Should Dipeptidyl Peptidase-4 (DPP-4) Inhibitors Be Avoided in Patients with Heart Failure?

http://cdiabetes.com/diabetes-news/

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Learning Objectives:

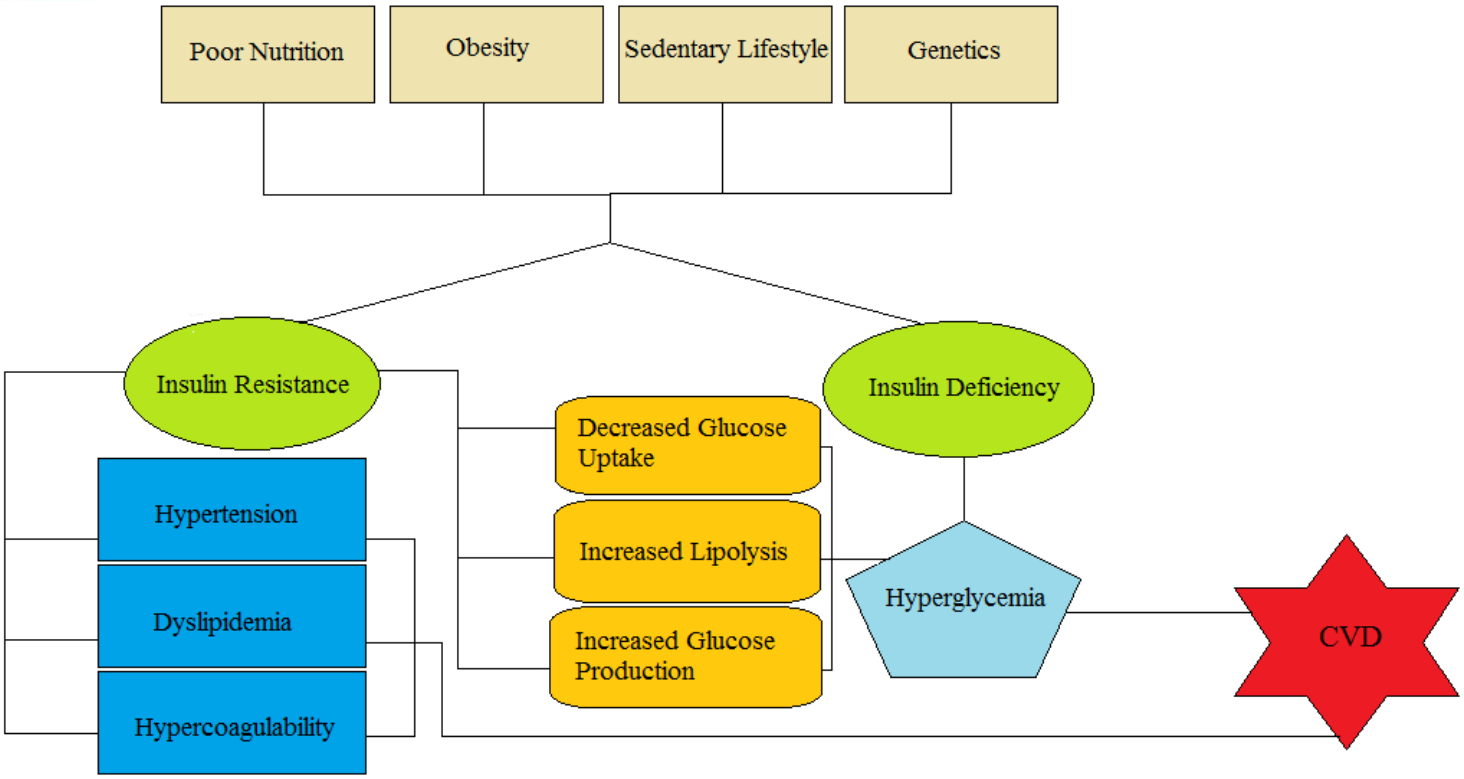
At the completion of this activity, the participant will be able to:

1. Identify benefits of DPP-4 inhibitors when used for diabetes management.
2. State the FDA's clinical trial recommendations for all new diabetes medications.
3. Evaluate current evidence for DPP-4 inhibitors in patients with cardiovascular disease.
4. Given a patient case, be able to make a recommendation regarding initiation of a DPP-4 inhibitor for patients with heart failure and diabetes.

Background:

A. Type 2 Diabetes Mellitus (T2DM) Pathophysiology: [2, 3, 4]

Figure 1: T2DM Pathophysiology



CVD: cardiovascular disease

B. Etiology: [3,4]

i. Overweight/obesity
ii. Sedentary lifestyle
iii. History of gestational diabetes
iv. Hypertension
v. Dyslipidemia
vi. African American, American Indian, Hispanic/Latino, Asian American
vii. Genetic predisposition

C. Epidemiology: [5,6,7,8]

i. **Prevalence:**
   a. From 2011-2014, 12.6% of United States population had diabetes
      1. In 2014, 22 million diagnosed with diabetes
         - In 2004, 5.5 million diagnosed with diabetes
           - Prevalence ↑ 4-fold in 10 years

ii. **Mortality:**

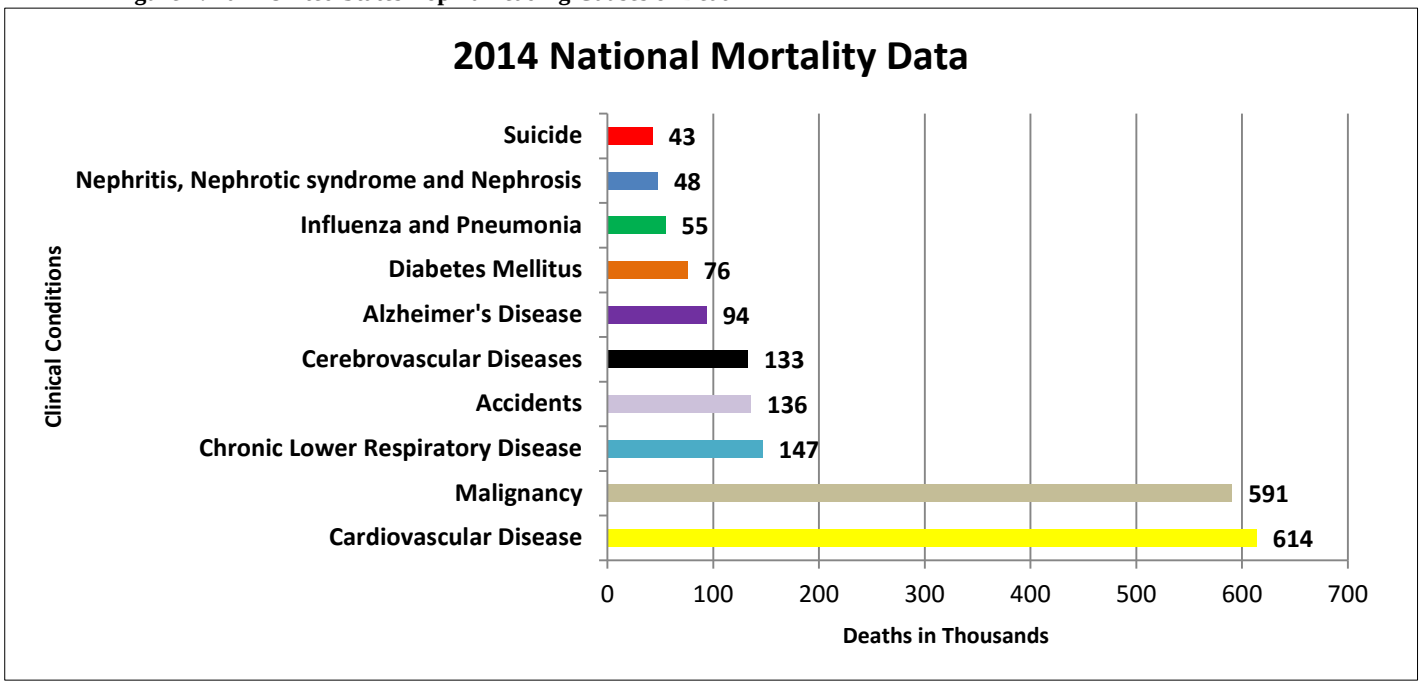
a. Globally in 2012, diabetes mellitus directly caused 1.5 million deaths

1. 8th leading cause of death
2. 2.2 million additional deaths due to secondary causes such as cardiovascular (CV) disease and chronic kidney disease (CKD)

b. Nationally, in 2014, diabetes mellitus caused approximately 76.5 thousand deaths

1. 7th leading cause of death (see Figure 2)

Figure 2: 2014 United States Top 10 Leading Causes of Death[8]



iii. **Cost:**

a. Globally, cost associated with diabetes is $827 billion

D. Classic Symptoms:[3]

i. **Classic Symptoms:**

a. Polydipsia
b. Polyphagia
c. Polyuria

E. Complications of Diabetes Mellitus[3]

i. **Microvascular Complications:**

a. Retinopathy
b. Nephropathy
c. Neuropathy

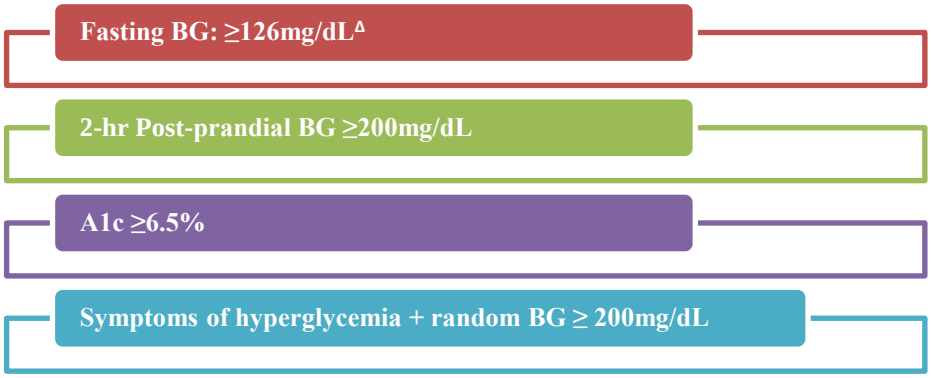
1. Sensory (e.g. history of foot lesions)
2. Autonomic (e.g. sexual dysfunction, tachycardia, hypertension)
3. Gastroparesis

ii. **Macrovascular Complications:**
   a. Coronary heart disease
   b. Cerebrovascular disease
   c. Peripheral vascular disease

F. Diagnosis:[3]

i. (See Figure 3)

Figure 3: Diabetes Mellitus Diagnosis

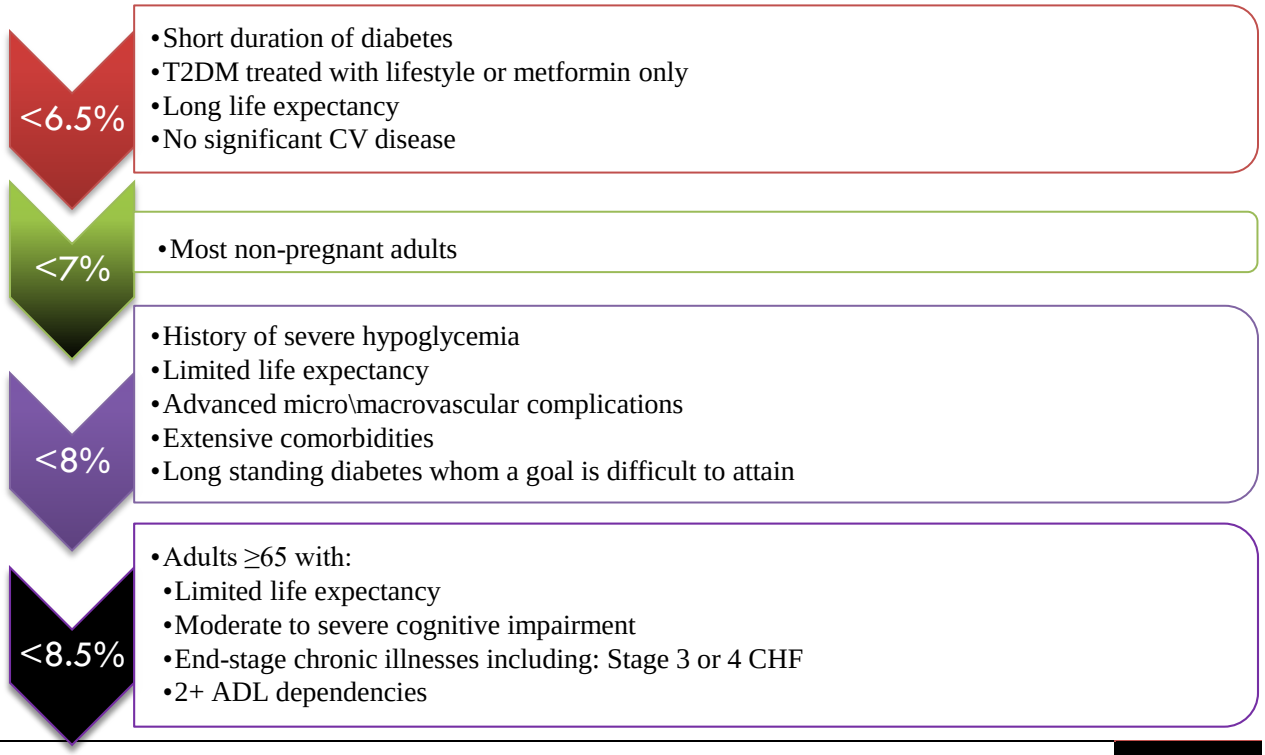


BG: blood glucose;
^Δ^no caloric intake ≥ 8 hrs

G. Goals of Care:[3]

i. **Goals:**
   a. Prevent mortality, microvascular and macrovascular complications
   b. Treat to A1c goal (See Figure 4)

Figure 4: Diabetes Mellitus A1c Goals



H. T2DM Treatment:[3]

i. **Non-pharmacological treatment:**

a. Diet
b. Weight loss
c. Physical activity

ii. **Pharmacological Treatment:**

Table 1: Pharmacological Diabetes Treatment

First Line:	Metformin					
	After 3 months if A1c target is not reached proceed to second line					
Second Line:	Metformin + SU	Metformin + TZD	Metformin + DPP-4i	Metformin + SGLT2i	Metformin + GLP-1RA	Metformin + basal insulin
	After 3 months if A1c target is not reached proceed to third line					
Third Line:	Metformin + SU + TZD or DPP-4i or SGLT2i or GLP-1RA or insulin	Metformin + TZD + SU or DPP-4i or SGLT2i or GLP-1RA or insulin	Metformin + DPP-4i + SU or TZD or SGLT2i or insulin	Metformin + SGLT2i + SU or TZD or DPP4-i insulin	Metformin + GLP-1RA + SU or TZD or insulin	Metformin + basal insulin + TZD or DPP-4i or SGLT2i or GLP-1RA
	After 3 months if A1c target is not reached proceed to fourth line					
Fourth Line:	If only on orals: try injectables			If on GLP-1RA add basal insulin		
Fifth Line:[Δ]						
	Metformin + Basal insulin + mealtime insulin or GLP-1RA					

[Δ]Consider starting at this stage if A1c 10-12% or blood glucose ≥300-350mg/dL
SU: sulfonylurea; TZD: thiazolidinedione; DPP-4i: dipeptidyl peptidase inhibitor; SGLT2i: sodium glucose co-transporter 2 inhibitor; GLP-1 RA: glucagon-like-peptide 1 receptor agonist

I. Cardiovascular Disease and Diabetes:[9]

i. Epidemiology:

a. Patients with diabetes without myocardial infarction (MI) history
    1. 20.2% incidence of MI over 7 years
    2. Similar rates vs. patients with history of MI without diabetes
b. HF risk ↑ 2.4 x in men and 5x in women with diabetes

ii. Etiology:

a. Hyperglycemia:
    1. Every 1% ↑ in A1c leads to 11% to 16% ↑ in CV events
    2. Every 18mg/dL ↑ in fasting blood glucose >105mg/dL correlates to 12% ↑ in ASCVD
    3. Every 18mg/dL ↑ in fasting blood glucose >100mg/dL correlates to 13% ↑ hazard ratio for vascular death
b. Insulin Resistance
c. Dyslipidemia
d. Hypercoagulability
e. Vascular Calcification

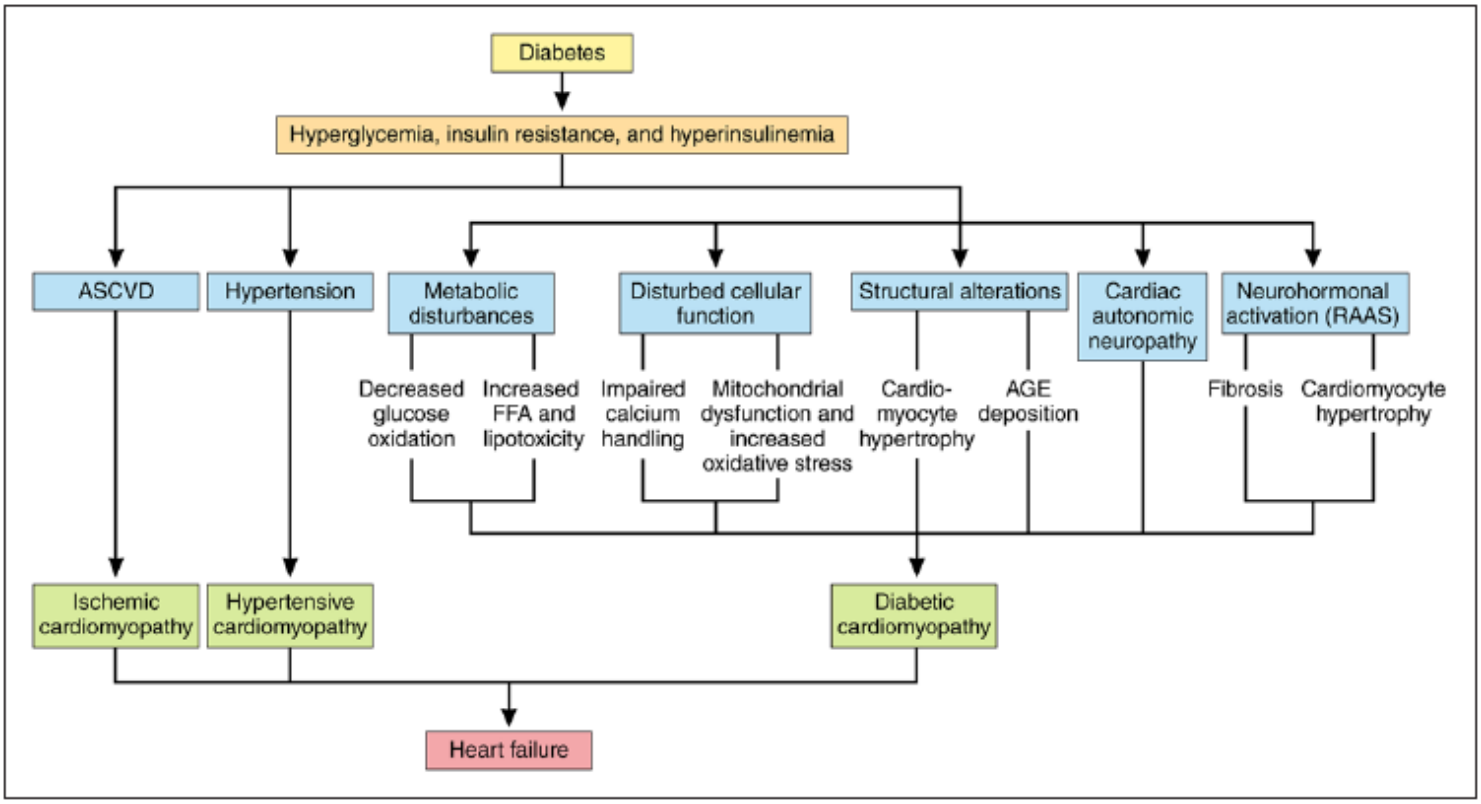
iii. Pathophysiology:

a. Patients with diabetes mellitus have > atherosclerotic plaque burden, higher atheroma volume, smaller coronary artery lumen diameter

b. Pathophysiology of heart failure (HF)

1. (See Figure 5)

Figure 5: Pathophysiology of Heart Failure in Diabetes



FFA: free fatty acid; AGE: advanced glycation end-product

d. Non-Glycemic Treatment of Cardiovascular Disease in Diabetes:

i. Lipid lowering therapy
ii. Antithrombotic therapy
iii. Blood pressure control
iv. ACE/ARB therapy
v. Life style modifications

e. Cardiovascular Findings Prior to 2008 FDA Guidance:

i. (See Table 2)

Table 2: Diabetes Medications and CV Outcomes

Medication Class	CV Findings and Considerations
Biguanide:[10,11] **Metformin**	• ↓ rates of diabetes-related death, MI, and all-cause mortality • Contraindicated in pts with CHF requiring pharmacological treatment
α-Glucosidase Inhibitors[12]	Delayed the advancement of impaired glucose intolerance to diabetes
Sulfonylureas[13]	• ↓ risk of microvascular complications • ↓ macrovascular complications over long term follow up • Clinical trials have contrasting results
Thiazolidinediones:[14.15.16.17] **Pioglitazone and Rosiglitazone**	• Contraindicated in pts with NYHA Class III or IV • Did not ↓ CV events • ↑ rates of HF and hospitalization for HF

f. 2007 Rosiglitazone Meta-Analysis:[18]

i. Reported 43% ↑ in MI (p=0.03) and 64% ↑ in death from CV causes (p=0.06)

g. 2008 FDA Guidance: [9, 19]

i. Recommends all manufacturers developing new drugs and biologics for T2DM provide evidence that therapy will not ↑ risk of CV events

a. From 1995 to 2008 trials:

1. Sole efficacy end point was A1c
2. Commonly ≤ 6 months in duration
3. Open label
4. Majority of patients diabetes mellitus drug naïve/short duration of disease
5. CV disease and renal disease were often excluded

h. Cardiovascular Findings Post 2008 FDA Guidance: [20,21,22,23]

i. (See Table 3)

Table 3: Recent Antihyperglycemic Medication Cardiovascular Literature

Trial	Population	Intervention	Primary Endpoint	Findings
EMPA-REG[20]	T2DM with established CV disease	empagliflozin 10-25mg daily vs. placebo	Composite of death from CV causes, nonfatal MI, nonfatal stroke	Empagliflozin ↓ rates of primary endpoint, death from CV/any cause, hospitalization for HF
ELIXA[21]	T2DM with MI or hospitalized with unstable angina within 180 days	lixisenatide 10 mcg/day x 2 wks then 20mcg vs. placebo	First occurrence of: CV death, hospitalization for unstable angina, nonfatal MI, nonfatal stroke	Lixisenatide did not alter the rates of CV events in patients with recent ACS
FIGHT[22]	LVEF ≤ 40% + recent hospitalization for HF in last 14 days or on furosemide PO mg daily 60% patients had T2DM	liraglutide 0.6mg/day uptitrated Q 2 weeks from 1.2mg/day to 1.8mg/day vs. placebo	Time to death, HF rehospitalization, and baseline to 180 day change in NT pro-BNP	Liraglutide did not alter rates of clinical stability
LEADER[23]	T2DM with CV disease or high risk of CV disease	liraglutide 1.8mg once daily vs. placebo	First occurrence of: CV death, nonfatal MI, nonfatal stroke	Liraglutide ↓ primary outcome, death from CV causes and rates of nephropathy Liraglutide numerically ↓ rates of hospitalization for HF but not statistically

NT pro-BNP (N-terminal pro b-type natriuretic peptide)

A. Controversy

a. DPP-4 Inhibitor Literature:[24,25,26,27]

i. Three randomized controlled trials available evaluating alogliptin, sitagliptin, and saxagliptin.

ii. Current evidence evaluating CV effects, such as HF incidence and/or HF hospitalizations are conflicting

b. Clinical Questions:

i. Do DDP-4 inhibitors worsen CV outcomes?

a. If so, is it a class effect?

ii. What are the adverse effects associated with DPP-4 inhibitors?

iii. May patients with HF be prescribed a DPP-4 inhibitor?

DPP-4 Inhibitors:

a. DPP-4 Inhibitors:[3,28.29, 9,30, 31]

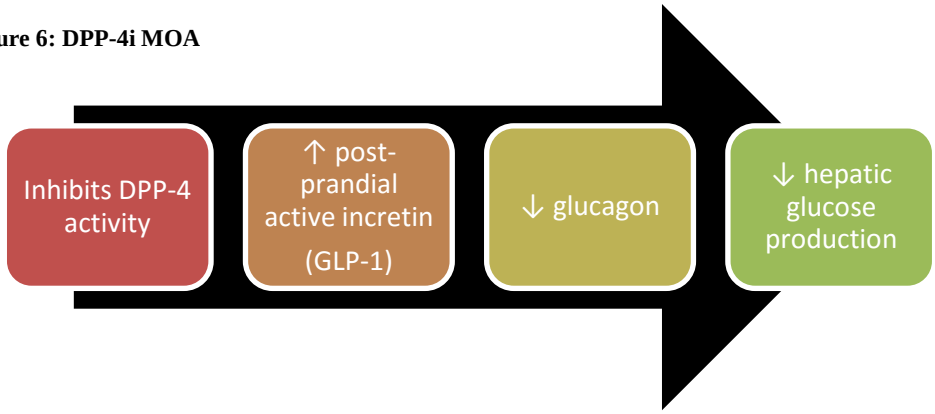
i. **Medications:**

a. alogliptin (Nesina)
b. sitagliptin (Januvia)
c. linagliptin (Tradjenta)
d. saxagliptin (Onglyza)

b. **MOA:**

a. (See Figure 6)

Figure 6: DPP-4i MOA



c. **A1c Lowering:**

a. 0.4% - 0.75%

d. **Advantages:**

a. Little hypoglycemia
b. Well tolerated
c. Weight neutral

e. **Disadvantages:**

a. Angioedema/urticaria/immune-mediated dermatological effects
b. Possible acute pancreatitis
c. Possible joint pain
d. Debated ↑ in HF hospitalizations
e. High cost
f. Weight neutral

vi. Proposed Effects on Heart Failure:

a. Exact mechanism unknown
b. Activation of glucagon like peptide 1 receptors → activation of the sympathetic nervous system → ↑ in heart rate and blood pressure
c. Works on multiples substrates beyond GLP-1such as:
    1. Inactivates natriuretic peptide altering fluid balance
    2. PYY and NPY resulting in ↑adipocyte differentiation

Table 4: 2013 Scirica, et al.[24] Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus (SAVOR-TIMI 53)

Objective	• To evaluate the CV safety and efficacy of saxagliptin	
Design	• Multicenter, randomized, double blind, placebo controlled trial	
Inclusion	• T2DM ○ A1c of 6.5-12% • History of CV disease[a] OR multiple risk factors for vascular disease[b]	

Exclusion	• Currently receiving incretin-based therapy or received in past 6 months
	• End stage renal disease (ESRD) and undergoing long-term dialysis
	  ○ Undergone renal transplant
	  ○ SCr > 6.0mg/dL	

Endpoints	**Primary**	**Secondary**
	Composite of CV death, nonfatal MI, or nonfatal ischemic stroke	Primary composite PLUS: • hospitalization for HF • hospitalization for coronary revascularization • hospitalization for unstable angina
Intervention	**Arm 1**	**Arm 2**
	• Saxagliptin 5mg daily • Saxagliptin 2.5mg daily (if GFR<50mL/min)	Placebo
Statistics	• Intention to treat • α=p<0.049 for the primary endpoint • 1040 events needed to provide a 98% power to test for non-inferiority at a boundary of 1.3 and provide a 85% power to detect a 17% relative risk reduction in the primary composite outcome	

Baseline Characteristics		
Characteristic	**Saxagliptin** n=8280	**Placebo** n=8212
Age mean, yrs	65.1+/-8.5	65+/-8.6
Female, No. (%)	2768 (33.4)	2687 (32.7)
Hispanic, No. (%)	1778 (21.5)	1763 (21.5)
BMI, mean	31.1 +/- 5.5	31.2 +/- 5.7
Duration of diabetes, median yr (IQR)	10.3 (5.2-16.7)	10.3 (5.3-16.6)
Established atherosclerotic disease, No. (%)	6494 (78.4)	6465 (78.7)
Hypertension, No. (%)	6725 (81.2)	6767 (82.4)
Dyslipidemia, No. (%)	5895 (71.2)	5844 (71.2)
Prior MI, No. (%)	3147 (38.0)	3090 (37.6)
Prior heart failure, No. (%)	1056 (12.8)	1049 (12.8)
Prior coronary revascularization, No. (%)	3566 (43.1)	3557 (43.3)
A1c, Mean %	8.0±1.4	8.0±1.4
A1c <6.5%, No. (%)	590 (7.3)	673 (8.3)
A1c 6.5 to <7.0%, No. (%)	1442 (17.7)	1414 (17.5)
A1c 7.0 to <8.0%, No. (%)	2759 (33.9)	2657 (32.9)
A1c 8.0 to <9.0%, No. (%)	1577 (19.4)	1562 (19.4)
A1c ≥ 9.0%, No. (%)	1761 (21.7)	1764 (21.9)
eGFR, mean, (mL/min)	72.5±22.6	72.7±22.6
Metformin, No. (%)	5789 (69.9)	5684 (69.2)
Sulfonylureas, No. (%)	3352 (40.5)	3281 (40.0)
Thiazolidinediones, No. (%)	513 (6.2)	465 (5.7)
Insulin, No. (%)	3448 (41.6)	3384 (41.2)
Aspirin, No. (%)	6249 (75.5)	6155 (75.0)
Statins, No. (%)	6482 (78.3)	6435 (78.4)
ACE inhibitor, No. (%)	4435 (53.6)	4505 (54.9)

ARB, No. (%)	2332 (28.2)	2263 (27.6)		
Beta-blockers, No. (%)	5101 (61.6)	5061 (61.6)		

Results

	Saxagliptin n=8280	**Placebo** n=8212	HR (95% CI)	p value
Primary Outcome No. (%)				
CV death, MI or stroke	613 (7.3)	609 (7.2)	1.00 (0.89 - 1.12)	0.99
Secondary Efficacy Outcomes No. (%)				
Primary composite + hospitalization for UA, HF or coronary revascularization	1059 (12.8)	1034 (12.4)	1.02 (0.94 - 1.11)	0.66
Hospitalization for HF	289 (3.5)	228 (2.8)	1.27 (1.07 to 1.51)	0.007
Safety Outcomes No. (%)				
Renal abnormality	483 (5.8)	418 (5.1)		0.04
Hypoglycemia	1264 (15.3)	1104 (13.4)		<0.001

Author's Conclusions

- Saxagliptin did not change rate of ischemic events; rate of hospitalization for HF was increased
- Saxagliptin improves glycemic control but other approaches are necessary to reduce CV risk in patients with diabetes

Strengths

- Randomized, placebo-controlled, double blind, multi-center
- Randomization was stratified by CV disease, renal function
- Baseline characteristics were well balanced
- Included patients with a wide range of A1cs
- Large sample size
- Intention to treat
- Adequately powered for the primary endpoint
- Funded by AstraZeneca and Bristol-Myers Squibb; did not take part in data-analysis
- Long duration of diabetes

Weaknesses

- Physicians were able to modify regimens which could confound the endpoint
- Planned follow up: 4.5 years
  - Median follow up was 2.1 years; maximum was 2.9 years
- Small differences in A1c at end of study 7.7% vs. 7.9%
- Baseline A1c of 8%

Take Away

- Saxagliptin did not change rates of CV death, nonfatal MI, or nonfatal ischemic stroke
- Saxagliptin associated with a statistically significant ↑ in hospitalization for HF
- ↑ incidence of hypoglycemia with saxagliptin vs. placebo

a) ≥40 y/o and have history of a clinical event associated with atherosclerosis involving the coronary, cerebrovascular or peripheral vascular system

b) men ≥ 55 y/o or women ≥60 y/o with at least 1 other risk factor: dyslipidemia, hypertension or active smoking

Table 5: 2015 Green, et al.[25] Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes (TECOS)

Objective	• To determine CV safety and efficacy of sitagliptin	
Design	• Randomized, double-blind, placebo-controlled, multi-center trial	
Inclusion	• T2DM with established CV disease[a] • ≥50 y/o • A1c 6.5% to 8.0% when treated with stable doses of 1 or 2 oral antihyperglycemic agents[b]	
Exclusion	• Treated with DPP-4 inhibitor, GLP-1RA or TZD[c] during the preceding 3 months • History of ≥ 2 episodes of severe hypoglycemia[d] during preceding 12 months • eGFR <30mL/min	
Endpoints	**Primary**	**Secondary**
	1st confirmed event of CV death, nonfatal MI, nonfatal stroke or hospitalization for unstable angina	• 1st confirmed event of CV death, nonfatal MI or nonfatal stroke • individual components of the primary composite outcome • fatal and nonfatal MI • fatal and nonfatal stroke • death from any cause • hospitalization for HF • changes in A1c • changes in eGFR • initiation of additional antihyperglycemic agents or long term insulin • frequency of severe hypoglycemia
Intervention	**Arm 1**	**Arm 2**
	• sitagliptin 100mg daily • sitagliptin 50mg daily (if GFR<50mL/min)	Placebo
Statistics	• Non-inferiority margin for composite outcome of 1.3 • Performed intention to treat and per protocol analysis • Cox proportional-hazards model to calculate hazard ratios and two-sided 95% CI • Calculated 611 patients needed to provide a 90% power to test for non-inferiority (hazard ratio 1.0) • Calculated 1300 patients needed with a primary composite outcome needed to provide a power of 81% for superiority (hazard ratio 0.85)	

Baseline Characteristics	**Characteristic**	**Sitagliptin** n=7332	**Placebo** n=7339
	Age (yrs)	65.4 +/- 7.9	65.5 +/-8.0
	Female sex, No. (%)	2134 (29.1)	2163 (29.5)
	Hispanic or Latino, No. (%)	886 (12.1)	912 (12.4)
	Black, No. (%)	206 (2.8)	241 (3.3)
	Asian, No. (%)	1654 (22.6)	1611 (22.0)
	Duration of diabetes mean, yrs	11.6 +/- 8.1	11.6 +/- 8.1
	A1c (%), mean	7.2 +/- 0.5	7.2 +/- 0.5
	BMI (kg/m^2), mean	30.2 +/- 5.6	30.2 +/- 5.6
	Systolic blood pressure (mmHg)	135 +/- 16.9	135 +/- 17.1
	Diastolic blood pressure (mmHg)	77.1 +/- 10.3	77.2 +/- 10.6
	eGFR (mL/min)	74.9 +/- 31.5	74.9 +/- 20.9
	Prior CV disease, No. (%)	5397 (73.6)	5466 (74.5)
	Prior cerebrovascular disease, No. (%)	1806 (24.6)	1782 (24.3)
	Prior peripheral arterial disease, No. (%)	1217 (16.6)	1216 (16.6)
	Prior congestive HF, No. (%)	1303 (17.8)	1340 (18.3)
	Current smoker, No. (%)	865 (11.8)	813 (11.1)
	Metformin, No. (%)	5936 (81.0)	6030 (82.2)
	Sulfonylurea, No. (%)	3346 (45.6)	3299 (45.0
	Thiazolidinedione, No. (%)	196 (2.7)	200 (2.7)
	Insulin, No, (%)	1724 (23.5)	1684 (22.9)
	Beta blocker, No. (%)	4647 (63.4)	4675 (63.7)

	ACE inhibitor or ARB, No. (%)	5743 (78.3)	5812 (79.2)
	Calcium channel blocker, No. (%)	2444 (33.3)	2517 (34.3)
	Diuretic, No. (%)	2976 (40.6)	3044 (41.5)
	Aspirin, No (%)	5764 (78.6)	5754 (78.4)
	Statin, No (%)	5851 (79.8)	5868 (80.0)

Results		**Sitagliptin** n=1434	**Placebo** n=1386	HR 95% CI	p value
	Primary Outcome No. (%)				
	CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina	839 (11.4)	851 (11.6)	0.98 (0.89 to 1.08)	0.65
	Secondary Outcomes No. (%)				
	CV death, nonfatal MI, or nonfatal stroke	745 (10.2)	746 (10.2)	0.99 (0.89 to 1.10)	0.84
	Hospitalization for HF	228 (3.1)	229 (3.1)	1.00 (0.83 to 1.20)	0.98
	Safety Outcomes No. (%)				
	Severe hypoglycemia	160 (2.2)	143 (1.9)	1.12 (0.89 to 1.40)	0.33

Author's Conclusions	Sitagliptin does not ↑ risk of major adverse CV events, hospitalization for HF or other adverse events in patients with T2DM and CV disease
Strengths	• Randomized, placebo controlled, double blind, multi-center • Large sample size • Well balanced baseline characteristics • Merck Sharp & Dohme had no role in data analysis • Adequately powered for the primary outcome • Intention to treat • Long duration of diabetes
Weaknesses	• Physicians were able to modify regimens which could confound the endpoint • Baseline A1c near goal (mean 7.2) • Excluded patients with an A1c >8.0% • Short term follow up: 3 years • Adjusted hospitalization for HF based on history of HF • Small differences in A1c at end of study; approximately 0.29% • Did not report non-severe hypoglycemia
Take Away	• Sitagliptin did not change CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina • Sitagliptin not associated with severe hypoglycemia • Sitagliptin did not ↑ rates of hospitalization for HF

a) History of major coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral artery disease
b) Metformin, pioglitazone, or sulfonylurea OR insulin +/- metformin
c) Other than pioglitazone
d) Requiring third party assistance

Table 6: 2013 Zannad, et al. [26]
Heart Failure and Mortality Outcomes in Patients with Type 2 Diabetes Taking Alogliptin Versus Placebo in EXAMINE: A Multicentre, Randomised, Double-Blind Trial

Objective
- To investigate HF outcomes in patients with a history of CV disease in prespecified exploratory analysis and in a post-hoc analysis

Design
- Multicenter, double-blind, randomized trial, post-hoc analysis

Inclusion
- T2DM
  - A1c 6.5-11%
  - A1c 7.0-11% if the patient was on insulin
- Receiving antidiabetic therapy[a]
- Had an acute coronary syndrome (ACS)[b] within 15-90 days before randomization

Exclusion
- Type 1 diabetes mellitus
- Unstable cardiac disorders[c]
- Dialysis within 14 days before screening

Endpoints

Primary	Secondary	Pre-specified Exploratory	Post-Hoc Analysis
Composite of CV death, nonfatal MI, or nonfatal stroke	Primary outcome + urgent revascularization due to unstable angina within 24 hours after hospital admission	1st occurrence of all-cause mortality, non-fatal MI, non-fatal stroke, urgent revascularization due to unstable angina and hospitalization for HF	• All-cause mortality • Hospital admission for HF

Intervention

	Arm 1	Arm 2
eGFR	alogliptin 25mg daily	Placebo
≥60 mL/min	alogliptin 12.5mg daily	
30 to <60 mL/min	alogliptin 6.25mg daily	
<30 mL/min	alogliptin 25mg daily	

Statistics
- Intention to treat
- 5400 patients needed to have 91% power to determine noninferiority of alogliptin for 1.8 and 1.3 margins
- True HR of 1.0 and α of 2.5%
- Two-sided significance level of 5%; 95% CI
- Time to first occurrence of primary and secondary endpoint component was analyzed with Cox proportional hazards model
- Interim analyses performed after 80, 100, 125, and 150 adjudicated primary end-point events occurred; α of 2.5%, HR >1.8
- Interim analyses performed after 550 and 650 adjudicated primary end-point events; α of 2.5%, HR 1.3
- Hypoglycemia analyzed with logistic regression
- Data are median (IQR), number (%) or mean (SD)

Baseline Characteristics

	History of HF at Baseline		No History of HF at Baseline	
	Alogliptin n=771	**Placebo** n=762	**Alogliptin** n=1930	**Placebo** n=1917
Age (yrs)	63 (56-70)	62 (55-70)	60 (53-67)	60 (53-67)
Male	467 (60.6%)	464 (60.9%)	1361 (70.5%)	1359 (70.9%)
Duration of diabetes, yrs	7.9 (0·0 to 39.2)	6.8 (0·0 to 48.5)	6.8 (0·0 to 44.3)	7.3 (0·0 to 49.9)
A1c	8.12 (1.12)	8.15 (1.12)	7.99 (1.07)	7.99 (1.10)
BMI (kg/m^3)	29.7 (26.1 to 33.5)	29.5 (25.8 to 33.5)	28.5 (25.3 to 32.2)	28.5 (25·4 to 32.3)
Asian	83 (10.8%)	107 (14.0%)	464 (24.0%)	435 (22.7%)
Black	39 (5.1%)	40 (5.2%)	62 (3.2%)	75 (3.9%)
eGFR, (mL/min)	66.40 (51.52 to 80.39)	64.96 (50.50 to 82.04)	72.65 (59.94 to 86.08)	73.17 (59.80 to 86.96)
Prior CV history				
Current Smoker	72 (9.3%)	105 (13.8%)	279 (14.5%)	278 (14.5%)
Hypertension	704 (91.3%)	694 (91.1%)	1525 (79.0%)	1546 (80.6%)
MI	689 (89.4%)	691 (90.7%)	1700 (88.1%)	1654 (86.3%)

	PCI	389 (50.5%)	391 (51.3%)	1300 (67.4%)	1292 (67.4%)
	CABG	125 (16.2%)	124 (16.3%)	222 (11.5%)	217 (11.3%)
	Stroke	29 (3.8%)	24 (3.1%)	46 (2.4%)	46 (2.4%)
	Peripheral artery disease	117 (15.2%)	124 (16.3%)	145 (7.5%)	128 (6.7%)
	Index ACS event				
	Myocardial infarction	536 (69.5%)	555 (72.8%)	1548 (80.2%)	1513 (78.9%)
	Unstable angina	234 (30.4%)	203 (26.6%)	375 (19.4%)	402 (21.0%)
	Days from index event to randomization	47.0 (32.0 to 69.0)	48.0 (31.0 to 69.0)	42.0 (29.0 to 62.0)	44.0 (29.0 to 62.0)
	Baseline concomitant cardiovascular medications				
	MRAs	207 (26.8%)	179 (23.5%)	145 (7.5%)	149 (7.8%)
	Beta-blockers	648 (84.0%)	629 (82.5%)	1560 (80.8%)	1574 (82.1%)
	Loop Diuretics	254 (32.9%)	250 (32.8%)	228 (11.8%)	208 (10.9%)
	ACEi/ARB/Both	668 (86.6%)	651 (85.4%)	1533 (79.4%)	1559 (81.3%)
	NYHA CHF Class				
	I	174 (22.6%)	157 (20.6%)		
	II	424 (55.0%)	441 (57.9%)		
	III	148 (19.2%)	136 (17.8%)		
	IV	10 (1.3%)	10 (1.3%)		

Results

	All Patients		**History of HF**		**No History of HF**	
	Alogliptin n=2701	**Placebo** n=2679	**Alogliptin** n=771	**Placebo** n=762	**Alogliptin** n=1930	**Placebo** n=1917
Primary MACE endpoint						
CV death, nonfatal MI, nonfatal stroke	305 (11.3%)	316 (11.8%)	123 (16.0%)	131 (17.2%)	182 (9.4%)	185 (9.7%)
HR (95% CI)	0.96 (≤1.16)		0.94 (0.74 to 1.20)		0.97 (0.79 to 1.19)	
p value	0.32		0.874		0.772	
Secondary MACE endpoint						
Primary endpoint + urgent revasc for UA	344 (12.7%)	359 (13.4%)	127 (16.5%)	141 (18.5%)	217 (11.2%)	218 (11.4%)
HR (95% CI)	0.95 (≤1.14)		0.89 (0.70 to 1.14)		0.98 (0.81 to 1.18)	
p value	0.26		0.358		0.832	
Post-Hoc Analysis						
CV death & hospitalization for HF	201 (7.4 %)	201 (7.5%)	107 (13.9%)	120 (15.7%)	94 (4.9%)	81 (4.2%)
HR (95% CI)	1.00 (0.82 to 1.21)		0.90 (0.70 to 1.17)		01.14 (0.85 to 1.54)	
p value	0.976		0.446		0.337	
CV Death	112 (4.1%)	130 (4.9%)	55 (7.1%)	69 (9.1%)	57 (3.0%)	61 (3.2%)
HR (95% CI)	0.85 (0.66 to 1.10)		0.77 (0.54 to 1.09)		0.92 (0.64 to 1.32)	
p value	0.212		0.141		0.643	
Hospitalization for HF	106 (3.9%)	89 (3.3%)	63 (8.2%)	65 (8.5%)	43 (2.2%)	24 (1.3%)
HR (95% CI)	1.19 (0.90 to 1.58)		1.00 (0.71 to 1.42)		1.76 (1.07 to 2.90)	
p value	0.220		0.996		0.026	
Safety Outcomes						
Hypoglycemia	173 (6.5%)	181 (6.7%)				
p value	0.74					

Author's Conclusions

In patients with T2DM and recent ACS, alogliptin did not ↑ risk of heart HF outcomes.

Strengths	• Randomized, placebo controlled, double-blind, multi-center • Large sample size • Intention to treat • Well balanced baseline characteristics • Included patients with a wide range of A1cs
Weaknesses	• Post-hoc analysis • Not powered to show statistical difference in hospitalization for HF • Short term follow up: 1.5 years • Shorter duration of diabetes • Patients experiencing the primary endpoint were not further followed • Excluded NYHA Class IV; Majority NYHA Class II, some III • Funding source had a role in data interpretation and writing of the report • Minimal change in A1c: approximately 0.33% • Baseline A1c of 8%
Take Away	• Alogliptin not associated with change in CV death, nonfatal MI, or nonfatal stroke • Alogliptin associated with overall numerically ↑ in hospitalizations for HF • Outcome was not adequately powered to demonstrate statistical significance • Alogliptin was not associated with hypoglycemia

a) Other than a DPPIV-inhibitor OR a GLP-1 agonist
b) Acute MI and unstable angina requiring hospitalization
c) NYHA Class IV HF, refractory angina, uncontrolled arrhythmias, critical valvular heart disease, severe uncontrolled hypertension

Ongoing Research:

Table 7: Ongoing DPP-4 Inhibitor Clinical Trials[32,33]

Trial	Population	Intervention	Primary Endpoint	Estimated Completion
CAROLINA[32]	T2DM with CV disease or diabetes end organ damage or >2 CV risk factors	Linagliptin 5mg daily vs. glimepiride1-4mg daily vs. placebo	Composite time to first occurrence of CV death, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina	February 2019
CARMELINA[33]	T2DM with high risk of CV events (albuminuria, previous macrovascular disease or impaired renal function)	Linagliptin 5mg daily vs. placebo	Composite first occurrence of CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina	January 2018

Conclusions:

A. Overview of Presented Trials:

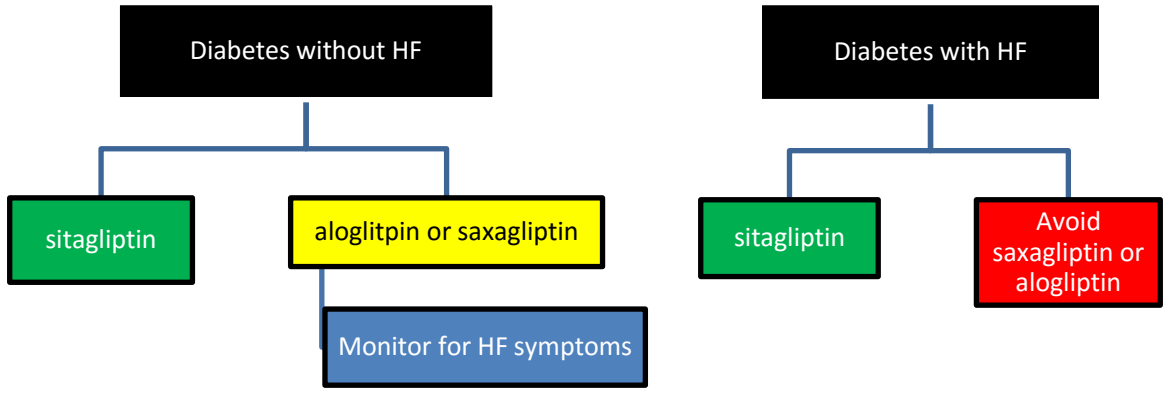
Table 8: Overview of Trials Presented[24,25,26]

Trial	Population	Intervention	Findings	Comment
SAVOR-TIMI 53[24]	T2DM + CV disease or risk factors	Saxagliptin 2.5-5mg vs. placebo	• No Δ in CV events • HF hospitalization ↑ • ↑ hypoglycemia	• Adequately powered
TECOS[25]	T2DM + CV disease	Sitagliptin 50-100mg vs. placebo	• No Δ CV events • No Δ HF hospitalization • No Δ in severe hypoglycemia	• Did not assess non-severe hypoglycemia • Lower A1c • Adjusted HF hospitalization endpoint
EXAMINE[26]	T2DM + recent ACS	Alogliptin 6.25-25mg vs. placebo	• No Δ CV events • No Δ HF hospitalization • No Δ in hypoglycemia	• Not adequately powered for HF hospitalization or hypoglycemia • More HF pts • Shorter duration of T2DM

Δ= difference; T2DM=type 2 diabetes mellitus, ACS=acute coronary syndrome

B. Treatment Algorithm:

Figure 7: DPP4i Treatment Algorithm



C. Concluding Remarks:

i. DPP-4 inhibitors are recommended by the ADA as a 2nd or 3rd line option for the treatment of diabetes.
ii. DPP-4 inhibitors have moderate efficacy, low rates of hypoglycemia and are weight neutral.
iii. If a patient has HF, saxagliptin and alogliptin should be avoided due to the ↑ risk of hospitalization for HF.
iv. Linagliptin's use in HF patients is uncertain due to lack of clinical data. Large randomized, controlled trials are currently in progress.
v. TECOS did not find an ↑ in hospitalization for HF or CV events; therefore, if a prescriber chooses to use a DPP-4 inhibitor for the treatment of T2DM in a patient with HF, sitagliptin may be used.
vi. Alogliptin and saxagliptin were associated with ↑ HF hospitalizations in patients with or without diabetes; therefore, patients without HF should be monitored for HF symptoms while taking these medications.

Post-Trial FDA Statement:

A. 2016 FDA Statement:[34]

i. The "warning and precaution" labels of alogliptin and saxagliptin will be updated to state may ↑ the risk of HF.

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Appendix:

Table 9: NYHA Functional Class[35]	
Class	**Patient Symptoms**
I	No limitation of physical activity
II	Slight limitation of activity; comfortable at rest; less than ordinary activity causes symptoms
III	Marked limitation of physical activity; comfortable at rest; less than ordinary activity causes symptoms
IV	Unable to carry on any physical activity without discomfort; symptoms at rest