitagliptin</th>
<th>Linagliptin</th>
<th>Exenatide</th>
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Case #2: Harvey

45 year old Caucasian male presents to the endocrine clinic for Type 2 DM follow up

Past medical history:
- Type 2 Diabetes
- Hypertension
- Hyperlipidemia
- 3 vessel CABG age 43

Current medications:
- Metformin 1,000mg BID
- Atorvastatin 20mg QHS
- Lisinopril 20mg QD
- Metoprolol 100mg QD
- ASA 81mg QD

Harvey: Clinical Application

Vital signs:
- BP 138/86
- Pulse 82
- Height: 74", weight 350 pounds, BMI 44 kg/m²

Lab evaluation:
- HbA1c 7.9%
- Total cholesterol 204mg/dL
- Triglycerides 135mg/dL
- HDL 43mg/dL
- LDL 66mg/dL
- Microalbumin <30mcg/mg creatinine
- CMP normal

Patient concerns: Does not want to add more pills

Clinician concerns?

Harvey: Minimizing Risk

Minimizing risk
- HbA1c reduction—what is Harvey's goal?
- Which medications should be avoided?
  - Rosiglitazone, pioglitazone
Agent HF risk reduction Cardiovascular protection and prevention INR reduction Weight loss

<table>
<thead>
<tr>
<th>Agent</th>
<th>HF risk reduction</th>
<th>Cardiovascular protection and prevention</th>
<th>INR reduction</th>
<th>Weight loss</th>
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<tr>
<td>Metformin</td>
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<td>Non-inferiority</td>
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<td>Neutral</td>
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<tr>
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<td>✔ Superiority</td>
<td>✔</td>
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**Summary of Cardiovascular Protection/Prevention**

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Thank You!
### Primary vs Secondary Prevention

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### References


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