

Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes

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Summary

背景：DPP4阻害薬はインクレチン関連薬で、単剤では低血糖を起こしにくく、体重増加も来たしにくいことから、ハードアウトカムにおいても大きな期待を寄せられていた薬剤であった。しかし、SAVOR-TIMI53 (saxagliptin: オングリザ) や EXAMINE試験 (alogliptin: ネシーナ) などで大血管症発症を抑制できないばかりか、心不全を増やす可能性が示唆されてしまった(図1, 2)。
sitagliptin (シヤヌビア グラクティブ) を加えた際に、心血管イベントへ及ぼす長期的な影響についてのデータはこれまでに報告がない。

方法：RCT, double blind, 非劣性 (RRR 1.3) +ITT解析
P: 50歳以上の2型糖尿病 (A1c 6.5~8.0%, eGFR >= 30 mL/min/1.73 m², BG, TZD, SUの内1-2剤またはインスリン±BGで安定している) + 心血管疾患 (冠動脈疾患, 虚血性脳血管疾患, 動脈硬化性末梢血管疾患の既往)

I: sitagliptin 100mg (eGFR 30-50 mL/min)
C: プラセボ

O: Primary Outcome: 複合心血管死, 非致死的心筋梗塞, 非致死の脳卒中, 不安定期心症による入院

結果: Primary Outcomeは非劣性 (hazard ratio 0.98, [95% CI: 0.88-1.09]), 心不全の入院も有意差なし, ITT解析では有意差なし。

結論: 2型糖尿病と循環器疾患をもつ患者において、Sitagliptinを加えることはプラセボと比較して主要心血管イベントや心不全入院, 他の有害事象を増やさなかった。

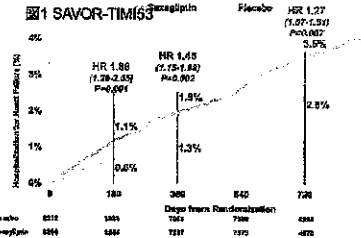


Figure 1. Kaplan-Meier failure estimates of hospitalization for heart failure according to treatment with saxagliptin versus placebo. Kaplan-Meier estimates and corresponding hazard ratios (HR) are presented at 6 months, 12 months, and 2 years. Circulation 2014;130:1578.

Hospitalization for heart failure (standardized (95% CI))	All patients		History of heart failure at baseline		No history of heart failure at baseline	
	Sitagliptin (n=7332)	Placebo (n=7332)	Sitagliptin (n=722)	Placebo (n=722)	Sitagliptin (n=6610)	Placebo (n=6610)
p-value	0.230	0.296	0.026	0.026		
p-value for treatment and history of heart failure		0.058				

*Analysis includes all cardiovascular events, including those that followed heart failure that were not contained in the composite endpoint. Lancet 2015;386:2076.

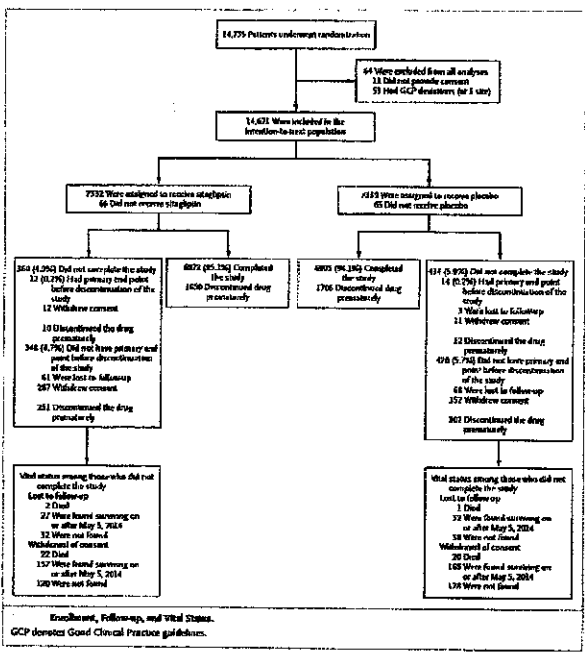
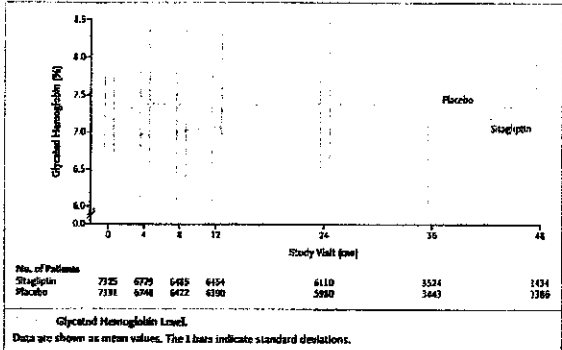


Table S1. Baseline Characteristics of the Trial Participants, According to Assigned Study Medication.*

Characteristic	All N=14,671	Sitagliptin N=7332	Placebo N=7339
Age (years)†	65.5 ± 8.0	65.4 ± 7.9	65.5 ± 8.0
Female sex	4297 (29.3%)	2134 (29.1%)	2163 (29.5%)
Race/Ethnicity			
White	9957 (67.9%)	4955 (67.6%)	5002 (68.2%)
Black	447 (3.0%)	206 (2.8%)	241 (3.3%)
Asian	3265 (22.3%)	1654 (22.6%)	1611 (22.0%)
Other	1002 (6.8%)	517 (7.1%)	485 (6.6%)
Hispanic or Latino	1798 (12.3%)	886 (12.1%)	912 (12.4%)
Duration of diabetes (years)‡			
Mean	11.6 ± 8.1	11.6 ± 8.1	11.6 ± 8.1
Qualifying HbA _{1c} (%)			
Mean	7.2 ± 0.5	7.2 ± 0.5	7.2 ± 0.5
Body mass index (kg/m ²)	30.2 ± 5.6	30.2 ± 5.6	30.2 ± 5.7
Systolic blood pressure (mmHg)	135 ± 17	135 ± 16.9	135 ± 17.1
Diastolic blood pressure (mmHg)	77.2 ± 10.5	77.1 ± 10.3	77.1 ± 10.6
eGFR (mL/min/1.73 m ²)§	74.9 ± 21.1	74.9 ± 21.3	74.9 ± 20.9
eGFR <50 mL/min/1.73 m ² ¶	1369 (9.3%)	686 (9.4%)	683 (9.3%)
Urinary albumin:creatinine ratio (mg/g)			
Median	10.6 (3.5, 35.5)	10.3 (3.5, 34.6)	11.4 (3.6, 36.2)
Total cholesterol (mg/dL)	165.8 ± 45.3	166.1 ± 44.8	165.4 ± 45.0
LDL cholesterol (mg/dL)	91.0 ± 37.8	91.2 ± 37.8	90.7 ± 37.8
HDL cholesterol (mg/dL)	43.5 ± 12.5	43.5 ± 12.0	43.4 ± 13.0
Triglycerides (mg/dL)	165.4 ± 89.9	166.0 ± 89.0	164.8 ± 89.8
Prior cardiovascular disease	10863 (74.0%)	5397 (73.6%)	5466 (74.5%)
Myocardial infarction	6255 (42.6%)	3133 (42.7%)	3122 (42.5%)
≥50% coronary stenosis	7687 (52.4%)	3904 (53.1%)	3883 (52.9%)
Prior PCI	5714 (38.9%)	2814 (38.5%)	2900 (40.1%)
CABG	5664 (38.6%)	2845 (38.8%)	2819 (38.5%)
Prior cerebrovascular disease	3388 (23.1%)	1806 (24.6%)	1782 (24.3%)
Prior peripheral arterial disease	2433 (16.6%)	1217 (16.6%)	1216 (16.6%)
Prior congestive heart failure	2649 (18.0%)	1303 (17.8%)	1340 (18.3%)
NVHA class 3 or higher	373 (2.5%)	171 (2.3%)	202 (2.8%)
Cigarette smoking			
Never smoked	7149 (48.7%)	3583 (48.9%)	3566 (48.6%)
Prior smoker	5844 (39.8%)	2884 (39.3%)	2960 (40.5%)
Current smoker	1678 (11.4%)	865 (11.8%)	813 (11.1%)
Medication use			
Antihyperlipemic			
Statins	11,956 (81.6%)	5936 (81.0%)	6020 (82.2%)
Fibrates	6645 (45.3%)	3346 (45.6%)	3299 (45.0%)
Thiazolidinedione	396 (2.7%)	200 (2.7%)	200 (2.7%)
Insulin	3408 (23.2%)	1724 (23.5%)	1684 (22.9%)
Antihypertensive			
Beta blocker	9322 (63.5%)	4647 (63.4%)	4675 (63.7%)
ACE inhibitor or ARB	11,585 (78.8%)	5743 (78.3%)	5812 (79.2%)
Calcium channel blocker	4961 (33.8%)	2444 (33.3%)	2517 (34.3%)
Diuretic	6020 (41.0%)	2976 (40.8%)	3044 (41.5%)
Antiplatelet			
Aspirin	11,518 (78.5%)	5764 (78.6%)	5754 (78.4%)
Other antiplatelet	3167 (21.7%)	1593 (21.7%)	1594 (21.7%)
Lipid lowering			
Statins	11,719 (79.9%)	5851 (79.8%)	5868 (80.0%)
Ezetimibe	763 (5.2%)	386 (5.3%)	375 (5.1%)



A1c -0.29 [95% CI -0.32 to -0.27]
sitagliptin群では、血糖コントロールのために他剤を追加せずにすみ、
(1592 vs. 2048人, hazard ratio 0.72 [0.68 to 0.77], P<0.001)
インスリン導入も少なかった
(542 vs. 744人, hazard ratio 0.70 [0.63 to 0.79], P<0.001)