CARDIOVASCULAR INDICATIONS AND DIABETES MEDICATIONS: A CARDIOLOGIST'S PERSPECTIVE

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Diabetes Mellitus

- Global burden of diabetes carries substantial adverse contributions to health related costs worldwide
- Cardiovascular disease is the leading cause of morbidity and mortality among patients with type 2 diabetes
- Despite strong indications of a causal link between hyperglycemia and CV disease, a direct protective effect of intensive glucose lowering remains unproven
- Until 2007, prevailing perception was that drugs capable of improving glycemic control would improve health outcomes

Effects of Rosiglitazone on the Risk of Myocardial Infarction and death from Cardiovascular causes
N Engl J Med 2007; 357:28-38
Nissen SE, Wolski K

- Meta-analysis of 42 randomized trials of rosiglitazone
- Peroxisome proliferator activated receptor (PPAR) agonists
- Available 8 years at time of publication
- Authors found a significantly greater odds of myocardial infarction and marginally significant adverse association with cardiovascular mortality
- Urgent interim analysis of randomized noninferiority trials failed to conclusively demonstrate increased risk of MI or CV death

US FDA

- Requires that all cardiovascular endpoints during phase 2 and phase 3 studies of new diabetic therapies be adjudicated, and that the events include CV mortality, MI and stroke
- Studies should focus on hi risk patients with cardiovascular disease, elderly, patients with impaired renal function and deliver at least 2 years of CV safety data
- Interestingly, heart failure was significantly increased in rosiglitazone group of RECORD trial, yet HF was not included as recommended endpoint in FDA guidelines

Diabetic Medications

- Metformin
- Sulfonylureas
- Meglitinides
- Thiazolidinediones (PPARS)
- Dipeptidyl peptidase-4 (DPP4) inhibitors
- Glucagon-like peptide-1 (GLP1) agonists
- Sodium glucose cotransporter 2 (SGLT2) inhibitors

Metformin

- In retrospective Canadian study using pharmaceutical data for 5795 subjects with initial monotherapy of metformin or sulfonylurea deaths per 1000 person years: 67.6% for 1st generation sulfonylureas, 61.4% for glyburide and 39.6% for metformin
- Retrospective cohort study comparing cardiovascular outcomes in 253,690 US Vets initiating metformin or sulfonylureas composite MI-Stroke-Death per 1000 person years: 18.2% for sulfonylureas and 10.4% for metformin

Sulfonylureas

- Most commonly prescribed class of oral antihyperglycemics
- Stimulate insulin secretion

Sulfonylureas

FIRST GENERATION

- Chlorpropramide (increased hypoglycemia and hyponatremia)
- Tolbutamide (increased CV risk)

SECOND GENERATION

- Glyburide (Diabeta)
- Glipizide (Glucotrol)
- Glicazide
- Glimepiride (Amaryl)
- Gibenclamide (Glynase)

TOSCAT.IT

Thiazolidinediones or Sulfonylureas Cardiovascular Accidents Intervention Trial

- Randomized, open label, multi-center
- Middle aged patients already taking metformin
- Randomized to pioglitazone or sulfonylurea (glibenclamide, glimepiride, glicazide)
- Primary endpoint: atherosclerotic ischemic events (CV death, MI, Stroke)

TOSCAT.IT

- No difference between treatment groups as far as primary endpoint
- Investigators excluded any patient with history of heart dysfunction
- Investigators did not include HF in endpoints, only after trial on-going did the data and safety monitoring board recommend HF as designated stand alone end point

TOSCAT.IT

- Incidence of HF low and not statistically different between groups
- Interestingly, HF events in pioglitazone group led to practitioners stopping medicine, in contrast to none of HF events led to practitioners stopping sulfonylureas
- Sulfonylureas commonly associated with increased body weight likely in part to action of insulin to cause sodium retention in the kidney

Sulfonylureas and Heart Failure

- UK General Practice Database: Sulfonylureas associated with 18-30% increased risk of HF
- National Veterans Health Administration Database: 32% increased risk of HF with larger doses leading to larger risk. In patients with established HF, use of sulfonylureas associated with increase risk of death

Meglitinides

- Short acting glucose lowering therapy
- Pharmacologically distinct from sulfonylureas but have similar effects increasing insulin secretion
- Repaglinide (Prandia)
- Nateglinide (Starlix)
- No studies with cardiovascular outcomes

Thiazolidinediones (PPARs)
Peroxisome proliferator activated receptor agonist

- Pioglitazone (Actos)
- Rosiglitazone (Avandia)
- Trioglitazone (removed in both US and UK secondary to liver toxicity)
- Increase insulin sensitivity by acting on adipose, muscle and liver to increase glucose utilization and decrease glucose production
- They bind to and activate one or more PPAR

PPARs

- 2010 European Medicines Agency suspended sales of rosiglitazone
- June 2011 French and German Medicines Agencies suspended sales of pioglitazone stating “overall risks exceed their benefits”
- European Medicines Agency has not suspended sales of pioglitazone
- In 2010, US FDA imposed marked restrictions in prescriptions of rosiglitazone because of concerns with risk of MI and CV death. These were largely removed in 2013 after re-evaluation of RECORD study

RECORD study

Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes study

- 4447 patients from Europe and Australia
- Patients who failed metformin or sulfonylurea monotherapy were randomly assigned to rosiglitazone, metformin or sulfonylurea
- Results of interim analysis, 3.75 years of followup, were inconclusive except an increased risk of HF in those assigned rosiglitazone combinations
- Lower than expected event rate and higher drop out rate (18%) decreased the power of the analysis

BARI 2D

Bypass Angioplasty Revascularization Investigation 2 Diabetes

- Trial studied whether initial bypass or angioplasty therapies was better in patients with T2DM
- At same time, compared two approaches to control blood sugar providing insulin and insulin sensitizing meds or providing meds that sensitize body to available insulin (metformin and rosiglitazone)
- After 5.8 years there was no difference in primary endpoint (death) or principal secondary endpoint (death-MI-stroke)

PROactive trial

Prospective Pioglitazone Clinical Trial in Macrovascular Events trial

- 5238 hi risk patients (prior MI, stroke, CABG, ACS, PAD)
- Stopped prematurely because of a significant decrease in the "main" secondary composite end point of all cause mortality-MI-stroke in the pioglitazone group HR 0.84 95% CI 0.72-0.98
- Insignificant effect on primary endpoint of all cause mortality-MI-stroke-ACS-surgical intervention on coronaries or legs or leg amp
- Incidence of angina lower in pioglitazone group (3% vs 5%), but reports of HF higher (16% vs 11.5%)
- Concerns: premature termination, late definition of "main" secondary endpoint after trial underway, more than 8 secondary endpoints, decreased study time

PPARs

- Bottom line: rosiglitazone and pioglitazone both carry higher risk of heart failure. Rosiglitazone use appears to carry higher risk of adverse CV events compared to pioglitazone

DPP4 inhibitors
Dipeptidyl peptidase 4 inhibitors

- Inhibit dipeptidyl peptidase 4 enzyme resulting in prolonged active incretin levels. Incretin hormones regulate glucose homeostasis by increasing insulin synthesis and release from pancreatic beta cells and decreasing glucagon secretion from alpha cells
- Saxagliptin (Onglyza)
- Alogliptin (Nesina)
- Sitagliptin (Januvia)

SAVOR-TIMI 53

Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus

- Randomized, double blind
- Patients with T2DM, HgbA1C 6.5-12.0% and high cardiovascular risk, either history of CV disease or multiple CV risk factors
- Saxagliptin 5 mg daily (2.5 if eGFR < 50) n=8280 or placebo n=8212, in addition to standard therapy at discretion of physician
- May 2010 through December 2011

SAVOR-TIMI 53

- Primary composite endpoint of death from CV cause, MI or ischemic stroke: 7.3% saxagliptin group 7.2% placebo HR=1.0
- HgbA1C decrease by 0.2% in saxagliptin group
- Unexpected greater risk of hospitalization for HF in saxagliptin group 3.5% vs 2.8% HR 1.27 95% CI 1.07-1.51

EXAMINE

Examination of Cardiovascular Outcomes with Alogliptin vs Standard of Care trial

- T2DM, HgbA1C 6.5-11.0, recent ACS with 15-90 days
- Randomized, double blind, Alogliptin (n=2701) vs placebo (n=2679)
- March 2009-March 2013
- Alogliptin dose varied form 6.25 mg/day (eGFR <30) to 25 mg/day (eGFR>60)
- Composite outcome: CV death-MI-stroke
- Alogliptin 11.3% v placebo 11.8% HR 0.96
- Alogliptin did not increase risk of hospitalization for HF Alogliptin 3.9% placebo 3.3% HR 1.19 95% CI 0.90-1.58

TECOS
Trial Evaluating Cardiovascular outcomes with Sitagliptin

- Randomized, placebo controlled, T2DM, HgbA1C 6.5-8.0 and established CAD, PAD, ischemic stroke
- Sitagliptin 100 mg daily (50 mg eGFR 30-50) n=7332 vs placebo n=7339
- At median 3.0 years sitagliptin noninferior to placebo with regards to primary composite endpoint of CV death-MI-stroke or hospitalization for UA 11.4% vs 11.6% HR 0.98
- Rates of hospitalization for HF similar 3.1% sitagliptin vs 3.1% placebo

GLP1 Agonists
Glucagon-like peptide 1 receptor agonists
(daily or weekly injectable meds)

- Lixisenatide (Adlyxin)
- Liraglutide (Saxenda, Victoza)
- Semaglutide (Ozempic)
- Exenatide (Bydureon, Byetta)
- Dulaglutide (Trulicity)
- Albiglutide (Tanzeum)

GLP1 Agonists

- Glucose homeostasis is dependent on interplay of multiple hormones and peptides
- GLP1 exerts main effect by stimulating glucose dependent insulin release from pancreatic islets
- GLP1 also slows gastric emptying, inhibits inappropriate post meal glucagon release and also reduces appetite

Liraglutide (Victoza, Saxenda) LEADER

- 9340 patients with T2DM and at least one coexisting CV condition (MI,stroke,renal failure)
- Liraglutide vs placebo,median followup 3.8 yr
- Composite endpoint (CV death-MI-stroke) lower in the liraglutide arm 13% vs 14.9% HR 0.87 95% CI 0.78-0.97
- CV mortality HR 0.78 95% CI 0.65-0.93
- Gallbladder disease more common in Liraglutide arm

Semaglutide (Ozempic)
SUSTAIN-6

- 3297 patients with T2DM, > 50 yrs of age with established CVD, heart failure or CKD or > 60 yrs of age with at least one CV risk factor
- Semaglutide vs placebo, median f/u 2 yrs
- Composite primary endpoint (CV death-MI-stroke) occurred in fewer of semaglutide patients 6.6% vs 8.9% HR 0.74 95% CI 0.58-0.95
- Driven primarily by reduction in stroke
- Diabetic retinopathy complication more frequent in the semaglutide arm

Lixisenatide (Adlyxin)
ELIXA

- 6068 patients with T2DM and either MI or hospitalization for UA in past 180 days
- Lixisenatide vs placebo, median f/u 25 months
- No difference in primary endpoint of CV death-MI-stroke-hospitalization for UA

Exenatide
EXSCEL

- 14,752 patients with T2DM with or without CV disease
- Exenatide vs placebo, median f/u 3.2 yrs
- Primary composite endpoint of CV death-MI-stroke 11% vs 12.2%, $p < 0.001$ noninferior and $p=0.06$ for superior
- All cause death 6.9% vs 7.9% HR 0.86 95% CI 0.77-0.98
- Exenatide noninferior to placebo at preventing adverse CV events, failed to demonstrate superiority

Albiglutide
Harmony Outcomes

- 9,463 patients with T2DM with established coronary, cerebrovascular or PAD
- Duration: 1.6 years
- Primary endpoint CV death-MI-Stroke
  7.0% vs 9% HR 0.78 95% CI 0.68-0.90
  $p < 0.0001$ noninferiority $p = 0.0006$ superiority
- CV death $p=0.53$, all MI $p=0.003$, stroke $p=0.30$
- Albiglutide is superior to placebo in improving glycemic control and reducing CV events driven by reduction in MI

Dulaglutide
REWIND

- 4,589 patients with T2DM, previous CV event or CV risk factors (Randomized, double blind, placebo controlled, multinational)
- Primary endpoint: CV death-MI-Stroke 12.0% vs 13.4% HR 0.88 95% CI .79-.99
- Nonfatal stroke 2.7% vs 3.5% p=0.017
- Dulaglutide superior to placebo in improving glycemic control and decreasing CV events particularly stroke
- Gastrointestinal adverse events higher in the Dulaglutide arm

GLP1 Agonists Summary

- Liraglutide, semaglutide, dulaglutide, albiglutide decreased occurrence of composite endpoint of CV death-MI-stroke in randomized trials. Primarily driven by reduction in CV death (liraglutide), stroke (semaglutide, dulaglutide) or MI (albiglutide)
- Meta-analyses support reduction in all cause mortality of this drug class

SGLT2 Inhibitors
Sodium glucose cotransporter 2 inhibitors

- Empagliflozin (Jardiance)
- Canagliflozin (Invokana)
- Dapaliflozin (Farxiga)
- Ertugliflozin (Steglatro)

SGLT2 Inhibitors

- Mechanism not fully elucidated but appears to have direct hemodynamic actions as well as metabolic effects
- Modulates both glucose and sodium reabsorption in the proximal tubule of the kidneys
- Tend to reduce weight and BP

EMPA-HEART Cardiolink 6-EMPA-HEART

LV remodeling in 97 patients over 6 months

PRINCIPAL FINDINGS

- Primary outcome of change in LV mass index on CMR from baseline to 6 mo for empagliflozin vs placebo was -2.6 vs 0.01 gm/m2 p=0.01. The greatest improvement among patients with LV mass index of > 60 gm/m2

SECONDARY OUTCOMES

- Syst BP -7.9 v-0.7 p=0.003
- Dias BP -2.0 v 0.8 p=0.22
- Hematocrit 2.4 v 0.4 p=0.006
- LV end-systolic volume index -1.0 v 0.04 p=0.36
- LVEF 2.2% v -0.01% p=0.07

EMPA-REG OUTCOME
Empagliflozin Cardiovascular Outcome Event Trial

- T2DM HgbA1C 7.0-9.0 pts not receiving glucose lowering drugs > 12 weeks or HgbA1C 7.0-10.0 pts on glucose lowering therapy > 12 weeks
- Established CV disease
- Double blind allocated to 10 mg or 25 mg empagliflozin n=4687 vs placebo n=2333
- Median duration 2.6 years
- Primary outcome composite CV death-MI-stroke

EMPA-REG OUTCOME

- Empagliflozin therapy resulted in 14% reduction in primary endpoint with a 38% reduction in CV death and 32% reduction in all cause death
- Also a 35% reduction in CHF hospitalizations Empagliflozin 10.5% placebo 12.1% HR 0.86 95% CI 0.84-0.99

CANVAS
Canagliflozin Cardiovascular Assessment Study

- Patients > 30 y/a with T2DM and established CV disease, also > 50 y/a without known CV disease but with 2 or more CV risk factors all with eGFR > 30 ml/min
- Primary endpoint: CV death-MI-stroke
- Canagliflozin had no effect on primary endpoint. On subgroup with known CV disease no reduction in any of the individual components but risk of CHF hospitalization decreased HR 0.67 95% CI 0.52-0.87

EMPA-REG vs CANVAS

- MACE and HF results similar in both studies
- CV mortality benefit much more evident in EMPA-REG
- Difference in drugs??
- Difference in studies (1/3 of CANVAS patients with established CV disease)??

CREDENCE

Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy

- 4,401 enrollees, 4.6 years
- Primary endpoint: doubling of serum creatinine, ESRD and renal or CV death
- HR 0.70 95% CI 0.59-0.82
- Major CV events HR 0.80 95%CI 0.67-0.95 p=0.01
- Canagliflozin significantly reduced major CV events and kidney failure in patients with T2DM and chronic kidney disease, including those who did not have previous CV disease

DECLARE-TIMI 58

Dapagliflozin Effect on Cardiovascular Events – Thrombolysis in Myocardial Infarction 58

Wiviott et al N Engl J Med 2018 Nov 10

- Phase 3 double blind, placebo controlled
- Randomized 17,160 patients, T2DM, 33 countries
- Approx 7,000 with ASHD remaining 10,000 with multiple risk factors
- At least 40 yrs age, eGFR at least 60 ml/min HgbA1C 6.5-12.0
- Randomly assigned to either Dapagliflozin 10 mg daily or placebo
- Primary endpoint: composite ischemic stroke-MI-CV death
- After EMPA-REG OUTCOME trial data published, added secondary primary endpoint: CV death or hospitalization for HF
- Secondary endpoint: renal composite of new ESRD, eGFR decrease by at least 40% or death from renal or CV disease and death from any cause

DECLARE TIMI 58

- Primary outcome dapagliflozin noninferior to placebo 8.8% dapagliflozin 9.4% placebo p=0.17 HR 0.93, 95% CI 0.84-1.03
- Composite of CV death or hospitalization for HF 17% lower in dapagliflozin group 4.9% vs 5.8% - HR 0.83, 95% CI 0.73-0.95, attributed mostly to 27% lower risk of HF hospitalization
- 7% fewer deaths of any kind 6.2% vs 6.6% (not statistically significant)
- Renal events 23% lower, 4.3% vs 5.6%
- Statistically increase in adverse events in daptagliflozin group for diabetic ketoacidosis and genital infections

DECLARE TIMI 58

- In broad population of patients with T2DM, dapagliflozin did result in significantly lower rate of CV death or hospitalization for HF compared to placebo, with additional findings supporting a possible lower rate of adverse renal outcomes
- Did not lower rate of CV death or death from any cause contrasting with EMPA-REG OUTCOME (drug differences? Patient populations? Renal criteria?)

DAPA-HF Trial

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

- 4,744
- Inclusion: symptomatic HF, LVEF <40%, NT-ProBNP >600 and EF >40%
- Primary endpoint: CV death, hospitalization for HF or urgent HF intervention
- HR 0.74 95%CI 0.65-0.85 $p < 0.001$
- CV death HR 0.82 95%CI 0.69-0.98
- May 6, 2020: FDA approved Dapagliflozin for adults with HF with reduced ejection fraction to reduce risk of CV death and hospitalization for heart failure

VERTIS-CV

Evalulation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial

- Multicenter, randomized, double blind and placebo controlled (8,252 enrollees)
- T2DM, > 40 y/o, established ASCVD including CAD, cerebrovascular and PAD
- Ertugliflozin (2 doses) vs placebo
- Primary endpoint: composite CV death, nonfatal MI, nonfatal stroke
- HR 0.91 95% CI 0.77-1.07
- Hospitalizations for HF 2.5% vs 3.6%
- HR 0.88 95% CI 0.54-0.90

SGLT2 Inhibitors Safety Profiles

- Canagliflozin had higher incidence of amputations and bone fractures in CANVAS not seen with empagliflozin
- Risk of dehydration higher with SGLT2 inhibitors
- Promotes glucosuria increasing risk of genitourinary infections

Swedish Registry Safety data

- Compared SGLT2 inhibitors vs GLP1 agonists
- Approximately 34,000 patients
- Found rate of DKA and lower extremity amputations higher in SGLT2 group
- Bone fractures, genitourinary infections, pancreatitis and DVT's similar in both groups
- Observational
- Empagliflozin, Dapaliflozin and Canagliflozin used, did not try to narrow data to specific agent, class studied

SGLT2 Inhibitors other precautions

- Dose of insulin or sulfonylureas may need to be lowered (20% reduction suggested)
- Increase of natriuretic effects of thiazide and loop diuretics
- Slower progression of kidney disease in EMPA-REG, but monitoring of eGFR recommended

Approximate Pricing

- Metformin
  - $11/mo
  - $16/3 mo
  - Insurance coverage good
- Sulfonylureas
  - Glyburide $30/mo $81/ 3 mo coverage good
  - Glipizide $43/mo $120/3 mo coverage good
  - Glimepiride $35/mo $67/ 3 mo coverage good

Approximate Pricing

MEGLITINIDES

- Nateglinide (Starlix) $169/mo $498/3m coverage med-poor
- Repaglinide (Prandia) $488/mo $1454/3m coverage med-poor

PPARS

- Pioglitazone (Actos)
  - $358/m o $1064/3m coverage med-good
- Rosiglitazone (Avandia) $306/mo $909/3m coverage poor

Approximate Pricing

- Sitagliptin (Januvia) $629/mo $1879/3m coverage medium
- Linagliptin (Tradjenta) $615/mo $1835/3m coverage medium
- Saxagliptin (Onglyza) $588/mo $1754/3 m coverage med-poor
- Alogliptin (Nesina) $529/mo $1577/3 m coverage poor

Approximate Pricing

GLP1 AGONISTS

- Liraglutide (Saxenda, Victoza) $856/mo $2560/3m coverage med-poor
- Exenatide (Bydureon, Byetta) $975/mo $2916/3m coverage med
- Lixisenatide (Adlyxin) $857/mo $2561/3m coverage poor
- Semaglutide (Ozempic) $1075/mo $3216/3m coverage med
- Dulaglutide (Trulicity) $1057/mo $3162/3m coverage med

SGLT2 INHIBITORS

- Empagliflozin (Jardiance) $694/mo $2073/3m coverage med
- Canagliflozin (Invokana) $689/mo $2058/3m coverage med
- Dapagliflozin (Farxiga) $687/mo $2053/3m coverage med
- Ertugliflozin (Steglatro) $394/mo $1173/3m coverage med

Summary
A Cardiologist's Perspective

- In DM, CV disease remains leading cause of morbidity and mortality
- Intensive glucose control reduces DM related microvascular complications with unclear effects on macrovascular complications
- In fact, intensive glucose control has been linked with increased CV mortality

First Line Therapy
Metformin

- Pleiotropic effect of metformin make it cornerstone agent to reduce CV events
- It increases insulin sensitivity, reducing total daily insulin use by as much as 20%
- It decreases body mass index by approx. 5% and systolic BP by 2 mm Hg
- It reduces serum triglycerides by approx. 11.5 mg/dl, total chol by 10 mg/dl and LDL by 8.5 mg/dl
- It reduces coronary artery calcium severity, risk of MI, and all cause mortality by 1/3
- Metformin has GI side effects and rarely causes lactic acidosis

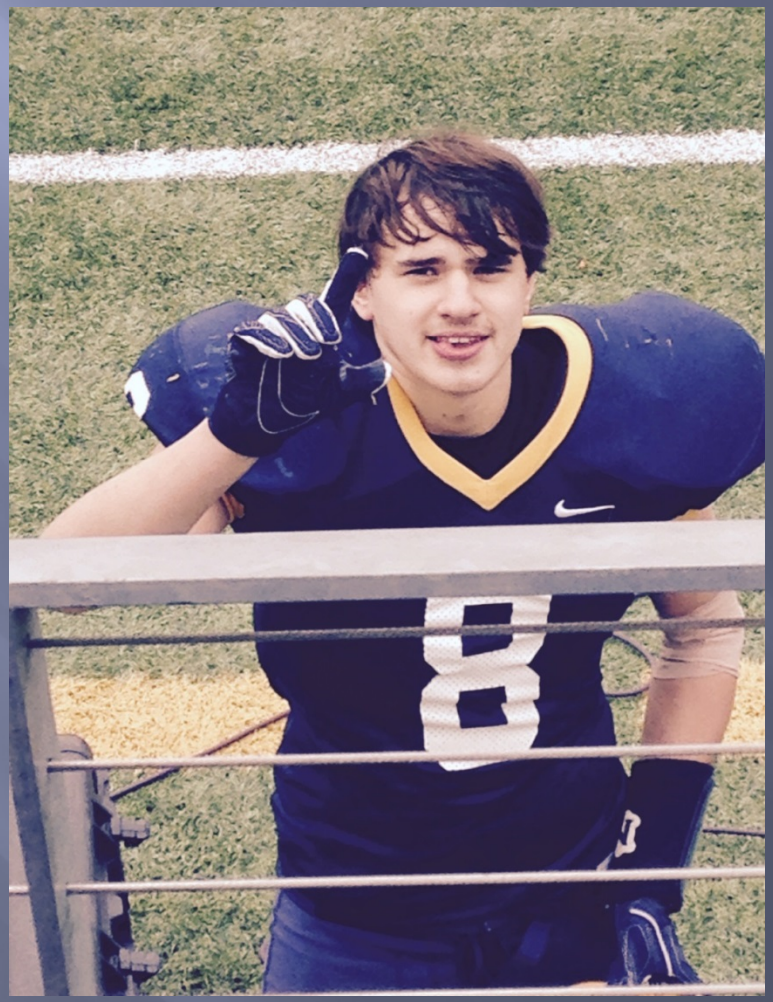
Second Line Therapy
GLP1 agonists and SGLT2 inhibitors

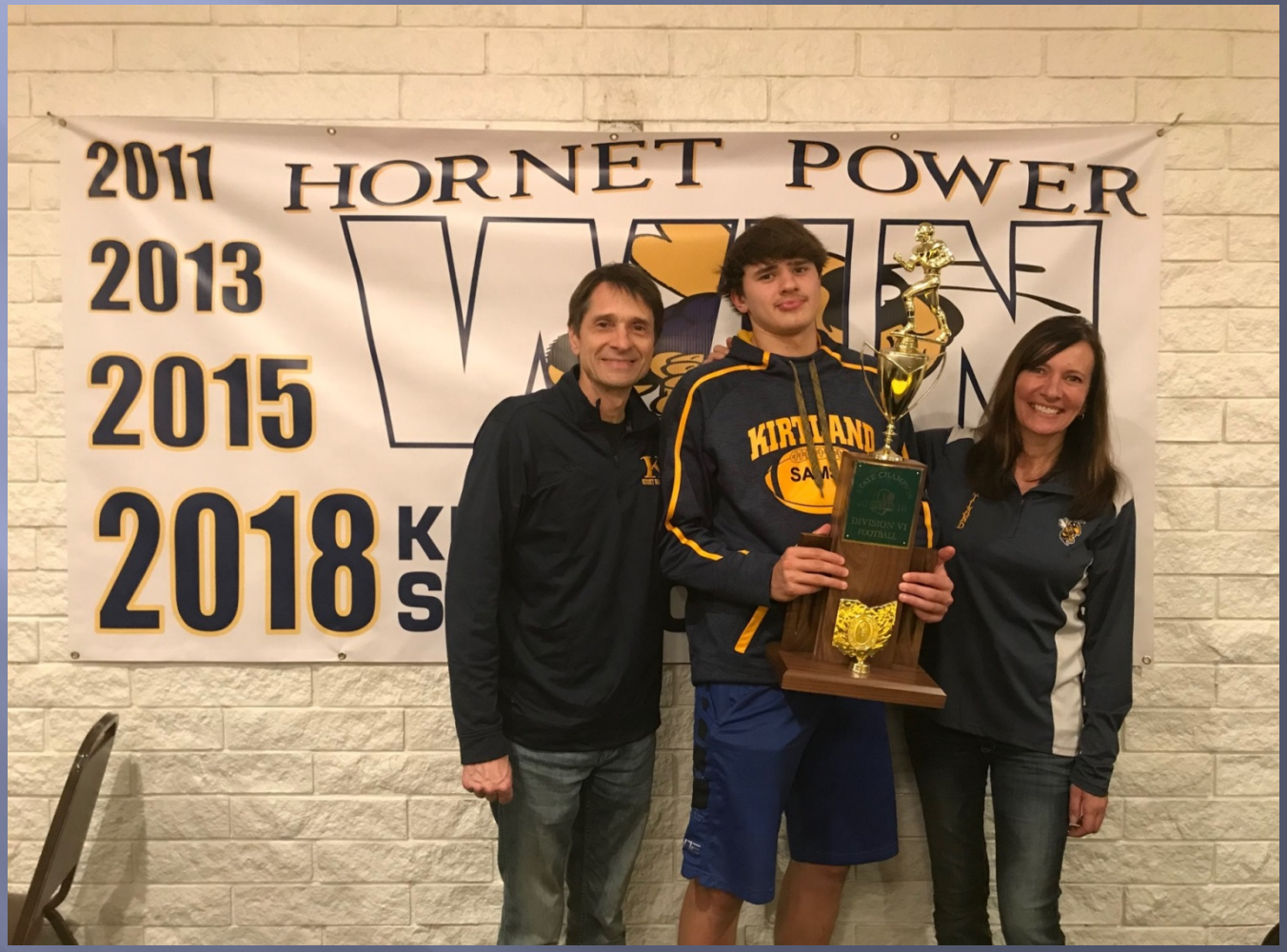
- Liraglutide, semaglutide and empagliflozin decrease primary composite endpoint of CV death-MI-stroke compared to placebo
- GLP1 agonists: reduce glucose, BP and weight also anti-inflammatory, antithrombotic and have lipid lowering effects. Side effects mainly GI
- SGLT2 inhibitors: limit glucose reabsorption in renal tubule resulting in sustained osmotic diuresis and natriuresis. Improves syst BP, weight, visceral adiposity and serum uric acid levels and decrease oxidative stress. Side effects include hypotension, UTI's and less commonly ketoacidosis. Large scale registry attempting to enroll 1.4 million patients to monitor CV outcomes

Third Line Therapy
Insulin, DPP4 inhibitors, Sulfonylureas

- DPP4 inhibitors with neutral CV benefit in 3 large placebo controlled trials
- Increased HF admissions with alogliptin and saxogliptin but not sitaglipitin
- Sulfonylureas may increase CV mortality, and possibly HF admissions. Shorter acting agents such as gliclazide may have safer profile
- Thiazolidinediones associated with increased risk of HF and are best avoided in patients with DM and CV disease

State Champs 2018

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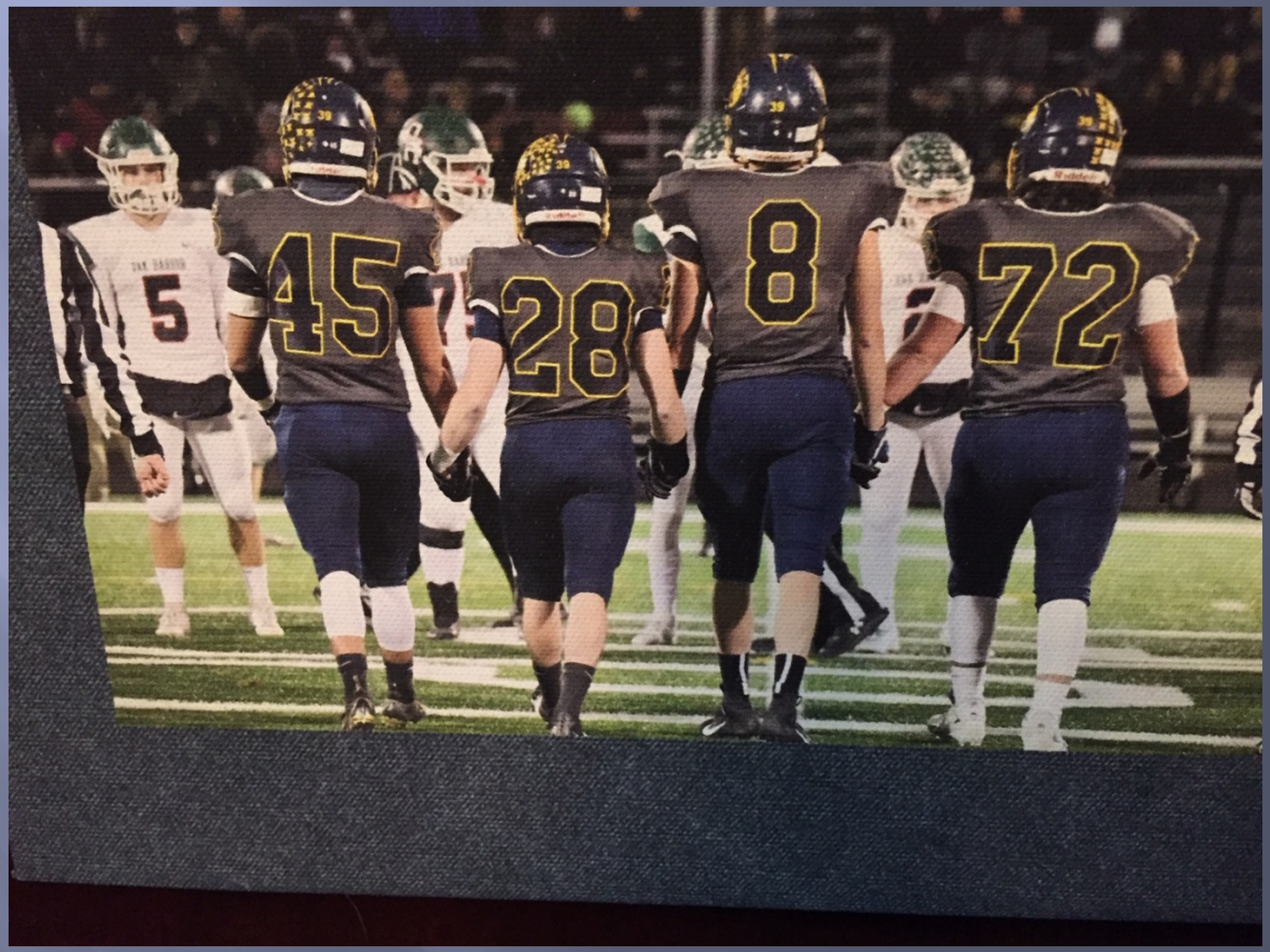
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State Champs 2019