Case Studies in T2DM
Addressing Cardiovascular Risk

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Case 1 George

- 58 yo WM with T2DM for 15 years
- History of CHF for 4 years. 2 admissions in past year
- NSTEMI January 2017
- History of pancreatitis due to alcohol in 2012
- Laboratory:
  - HgbA1C 8.4%
  - LDL-C 134 mg/dl
  - HDL-C 34 mg/dl
  - TG 165 mg/dl
  - eGFR 62 ml/min
- Echo: EF 40%

Case 1 George

- Employed by a large retailer, stocks shelves at night 11 pm – 7 am
- No exercise
- Former smoker (quit 2011)
- Drinks some beer
- FHx: father died of MI age 56 yo with hx T2DM mother died from stroke age 64
**Case 1 George**

Physical Examination:
- Wt: 234 kg
- Ht: 5’10”
- BMI: 33.57
- BP: 150/92
- P: 82
- Neck: no JVD
- Cardiac: No murmurs, NML S1S2
- ABD: no hepatomegaly
- EXTR: 1-2+ edema, intact peripheral pulses
- CNS: loss of vibratory sensation in feet, intact ankle reflexes and hot & cold sensations

**Case 1 George**

Medications:
- Metformin: 1000 mg BID
- Glargine u100: 34 units QHS
- Glipizide: 5 mg BID
- Metoprolol: 50 mg BID
- ASA: 81 mg daily
- Atorvastatin: 80 mg daily
- Lisinopril/HCTZ: 20/12.5 2 pills daily
- Clopidogrel: 75 mg daily
- Spironolactone: 25 mg daily
- Hydralazine: 25 mg BID
- Isosorbide: 20 mg BID

**Case 1 George**

George’s Concerns:
- Some DOE while at work
- Unable to achieve his target A1C
- 1-2 episodes of nocturnal hypoglycemia – only takes Glipizide when glucose levels “go high”
- Afraid of dying
Higher HbA1c Predicts Higher CV Risk

- **Reference category** (hazard ratio 1.0) is HbA1c < 6% with log linear scales.
- **Stratton IM et al. BMJ. 2000;321:405–412.**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Number of Cases</th>
<th>HR 95% CI</th>
<th>P 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>26,585</td>
<td>2.00 (1.83, 2.19)</td>
<td>64 (54, 75)</td>
</tr>
<tr>
<td>Coronary death</td>
<td>11,556</td>
<td>2.31 (2.05, 2.60)</td>
<td>41 (24, 54)</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>14,741</td>
<td>1.82 (1.64, 2.00)</td>
<td>37 (29, 45)</td>
</tr>
<tr>
<td>Stroke subtypes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>3789</td>
<td>2.27 (1.95, 2.60)</td>
<td>1 (0, 30)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>1183</td>
<td>1.56 (1.39, 1.76)</td>
<td>0 (0, 26)</td>
</tr>
<tr>
<td>Unclassified stroke</td>
<td>4571</td>
<td>1.84 (1.59, 2.13)</td>
<td>32 (23, 42)</td>
</tr>
<tr>
<td>Other vascular deaths</td>
<td>3626</td>
<td>1.73 (1.51, 1.98)</td>
<td>0 (0, 26)</td>
</tr>
</tbody>
</table>

*Includes both fatal and nonfatal events.*


ADA-EASD Position Statement:
Management of Hyperglycemia in T2D

- **Target HbA1c** for MOST patients is <7%
- **Age:** older adults
  - Reduced life expectancy
  - Higher CVD burden
  - Reduced GFR
  - At risk for adverse events from polypharmacy
  - More likely to be compromised from hypoglycemia
- **Less ambitious targets**
  - HbA1c <7.5% to 8.0% if tighter targets not easily achieved
  - Focus on drug safety


Diabetes Doubles the Risk of Vascular Outcomes
Case 1 George

So what intervention would you recommend for George?

EMP A-REG OUTCOME
Primary Outcome: 3-Point MACE

HR = 0.86
(95% CI: 0.74, 0.99)
P = .0382

N = 7020

CV Death

HR = 0.62
(95% CI: 0.49, 0.77)
P < .0001
EMPA-REG OUTCOME
Hospitalization for HF

HR = 0.65
(95% CI: 0.56, 0.85)
P = 0.0017

N = 7020

Canakinumab incidence function.

CANVAS: Primary MACE Outcome
CV Death, Nonfatal MI, or Nonfatal Stroke

HR = 0.86 (95% CI: 0.71, 0.97)
P < 0.001 for noninferiority
P = 0.0158 for superiority

No. of patients:
Placebo: 434
Canagliflozin: 745

Patients With an Event, %

Years Since Randomization

Canagliflozin Canagliflozin

CANVAS
Hospitalization for HF

HR = 0.67 (95% CI: 0.52, 0.87)

No. of patients:
Placebo: 434
Canagliflozin: 745
**Case 1: George**

George’s 3 month follow-up:
- A1C reduced to 7.4
- Weight down 8 lbs
- Improvement in SOB
- BP reduced to 140/84
- Able to decrease insulin dose
- Reduction in peripheral edema

Medications:
- Canagliflozin, 300 mg daily
- Metformin, 1000 mg BID
- Alirocumab, 300 mg monthly
- Glargine, u 100 25 units QHS

**Case 2: Jeanine**

- 75 yo WF with a history of T2DM for 19 years
- History of unstable angina and cardiac stenting 3 months earlier
- Admits to skipping insulin at times due to fear of hypoglycemia (has hypoglycemic unawareness)
- Laboratory:
  - HgbA1C: 8.6%
  - LDL-C: 84 mg/dl
  - eGFR: 42 ml/min

**Physical Examination:**
- Wt: 167
- Ht: 5’5”
- BMI: 27.79
- BP: 130/84
- P: 78
- PE otherwise unremarkable
Medications:
- Degludec u-100 28 units QHS
- Insulin aspart 12 units before dinner
- Metformin 500 mg BID
- Rosuvastatin 40 mg daily
- Metoprolol 25 mg BID
- ASA 81 mg daily
- Clopidogrel 75 mg daily
- Losartan 100 mg daily

Jeanine’s Concerns:
- Fear of hypoglycemia, especially while babysitting and driving (multiple grandchildren and great-grandchildren)
- Cares for husband who has advancing Parkinson’s disease
- Admits to missing doses of insulin several times a week

Consequences of Poor Medication Adherence

1-point drop in self-reported medication adherence (MMAS) is associated with:
- ↑ 0.21% HbA1c
- ↑ 4.6% Physician visits
- ↑ 20.4% ED visits
- ↑ 20.9% Hospital visits
- ↑ 1.6 All-cause mortality

With Longer Insulin-Therapy Duration in T2D, Hypoglycemia Becomes Comparable to That in T1D

Hurdles to Intensive Therapy

Rates of Severe Hypoglycemia

Hypoglycemia, Diabetes, and CV Events
**Frequency of Adverse Outcomes in Patients With T2D Experiencing Severe Hypoglycemia**

The median time from an episode of severe hypoglycemia until death in T2D is ≤1.05 years.

**Conclusion** - severe hypoglycaemia is associated with a higher risk of mortality.

**Abnormal QT Prolongation and T-Wave Morphology During Hypoglycemia in a Single Patient**

- Normal QT interval = 0.36 to 0.44 second (varies slightly with age, sex, pulse)
- Baseline QT: 456 ms
- Glucose nadir: 2.51 mmol/QT: 547 ms
- Progressive flattening of T wave is noted with fall in glucose over time

**Case 2 Jeanine**

So what intervention would you recommend for Jeanine?
**LEADER and SUSTAIN 6: Primary Outcome**

**CV Death, Nonfatal MI, or Nonfatal Stroke**

**LEADER**

- Patients: 563 events/1648 patients (3.4%)

**SUSTAIN 6**

- Patients: 534 events/1649 patients (3.2%)

**Primary Outcome**

CV Death, Nonfatal MI, or Nonfatal Stroke

**LEADER:** Cumulative incidences estimated using the Kaplan–Meier method, and HRs using Cox proportional hazards regression model.

**SUSTAIN 6:** Kaplan–Meier plot for first event adjudication committee–confirmed CV death, nonfatal MI and nonfatal stroke using 'in-trial' data.

*Not prespecified.*


**Case 2 Jeanine**

Jeanine’s 3 month follow-up:

- Placed on Liraglutide titrated to 1.2 mg daily
- Metformin continued
- Stopped insulin aspart
- HgbA1C decreased to 7.7%
- No hypoglycemic episodes
Case 3  Larry

- 48 yo BM with 9 years of T2DM and CKD Stage 3a
- Father died from complications of CKD and T2DM at age 55
- Works as a High School teacher and assistant football coach
- Evidence of PAD with hx of a TIA in 2010
- No diabetic retinopathy of neuropathy
- Laboratory:
  - HgbA1C 8.6%
  - eGFR 53 ml/min
  - Microalbumin 78 mg/min
  - normal lipids

Case 3  Larry

Physical Examination:
- Wt: 245
- Ht: 6’0”
- BMI: 33.22
- BP: 140/92
- P: 76
- PE otherwise unremarkable

Medications for Glycemia:
- Pioglitazone 30 mg daily
- Glimepiride 4 mg daily (AM)
- Sitagliptin/Metformin 100/1000mg daily

Case 3  Larry

Larry’s Concerns:
- Would like to lose some weight
- Wants to avoid kidney failure
Comparisons Between CANVAS and EMPA-REG OUTCOME

- There is interest in interpreting CANVAS data in the context of EMPA-REG OUTCOME
- Comparisons between trials are complicated by differences in:
  - Populations
  - Trial designs
  - Analytic approaches
  - Drug effects
- Comparisons are therefore hazardous, subject to bias, and may be confounded by multiple uncontrolled factors

Key Outcomes in the CANVAS Program and EMPA-REG OUTCOME

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CV death, nonfatal MI, or nonfatal stroke</th>
<th>CV death</th>
<th>Nonfatal MI</th>
<th>Nonfatal stroke</th>
<th>Hospitalization for HF</th>
<th>CV death or hospitalization for HF</th>
<th>All-cause mortality</th>
<th>Progression to macroalbuminuria*</th>
<th>Renal composite*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>1.00 [0.57 2.19]</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*CANVAS Program endpoints are comparable with EMPA-REG OUTCOME endpoints.
**Case 3 Larry**

Larry's 6 month follow-up:
- HgbA1C 7.1%
- Weight down 8 lbs
- BP 132/74 mmHg
- eGFR up to 60 ml/min

**Medications:**
- **Empagliflozin** 25 mg daily
- **Sitagliptin/Metformin** 100/1000 mg BID
- **Pioglitazone** 15 mg daily