Impact of Sitagliptin on Heart Failure and Related Outcomes

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DECLARATION OF INTEREST

- Research contracts
- Consulting/Royalties/Owner/ Stockholder of a healthcare company

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Disclosures

- **Research grants :**
  Boehringer Ingelheim, Merck, Bayer, CSL

- Educational Grants: Bayer,Astra Zeneca, Merck, Servier,Novartis

- **Consulting:**
  Boehringer Ingelheim, Merck, AstraZeneca, Eli Lilly

- Full Details:
  http://www.vigour.ualberta.ca/en/About/~/media/vigour/Publication%20Resources/COI2015/Financial_Disclosure_form_PWA_May_2015.pdf

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TECOS Study

- Large, pragmatic international trial designed to assess the impact of sitagliptin versus placebo on cardiovascular event rates
  - When added to usual diabetes care
  - Minimize difference in glycemia between groups
- Randomized, double-blind, placebo-controlled
- 14,671 patients with T2DM and established CVD: median F/up 3yrs
- Academically led in collaboration with industry sponsorship

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Objectives of TECOS

Primary:

To demonstrate that the risk of cardiovascular events (CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina) in patients treated with sitagliptin in addition to usual care was **non-inferior** to that in patients treated without sitagliptin in addition to usual care

Prespecified secondary:

To analyze effects on hospitalization for heart failure and related outcomes

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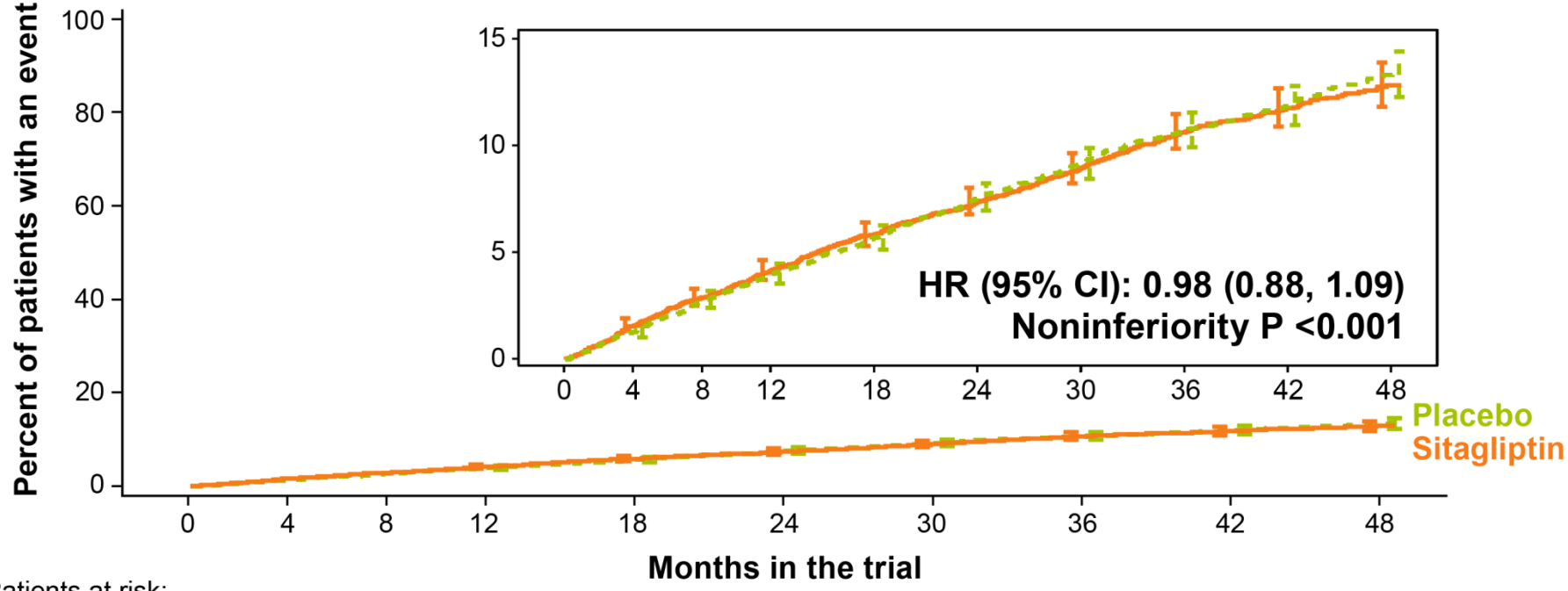
Primary Composite Cardiovascular Outcome*
Per Protocol Analysis for Noninferiority



Patients at risk:

Sitagliptin	7,257	6,857	6,519	6,275	5,931	5,616	3,919	2,896	1,748	1,028
Placebo	7,266	6,846	6,449	6,165	5,803	5,421	3,780	2,743	1,690	1,005

** CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina*

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Background: Diabetes & Heart Failure

- Diabetes is associated with an increased risk of heart failure(HF) similar to that seen with MI and stroke
- Incidence increases with age *but* relative risk actually higher in younger patients
- In patients with atherosclerosis type 2 DM is known to increase the risk of hospitalization for heart failure by ~30%
- Mortality from HF in diabetics is ~ double that of non-diabetics
- Diabetes in heart failure is “frequent, forgotten & often fatal” (Bell)
- Anti-diabetic therapy (insulin, thiazolidinediones: pioglitazone & rosiglitazone, some dipeptidyl peptidase-4 (DPPP-4) inhibitors) *have been associated with an increased incidence of HF*

Lancet 2015 Gilbert & Krum

Impact of Sitagliptin on Heart Failure Hospitalization

- Observations from 2 recent large trials suggest an increased risk for hospitalization for heart failure with DPP4 inhibitors:
  - saxagliptin in SAVOR-TIMI 53 (n=16,492)
  - alogliptin in EXAMINE (n= 5380)
- **We evaluated -*according to a prespecified analysis plan*- the potential impact of sitagliptin on HF hospitalization in the overall TECOS population and in key relevant subgroups**

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Baseline Characteristics *According to HF Hospitalization (*1)

Characteristic	With hHF n=457	Without hHF n=14,214
Age, yrs (SD)	68.5 (7.6)	65.4 (8.0)
Women, %	25.2	29.4
Duration of diabetes, yrs (SD)	12.3 (8.7)	11.6 (8.1)
HbA_{1c}, % (SD)	7.3 (0.5)	7.2 (0.5)
eGFR, mL/min/1.73m^2 (SD)	66.5 (20.9)	75.2 (21.1)
Prior vascular disease, %		
Coronary artery disease	85.3	73.7
Cerebrovascular disease	29.1	24.3
Peripheral artery disease	17.3	16.6
Prior myocardial infarction	**58.2**	**42.1**
Prior heart failure, %	**41.8**	**17.3**

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Baseline Characteristics *According to HF Hospitalization (2)*

Characteristic	With hHF n=457	Without hHF n=14,214
Antihyperglycemic therapies, %		
Metformin	72.2	81.9
Sulfonylurea	46.2	45.3
Pioglitazone	2.8	2.7
Insulin	32.4	22.9
Cardiovascular medications, %		
Statin	83.6	79.8
Aspirin	74.6	78.6
Non-aspirin anti-platelet agent	21.7	21.7
ACE inhibitor/angiotensin receptor blocker	85.6	78.5
Beta blocker	71.8	63.3
Diuretic	69.1	40.1
Calcium channel blocker	39.2	33.6

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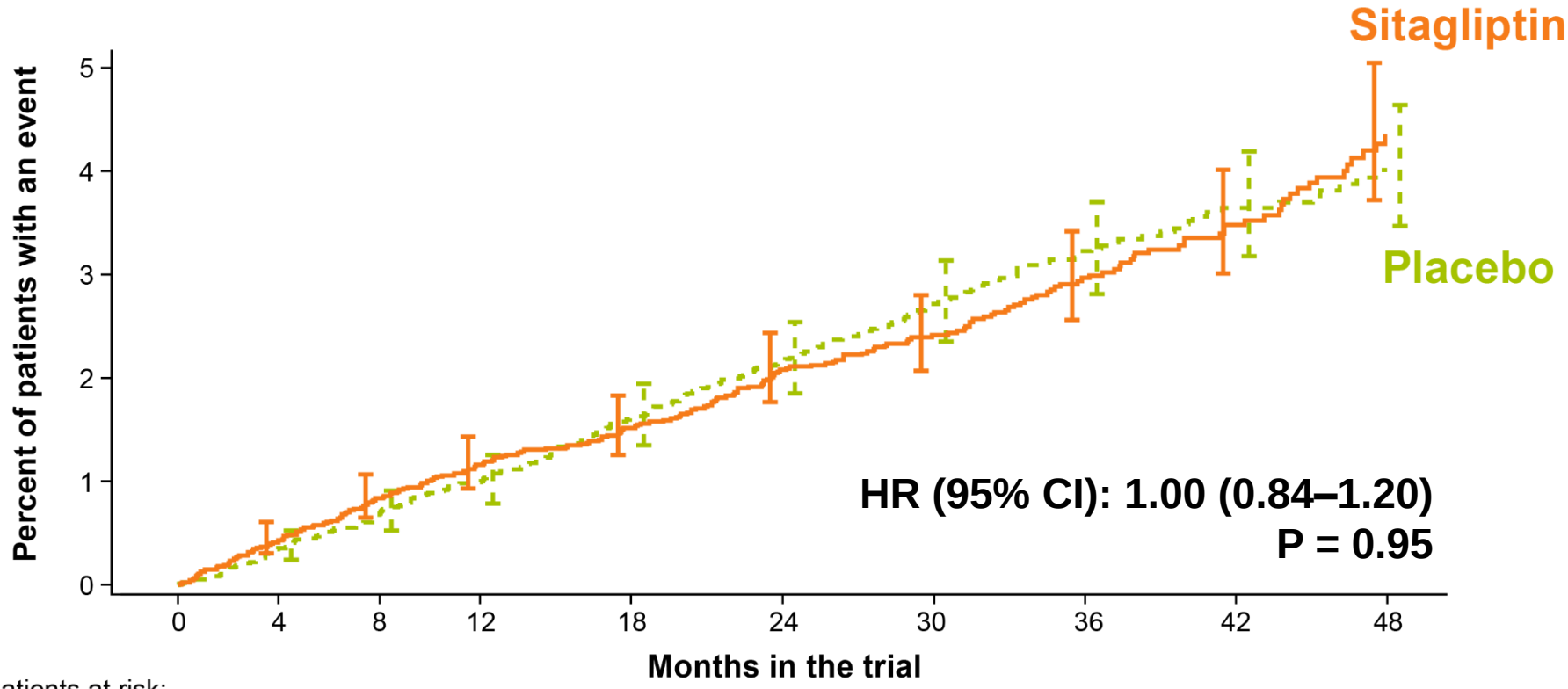
Time to First Hospitalization for Heart Failure*



Patients at risk:										
Sitagliptin	7,332	7,189	7,036	6,917	6,780	6,619	4,728	3,515	2,175	1,324
Placebo	7,339	7,204	7,025	6,903	6,712	6,549	4,599	3,443	2,131	1,315

** ITT population*

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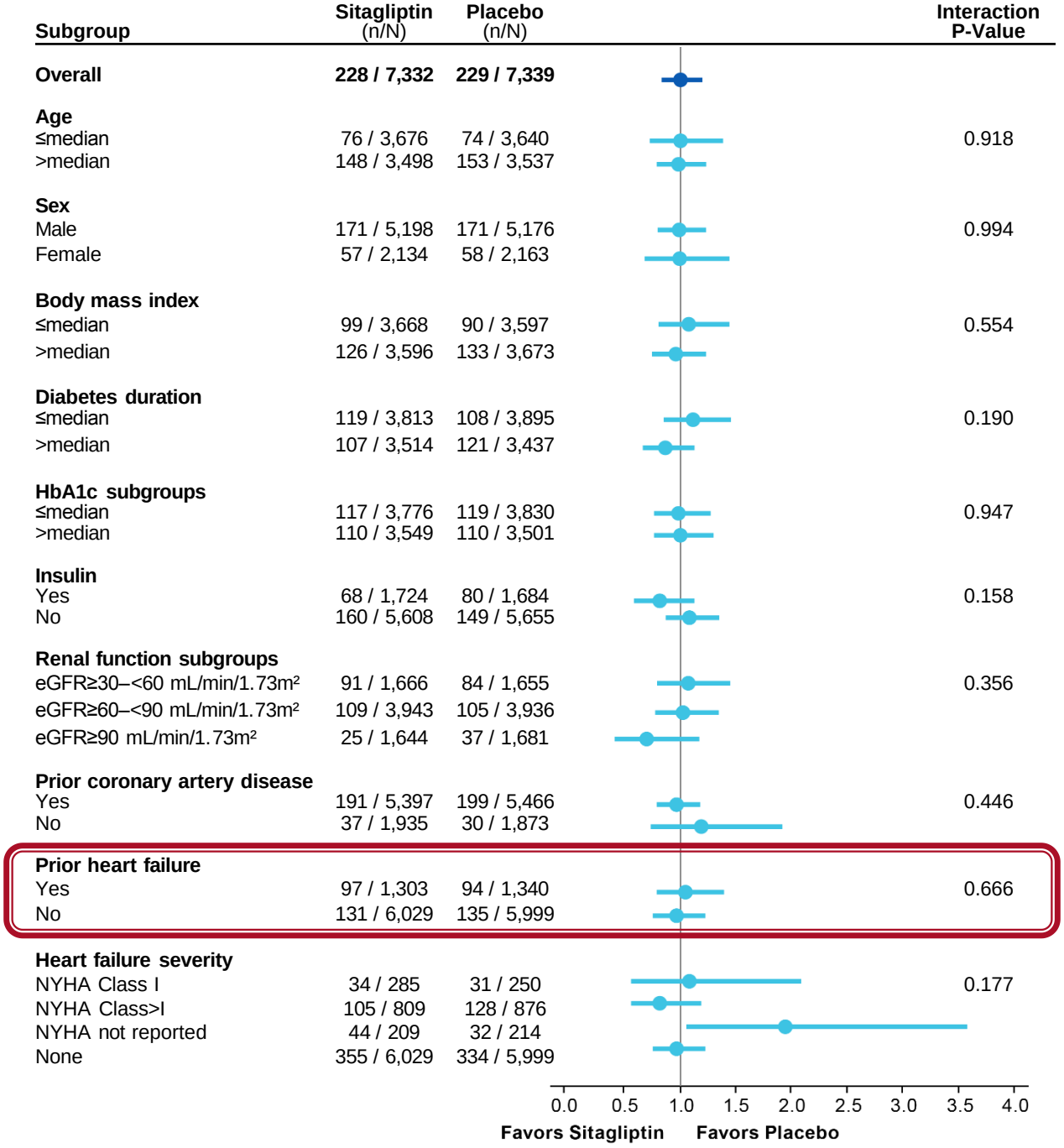
Hospitalization for Heart Failure



** ITT Population*

Heart Failure-related Outcomes: Sitagliptin vs Placebo* (1)

	Sitagliptin n=7332	Placebo n=7339	HR (95% CI)	P-value
Hospitalization for heart failure	228 (3.1%)	229 (3.1%)	1.00 (0.84–1.20)	0.95
Adjusted for baseline heart failure	-	-	1.00 (0.83–1.20)	0.98
Multivariable adjusted*	-	-	1.02 (0.83–1.26)	0.82
Hospitalization for heart failure or cardiovascular death	538 (7.3%)	525 (7.2%)	1.02 (0.90–1.14)	0.81
Adjusted for baseline heart failure	-	-	1.02 (0.90–1.15)	0.74
Hospitalization for heart failure or all-cause death	685 (9.3%)	682 (9.3%)	1.00 (0.90–1.11)	0.93

Adjusted for: ethnicity, race, history of MI, history of coronary artery disease, history of coronary artery bypass graft surgery, history of peripheral arterial disease, history of heart failure, smoking status, diuretic use, age, BMI, systolic blood pressure, diastolic blood pressure, estimated glomerular filtration rate, glycosylated hemoglobin, HDL-cholesterol, and triglycerides.

**ITT population*

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Heart Failure-related Outcomes:Sitagliptin vs Placebo* (2)

	Sitagliptin n=7332	Placebo n=7339	HR (95% CI)	P-value
Total hospitalization for heart failure events (first + recurrent)#	345	347	1.00 (0.80–1.25)	0.996
Patients with 2 events	37	44	-	-
Patients with ≥3 events	26	25	-	-
Mortality among patients with at least 1 hospitalization for heart failure				
Cardiovascular mortality	51/228 (22.4%)	53/229 (23.1%)	-	-
All-cause mortality	68/228 (29.8%)	66/229 (28.8%)	-	-

*#Analyzed by the Andersen-Gill method *ITT population*

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Overall TECOS CV mortality 4.1% All cause 7.4%

Heart Failure-related Outcomes:Sitagliptin vs Placebo
Patients with Prior Heart Failure at Baseline

	Sitagliptin n=1303	**Placebo** n=1340	**HR** (95% CI)	**P-value**
Hospitalization for heart failure	97 (7.4%)	94 (7.0%)	1.03 (0.77–1.36)	0.86
Cardiovascular death	120 (9.2%)	133 (9.9%)	0.91 (0.71–1.17)	0.46
Hospitalization for heart failure or cardiovascular death	183 (14.0%)	191 (14.3%)	0.96 (0.79–1.18)	0.71
All-cause death	166 (12.7%)	182 (13.6%)	0.92 (0.75–1.14)	0.46

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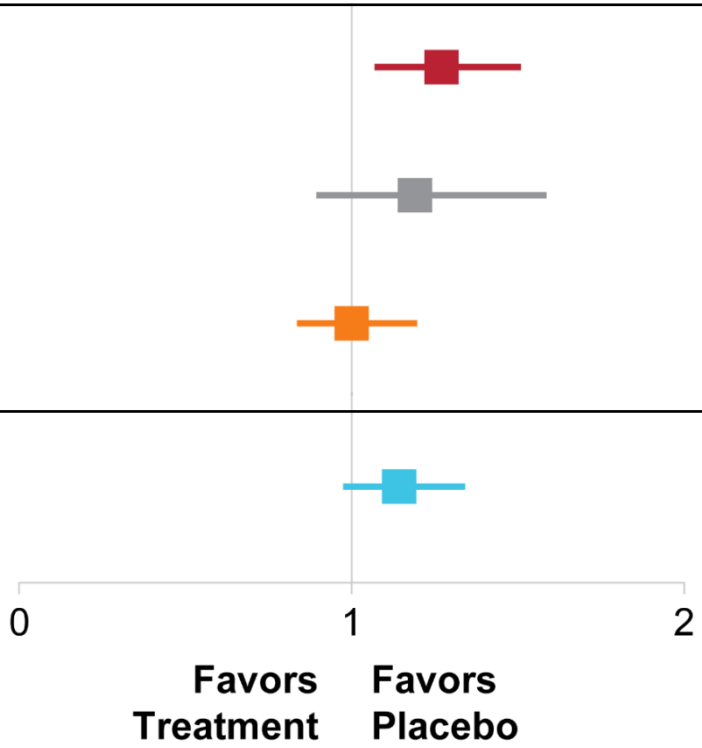
SAVOR-TIMI 53, EXAMINE, and TECOS*: Hospitalization for Heart Failure

Subgroup	HR (95% CI)	P-Value
SAVOR-TIMI	1.27 (1.07–1.51)	0.007
EXAMINE	1.19 (0.89–1.59)	0.235
TECOS	1.00 (0.84–1.20)	1.000
SAVOR-TIMI + EXAMINE + TECOS	1.14 (0.97–1.34)	0.102



Test for heterogeneity for 3 trials: p=0.16, I^2=44.9

** Unadjusted*

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Conclusions

- **In this comprehensive analysis of TECOS we found no increased risk of heart failure or related adverse outcomes after Sitagliptin therapy**
- ***Potential reasons for the different findings versus* SAVOR-TIMI 53 and EXAMINE:**
  - Differences in patients enrolled
  - Differences in background care provided
  - Variation in acquisition/definition of HF events among trials
  - Intrinsic pharmacologic differences among the DPP4 inhibitors
  - Play of chance
- **Sitagliptin can be safely used in type 2 DM patients without concern for worsening heart failure**

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Acknowledgements

Manuscript: No Impact of Sitagliptin on Heart Failure Hospitalization and Related Outcomes in Type 2 Diabetes

Darren McGuire, Frans Van de Werf, Paul Armstrong, Eberhard Standl, Joerg Koglin, Jennifer Green, Angelyn Bethel, Jan Cornel, Renato Lopes, Sigrun Halvorsen, Giuseppe Ambrosio, John Buse, Robert Josse, John Lachin, Michael Pencina, Jyotsna Garg, Yuliya Lokhnygina, Rury Holman and Eric Peterson, on behalf of the TECOS Study Group

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