Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) – TIMI 53

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On behalf of the SAVOR-TIMI 53
Steering Committee and Investigators

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Disclosures for Dr. Bhatt

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This presentation discusses off-label and/or investigational uses of diabetes drugs including saxagliptin.

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Type 2 Diabetes and Cardiovascular Risk

- Many studies in patients with DM have demonstrated that improved glucose control reduces *microvascular* complications.
- However, uncertainty remains regarding whether any particular glucose-lowering strategy is safe from a CV standpoint or can actually lower *macrovascular* complications (e.g., MI, stroke, or CV death).
- Saxagliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor that lowers glucose.

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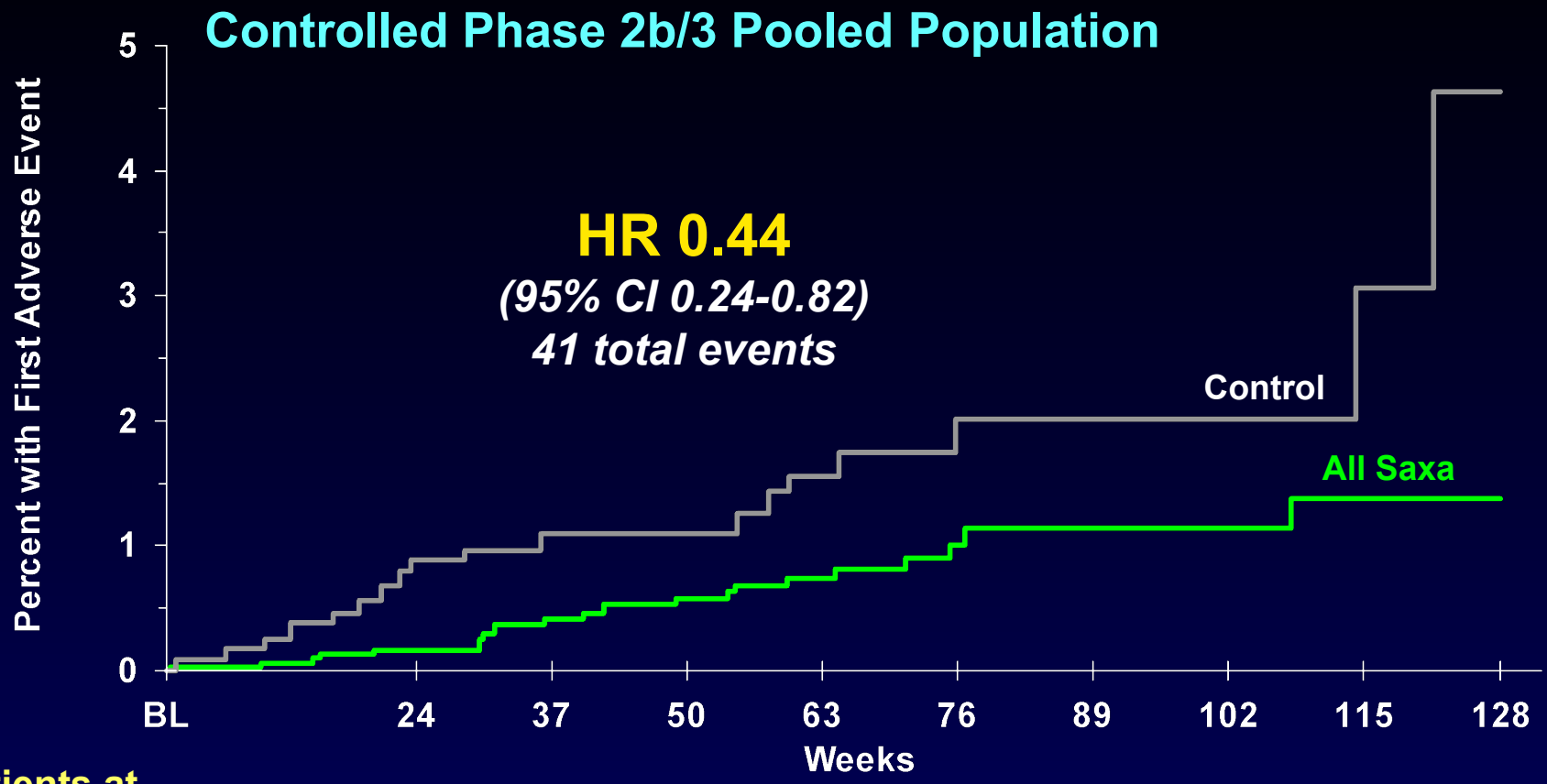
Time to Onset of First Primary MACE in Prior Pooled Analysis



Patients at Risk										
Control	1251	935	860	774	545	288	144	123	102	57
All Saxa	3356	2615	2419	2209	1638	994	498	436	373	197

Frederich R, et al. Postgraduate Medicine 2010;122(3). doi: 10.3810/pgm.2010.05.2138.

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Primary Objective

- To determine whether when added to background therapy, saxagliptin would be non-inferior to placebo for the composite endpoint of CV death, non-fatal MI, or non-fatal ischemic stroke (Upper 95% CI of HR < 1.3).
- And if non-inferiority were met, to determine if saxagliptin would be superior to placebo.

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Trial Organization

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N = 16,492

Documented Type 2 Diabetes

Established CV Disease or Multiple Risk Factors

RANDOMIZED 1:1 DOUBLE BLIND

SAXAGLIPTIN 5 mg/d

2.5 mg/d if eGFR ≤ 50 ml/min

All other DM Rx per treating MD

PLACEBO

Duration
Event driven (n=1040)
Median duration 2.1y
LTFU 0.2%
W/C 2.4%

Follow up Visits Q6 months

Final Visit

Primary EP
CV Death, MI, Ischemic Stroke

Major Secondary EP: CV death, MI, ischemic stroke, or hosp. for heart failure, unstable angina, or coronary revascularization

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Inclusion Criteria
Patient Population

All patients were to have the diagnosis of T2DM and <u>all</u> of the following:

1. **Age ≥40 years, *and***
2. **Documented HbA1c ≥6.5% in the previous 6 months, *and***
3. **High risk for a CV event with:**
    1. **Established CV Disease**

    or

    2. **Multiple Risk Factors** ***Cap at 25% of initial pts.***
        - **Must be ≥ 55 y.o. (male) or 60 y.o. (female)**
        - **Dyslipidemia, hypertension, or current smoking**

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Definition of High Risk for CV Disease
Established CV Disease

Evidence of atherosclerosis in at least 1 vascular bed

Stable CAD or **Stable CVD** or **PAD**

- Prior MI*, *or*
- PCI/CABG of at least 2 arteries, *or*
- Known stenosis ≥50% in at least 2 arteries

Prior Ischemic Stroke*

Hx Claudication
AND
- ABI<0.9, *or*
- Prior revasc or amputation

* Must be >2 months before randomization

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Baseline Characteristics

	Placebo (N = 8,212)	Saxagliptin (N = 8,280)
Age	65 yr	65 yr
Female (%)	33	33
Established CVD *n=12,959*	79	78
Multiple Risk Factors *n=3,533*	21	22
Cardiac Risk Factors (%)		
Dyslipidemia	71	71
HTN	82	81
Prior MI	38	38
Prior CHF	13	13
Prior Coronary Revasc.	43	43

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Baseline Medications

	Placebo (N = 8,212)	Saxagliptin (N = 8,280)
Cardiovascular Medications (%)		
Aspirin	75	76
Statin	78	78
ACEi	55	54
ARB	28	28
Beta Blocker	62	62
Diabetic Medications (%)		
Insulin	41	42
Sulfonylurea	40	41
TZD	6	6
Metformin	69	70
None	5	4

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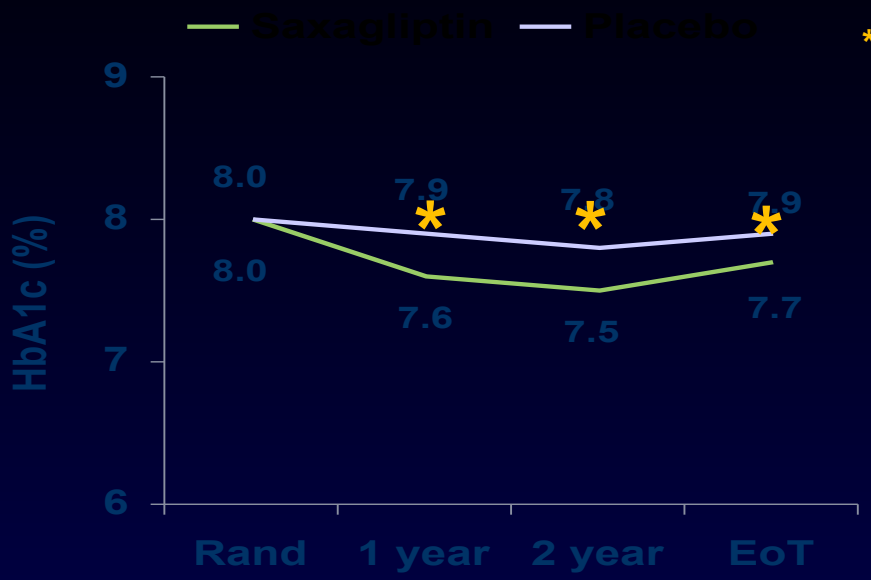
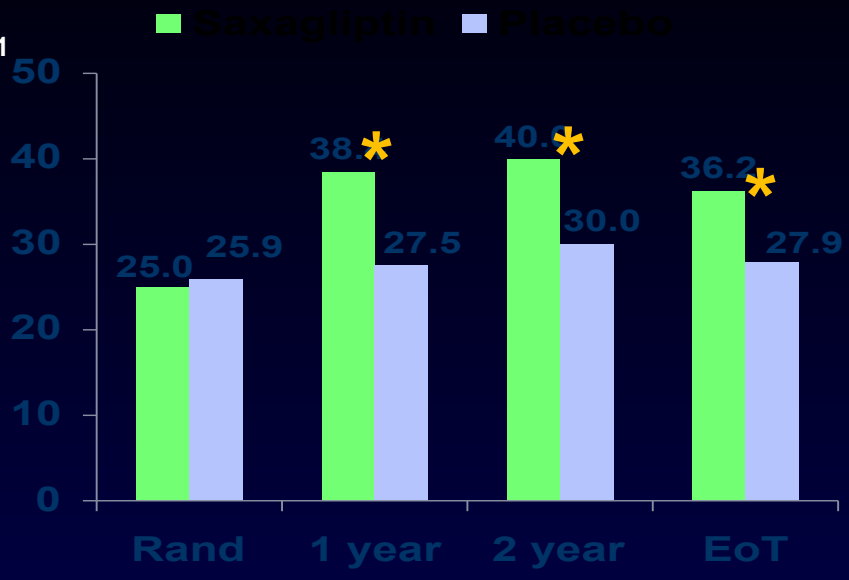
Glycemic Indices Over Time

Mean HbA1c (%)



HbA1c <7.0%



These changes were in the context of:

- **23% ↓ in the intensification of anti-hyperglycemic medications with saxagliptin compared to control (p<0.001), and**
- **30% ↓ in the initiation of insulin therapy for more than 3 months with saxagliptin compared to control (p<0.001).**

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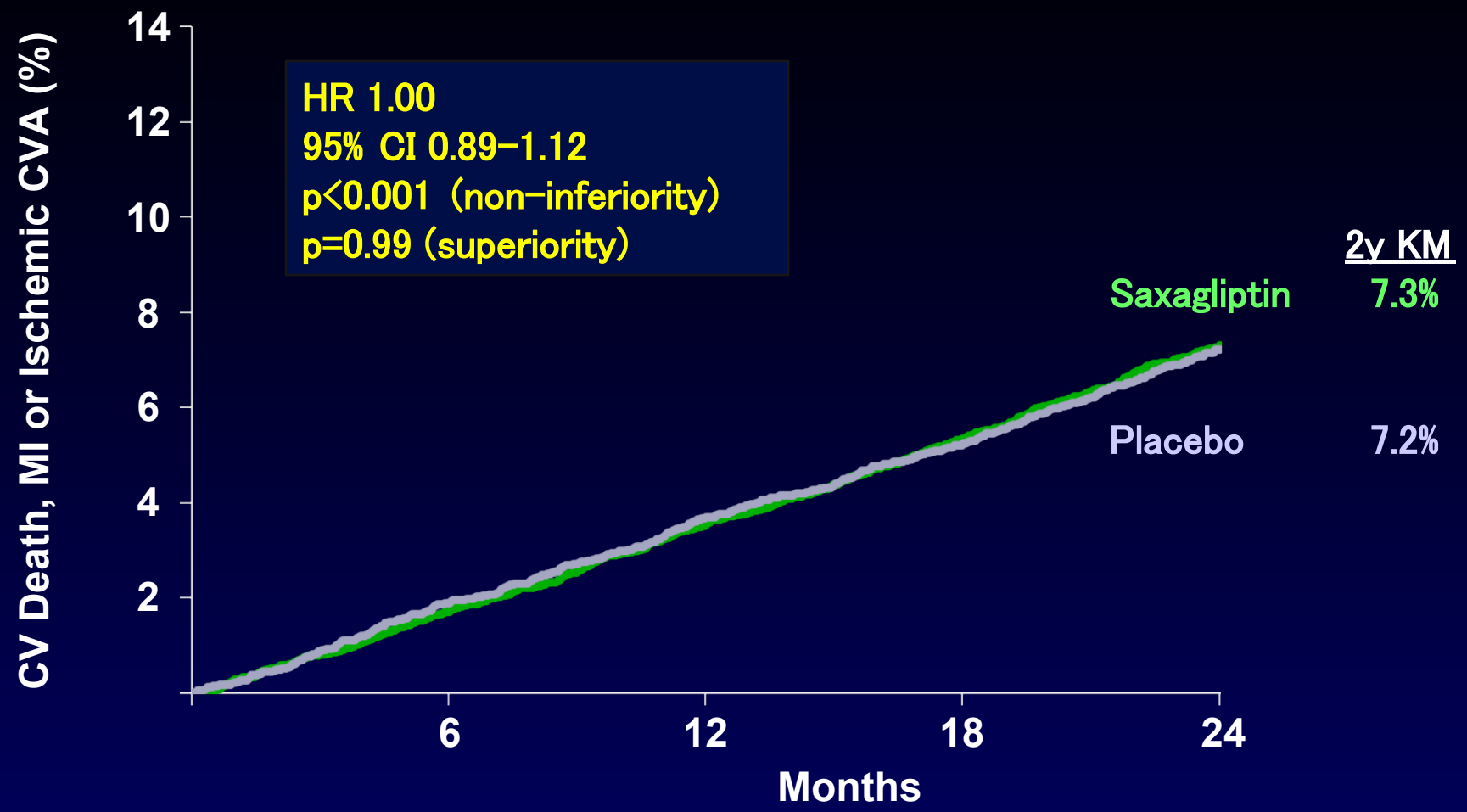
Primary Endpoint



Placebo	8212	7983	7761	7267	4855
Saxagliptin	8280	8071	7836	7313	4920

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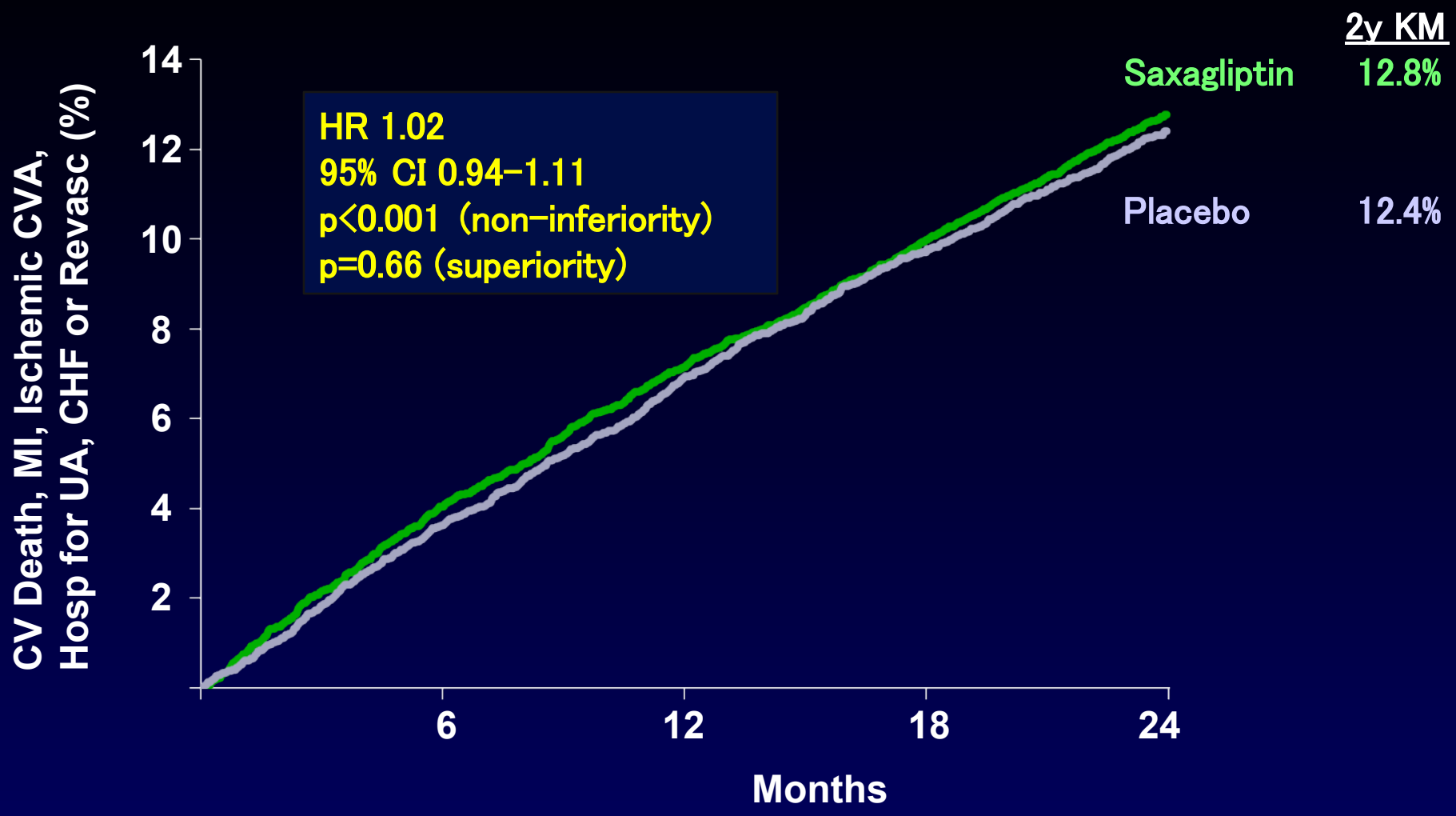
Secondary Endpoint



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Individual Endpoints

ITT Population

	2-year KM rate (%)			
	Placebo (N=8,212)	Saxagliptin (N=8,280)	HR	*p value for superiority*
CV Death	2.9	3.2	1.03 (0.87-1.22)	0.72
MI	3.4	3.2	0.95 (0.80-1.12)	0.52
Ischemic Stroke	1.7	1.9	1.11 (0.88-1.39)	0.38
Hosp for Cor. Revasc	5.6	5.2	0.91 (0.80-1.04)	0.18
Hosp for UA	1.0	1.2	1.19 (0.89-1.60)	0.24
Hosp for Heart Failure	2.8	3.5	1.27 (1.07-1.51)	0.007
All-Cause Mortality	4.2	4.9	1.11 (0.96-1.27)	0.15

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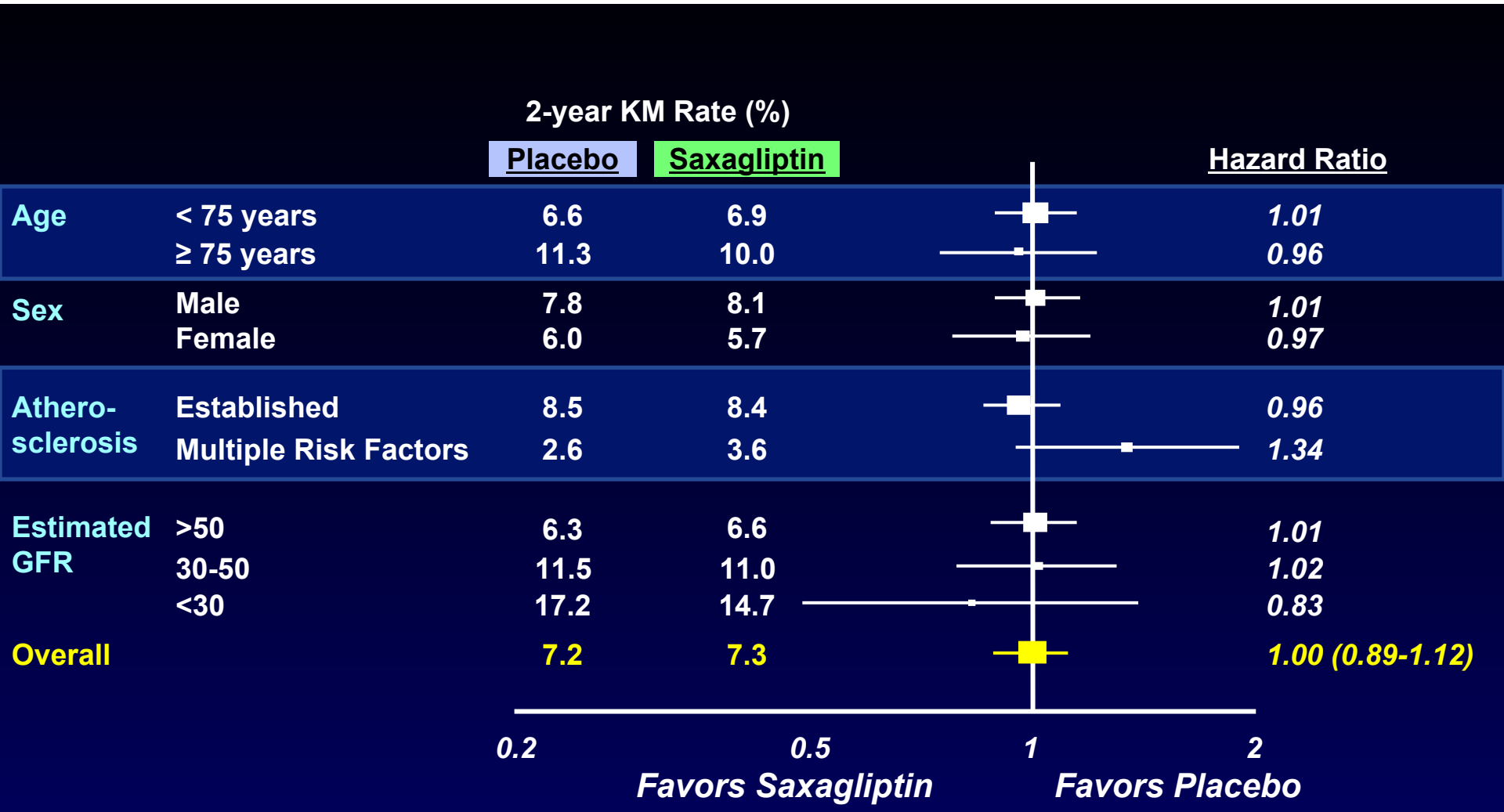
Sub-Group Analysis
Primary Endpoint



p>0.05 for all interactions between treatment and subgroups

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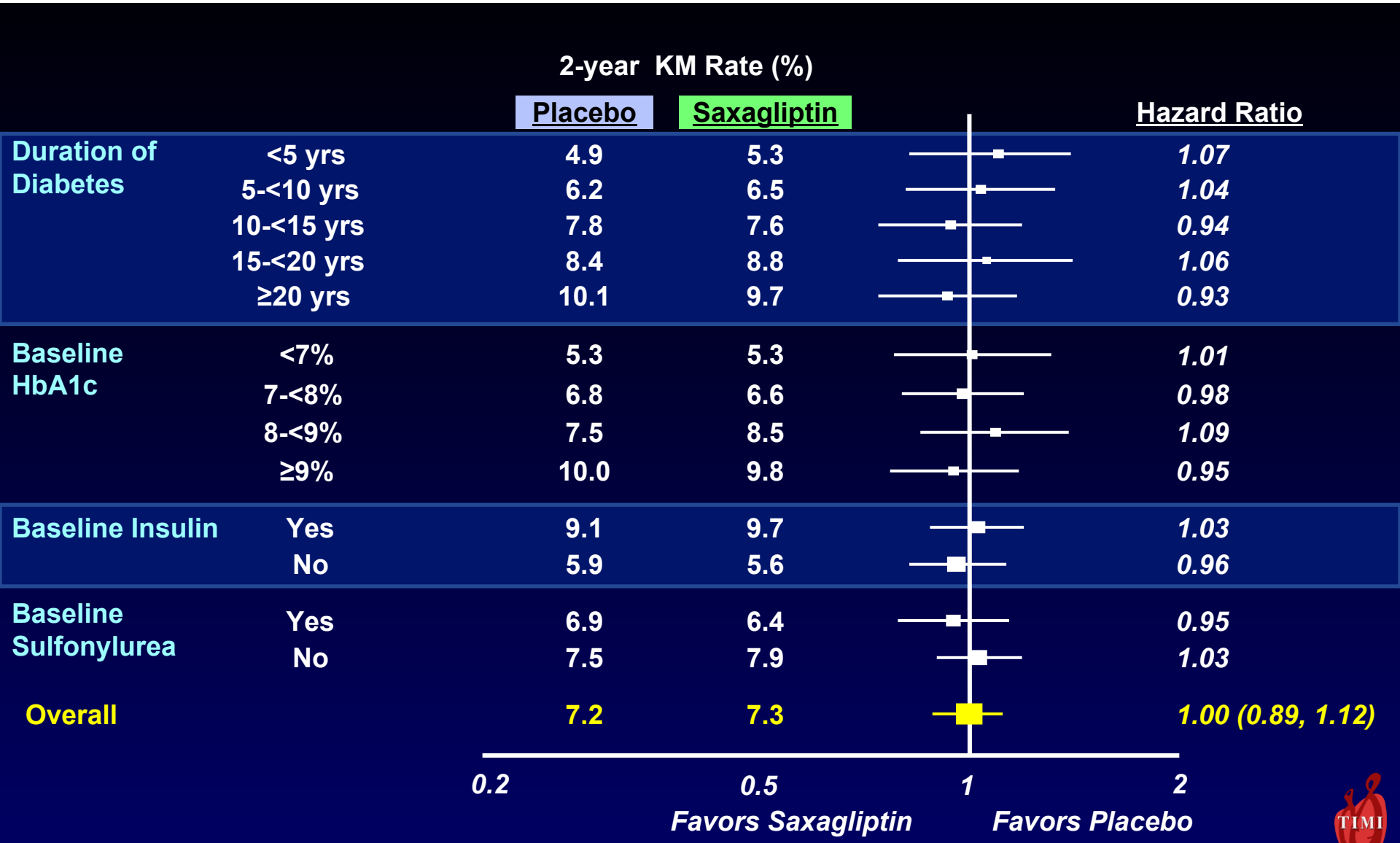
Sub-Group Analysis
Primary Endpoint



p>0.05 for all interactions between treatment and subgroups

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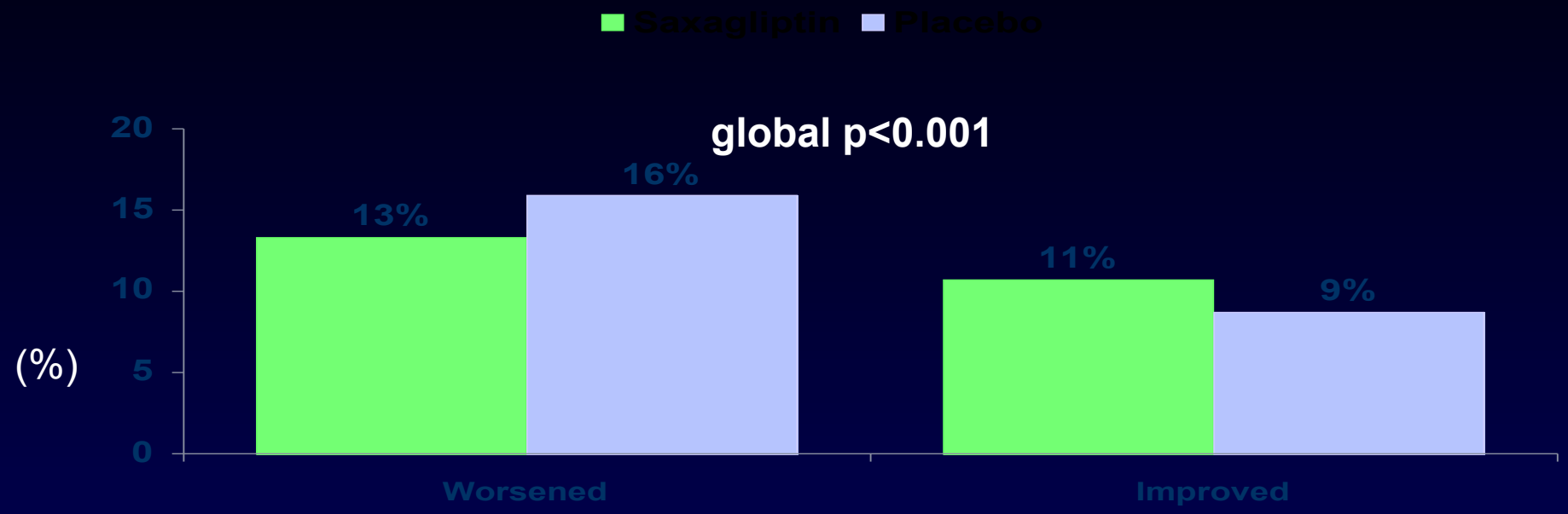
Changes in Microalbuminuria

Shift from baseline category (<3.4, ≥3.4 - ≤33.9, or >33.9 mg/mmol)



End of Treatment

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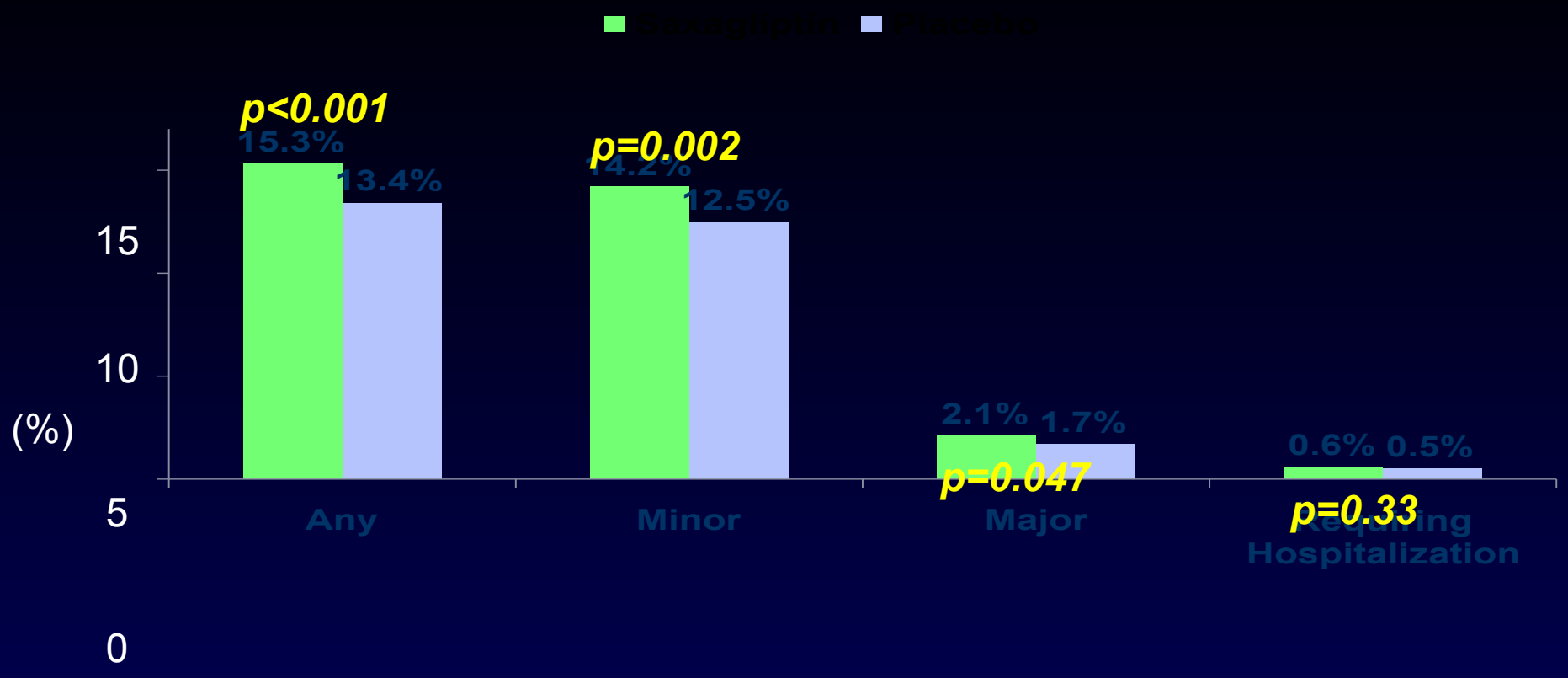
Hypoglycemia



Major – required assistance to actively intervene
Minor – symptoms, but recovered by themselves within 30 minutes, or glucose level < 54 mg/dl, regardless of symptoms.

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Endpoints of Special Interest

	Placebo (N=8,212)	Saxagliptin (N=8,280)	p value
Severe Infection (%)	7.0	7.1	0.78
Opportunistic Infection (%)	0.4	0.3	0.06
Any Liver EOSI/Abnormality (%)	0.8	0.7	0.28
Bone Fracture (%)	2.9	2.9	1.00
Cancer (%)	4.4	4.0	0.15

EOSI, endpoint of special interest

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Pancreatic Events

	Placebo (N=8,212)	Saxagliptin (N=8,280)	p value
Pancreatitis (adjudicated), n (%)			
Any	21 (0.3)	24 (0.3)	0.77
Acute (Definite)	9 (0.1)	17 (0.2)	0.17
Acute (Definite or Possible)	16 (0.2)	22 (0.3)	0.42
Acute (Possible)	7 (0.1)	6 (0.1)	0.79
Chronic	6 (0.1)	2 (0.02)	0.18
Pancreatic Cancer, n (%)	12 (0.1)	5 (0.06)	0.095

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Baseline NT-pro BNP and Hospitalization for Heart Failure

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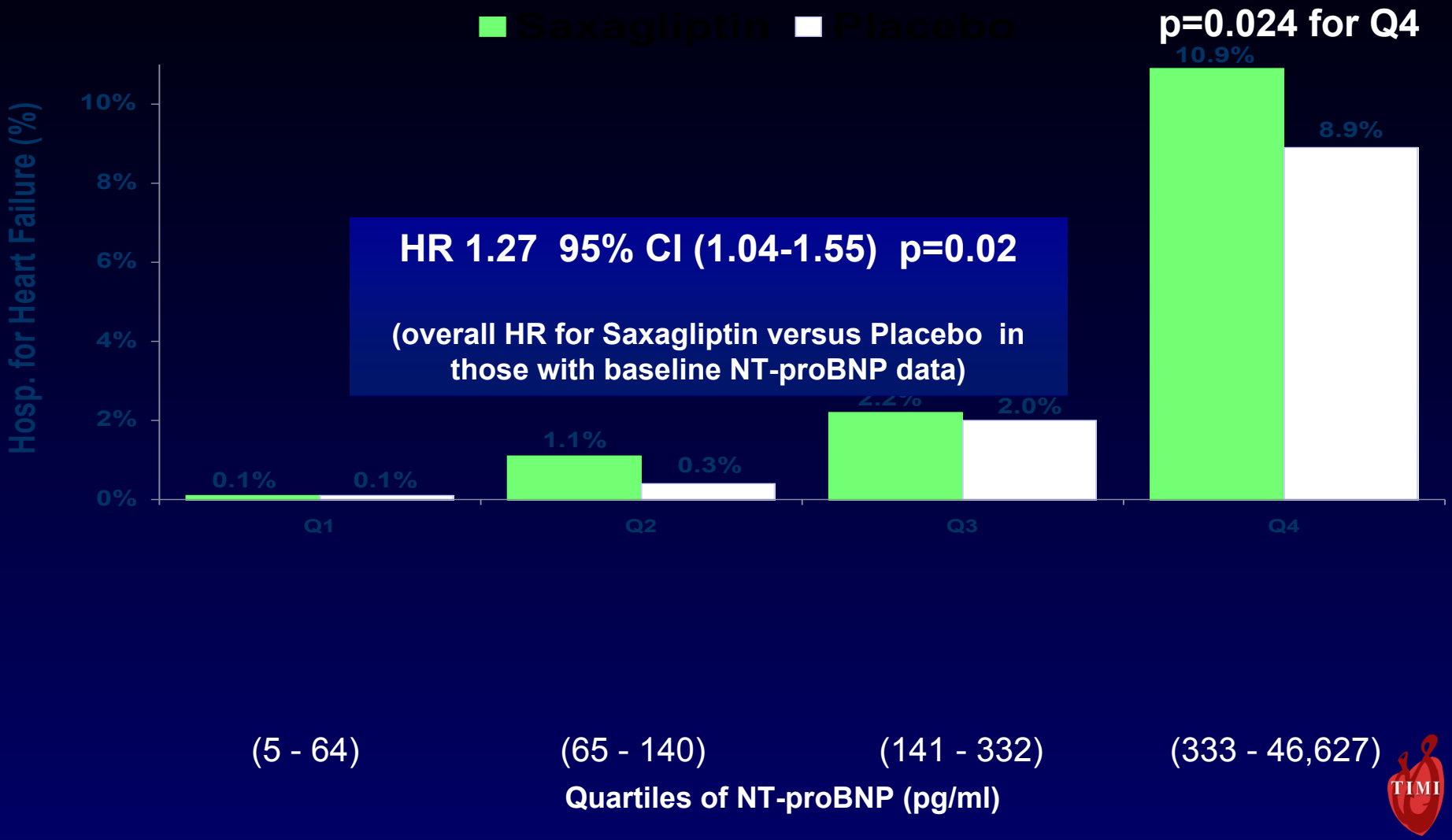
Preliminary data (N=12,397 patients; 387 HF events)



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Caveats

- Modest difference in glycemic control, as add-on therapy had to be allowed and was significantly greater in placebo.
- Median follow-up of 2.1 years, so cannot comment on potential for cardiovascular benefit with longer treatment.
- Not designed to assess impact of therapy on microvascular events.

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Conclusions

- When added to standard of care in patients with T2DM at high CV risk, saxagliptin neither reduced nor increased the risk of the primary composite endpoint of CV death, MI, or ischemic stroke.

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Conclusions

- In addition, saxagliptin:
  - Improved glycemic control
  - Decreased the need for insulin and other diabetes medications
  - Increased hypoglycemic events, but not hospitalization for hypoglycemia
  - Prevented progression of microalbuminuria
  - Did not increase risk of pancreatitis or pancreatic cancer

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Conclusions (Heart Failure)

- The higher incidence of hospitalization for heart failure was unexpected, but it was a pre-defined, adjudicated endpoint.
- It merits further evaluation given the history of other diabetic agents and heart failure.
- Additional analyses are ongoing, and preliminary data suggest that the absolute risk is highest in those with elevated baseline clinical risk for heart failure and/or elevated BNP levels.

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Implications

- SAVOR-TIMI 53 highlights the importance of performing large trials with clinical cardiovascular endpoints for diabetes drugs.
- Further research is needed to explore the relationship between HbA1c and cardiovascular outcomes.

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ORIGINAL ARTICLE

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

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Scirica BM, Bhatt DL, Braunwald E, et al…. Raz I. *NEJM* 2013 at www.NEJM.org.

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