

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: James WPT, Caterson ID, Coutinho W, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *N Engl J Med* 2010;363:905-17.

## **SUPPLEMENTAL ON-LINE APPENDIX**

### **Primary Outcome**

The primary outcome (primary endpoint) was the time from randomization to the first occurrence of any of the following outcome events:

- Nonfatal myocardial infarction,
- Nonfatal stroke,
- Resuscitated cardiac arrest, or
- Cardiovascular death (including events such as fatal myocardial infarction and fatal stroke).

### **Secondary Outcomes**

There were 6 secondary outcomes, which were the time from randomization to the onset of each of the following:

- Death due to any cause
- First myocardial infarction
- First stroke
- Cardiovascular death (including events such as fatal myocardial infarction and fatal stroke)
- First occurrence of a composite outcome that included nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest, cardiovascular death (including events such as fatal myocardial infarction and fatal stroke), and any of

the following revascularization procedures: PTCA, CABG, coronary artery stent placement, cardiac transplant, peripheral vascular bypass or angioplasty, and carotid endarterectomy)

- First occurrence of either hemodialysis or renal transplantation

For secondary outcomes of first myocardial infarction, first stroke, and cardiovascular death, analyses were conducted for (1) events restricted to the primary outcome and (2) events not restricted to the primary outcome.

**Adverse Events leading to discontinuation of study drug or serious adverse events with at least 0.5% incidence or with a statistically significant difference in incidence between groups**

MedDRA Preferred Term#	Number (%) of Subjects	
	Placebo N = 4881	Sibutramine N = 4904
<b>Any adverse event leading to discontinuation of study drug</b>	<b>607 (12.4)</b>	<b>667 (13.6)</b>
Myocardial infarction	33 (0.7)	34 (0.7)
Atrial fibrillation	13 (0.3)	26 (0.5)
Constipation	10 (0.2)	22 (0.4)*
Acute myocardial infarction	32 (0.7)	20 (0.4)
Sudden death	26 (0.5)	18 (0.4)
Tachycardia	1 (<0.1)	8 (0.2)*
Abdominal pain upper	0	7 (0.1)*
Cardiac failure acute	6 (0.1)*	0
Left ventricular failure	5 (0.1)*	0
<b>Any serious adverse event</b>	<b>1977 (40.5)</b>	<b>2063 (42.1)</b>
Coronary artery disease	118 (2.4)	135 (2.8)
Angina unstable	104 (2.1)	122 (2.5)
Atrial fibrillation	135 (2.8)	115 (2.3)
Angina pectoris	133 (2.7)	111 (2.3)
Osteoarthritis	88 (1.8)	107 (2.2)
Acute myocardial infarction	87 (1.8)	87 (1.8)

Myocardial infarction	80 (1.6)	87 (1.8)
Coronary artery stenosis	74 (1.5)	76 (1.5)
Cardiac failure	80 (1.6)	82 (1.7)
Diabetes mellitus inadequate control	50 (1.0)	67 (1.4)
Myocardial ischaemia	36 (0.7)	57 (1.2)*
Cardiac failure congestive	41 (0.8)	53 (1.1)
Peripheral artery occlusive disease	39 (0.8)	52 (1.1)
Pneumonia	59 (1.2)	51 (1.0)
Cerebrovascular accident	44 (0.9)	46 (0.9)
Ischaemic stroke	22 (0.5)	42 (0.9)*
Benign prostatic hyperplasia	30 (0.6)	39 (0.8)
Transient ischemic attack	36 (0.7)	34 (0.7)
Carotid artery stenosis	32 (0.7)	30 (0.6)
Diabetes mellitus	28 (0.6)	30 (0.6)
Cataract	29 (0.6)	33 (0.7)
Cholelithiasis	25 (0.5)	26 (0.5)
Prostate cancer	20 (0.4)	26 (0.5)
Acute coronary syndrome	26 (0.5)	25 (0.5)
Death	18 (0.4)	25 (0.5)
Ventricular tachycardia	18 (0.4)	25 (0.5)
Cardiac arrest	14 (0.3)	24 (0.5)
Erysipelas	14 (0.3)	23 (0.5)
Atrial flutter	29 (0.6)	21 (0.4)

Sudden death	26 (0.5)	19 (0.4)
Hypertension	26 (0.5)	17 (0.3)
Urinary tract infection	23 (0.5)	16 (0.3)
Varicose vein	2 (< 0.1)	14 (0.3)*
Osteomyelitis	4 (< 0.1)	13 (0.3)*
Duodenal ulcer haemorrhage	2 (< 0.1)	12 (0.2)*
Pancreatitis acute	14 (0.3)*	3 (< 0.1)
Atrioventricular block second degree	16 (0.3)*	3 (< 0.1)
Tendon rupture	10 (0.2)*	2 (< 0.1)
Respiratory failure	9 (0.2)*	1 (< 0.1)
Arrhythmia	6 (0.1)*	0
Hip fracture	6 (0.1)*	0

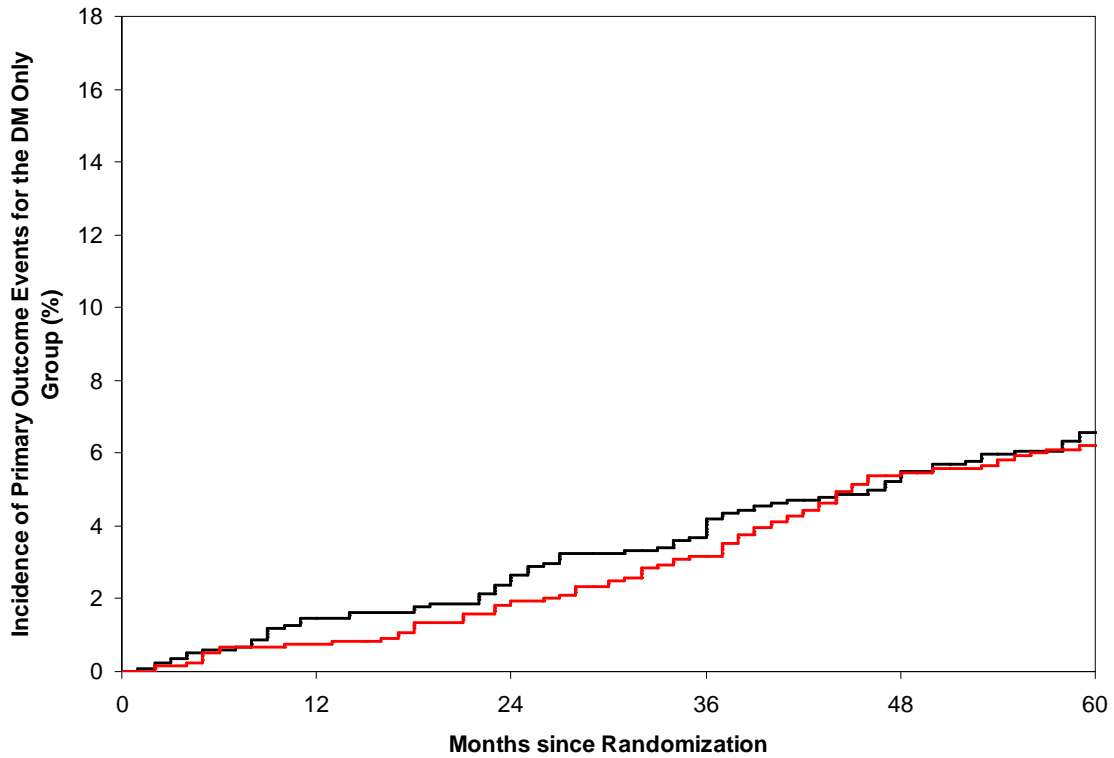
\*  $P \leq 0.05$  for greater incidence compared with other group (Chi-squared test).

# The adverse events listed as those reported by the individual investigators and do not necessarily reflect adjudicated primary outcome events.

A serious adverse event was defined as an adverse event that resulted in any one of the following outcomes: death from any cause, a life-threatening episode, hospitalization or prolongation of pre-existing hospitalization, persistent disability or incapability, congenital anomaly, or the requirement for medical or surgical interventions to prevent the above serious outcomes (important medical event).

**Kaplan-Meier plots of the time to the primary outcome events and all-cause mortality for the three cardiovascular risk groups of DM only, CV only and CV+DM**

**Figure A: Primary outcome events for the DM only group**

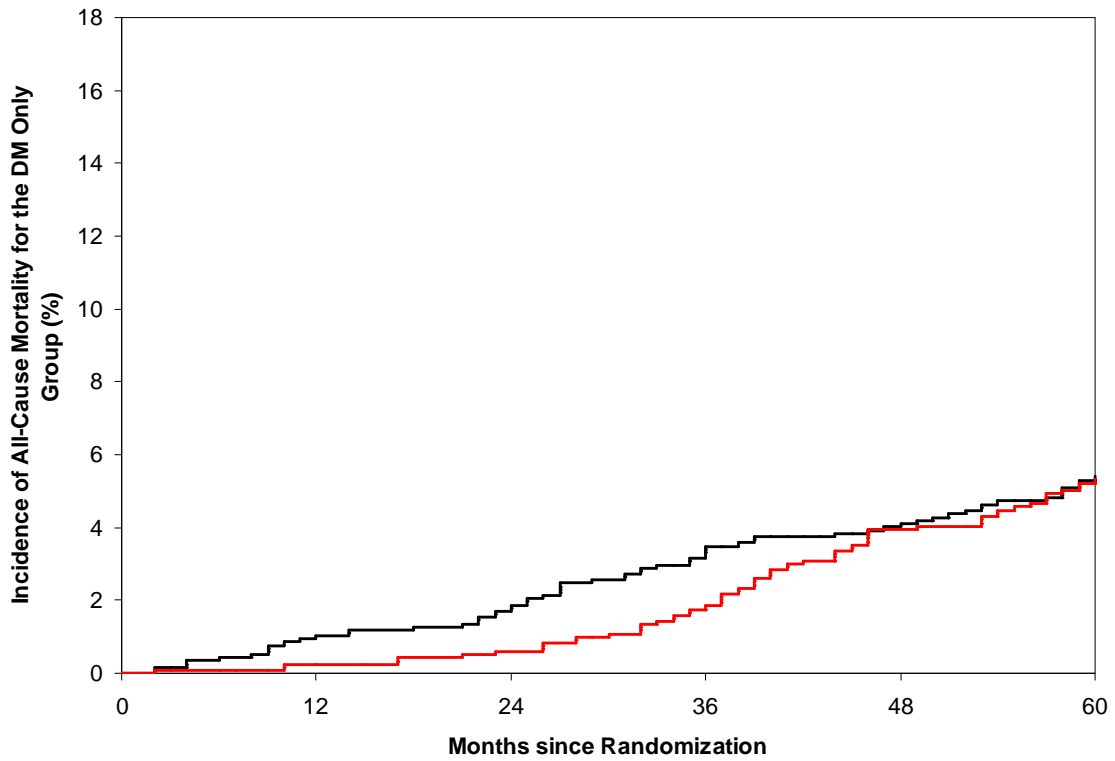


Figures adjusted for age (1.05 [1.02-1.08]), gender (0.60 [0.44-0.83]) and country ( $P < 0.001$ )

**Numbers at risk:**

Time point	R	M12	M24	M36	M48	M60
PLA	1178	1156	1141	1118	1063	855
SIB	1207	1188	1174	1150	1082	866

**Figure B: All-cause mortality for the DM only group**

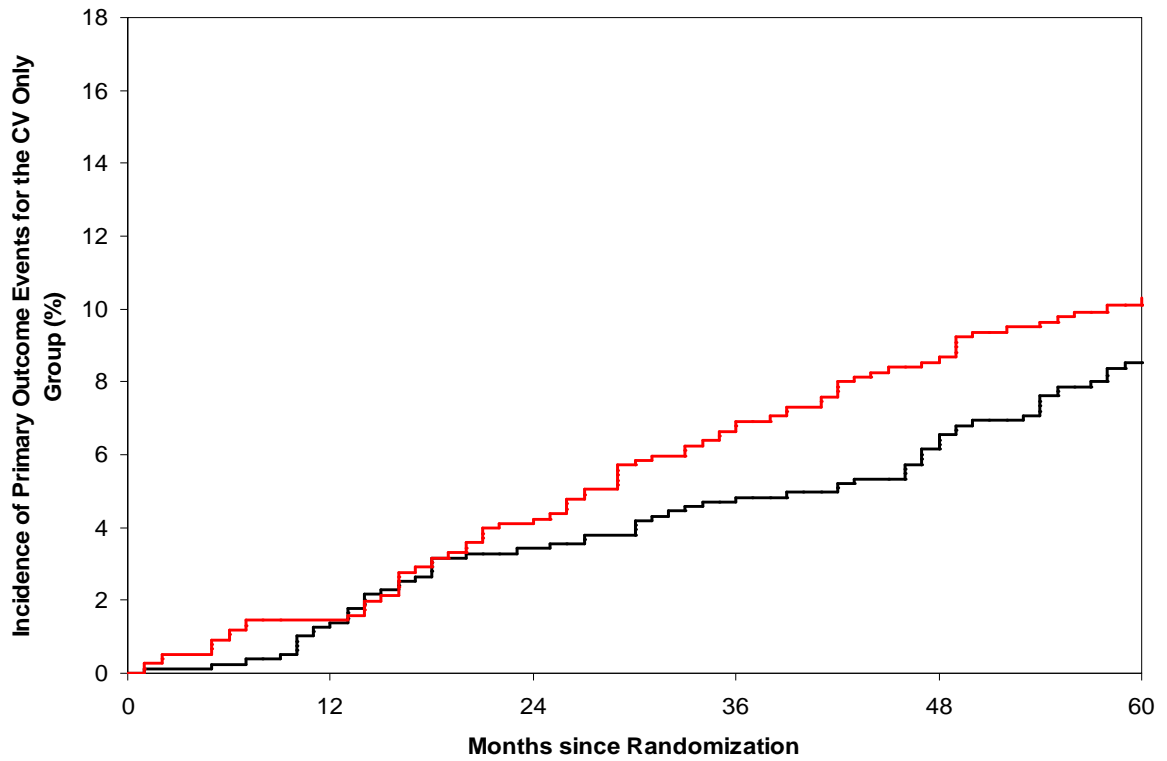


Figures adjusted for age (1.08 [1.05-1.11]), gender (0.68 [0.48-0.96]) and country ( $P < 0.001$ )

**Numbers at risk:**

Time point	R	M12	M24	M36	M48	M60
PLA	1178	1164	1155	1136	1090	882
SIB	1207	1196	1190	1173	1113	894

**Figure C: Primary outcome events for the CV only group**

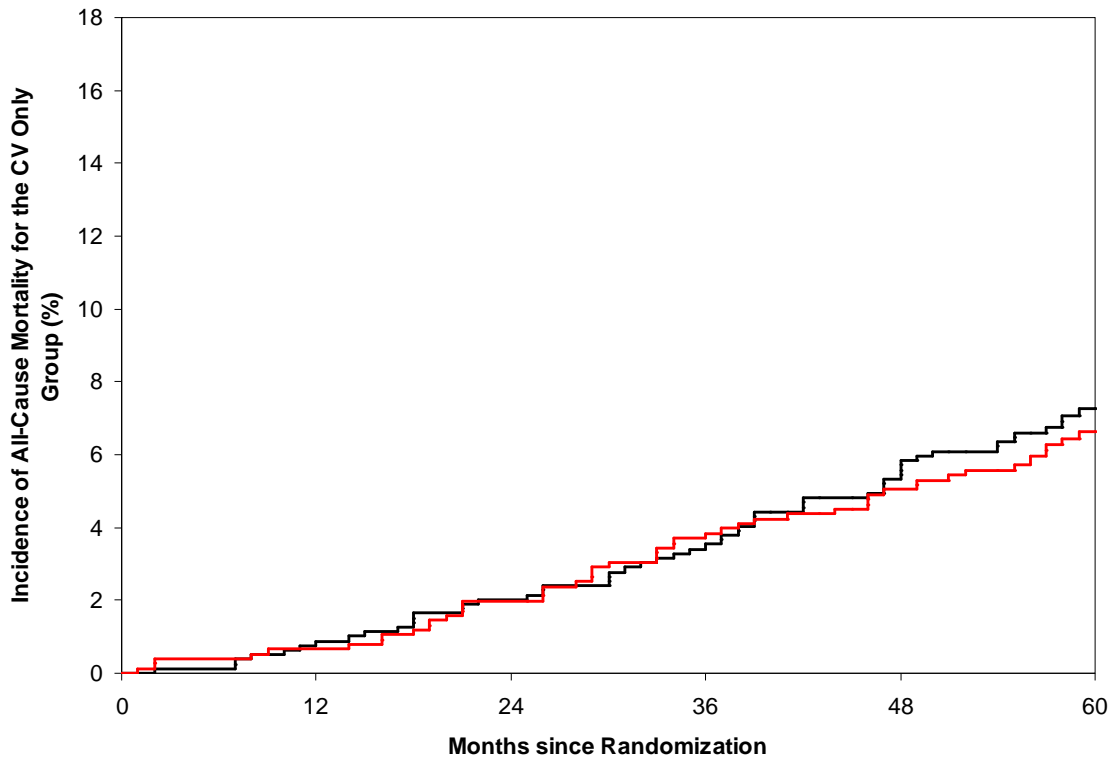


Figures adjusted for age (1.05 [1.03-1.08]), gender (0.55 [0.37-0.81]) and country ( $P=0.989$ )

**Numbers at risk:**

Time point	R	M12	M24	M36	M48	M60
PLA	793	779	758	741	712	473
SIB	759	744	720	695	668	443

**Figure D: All-cause mortality for the CV only group**

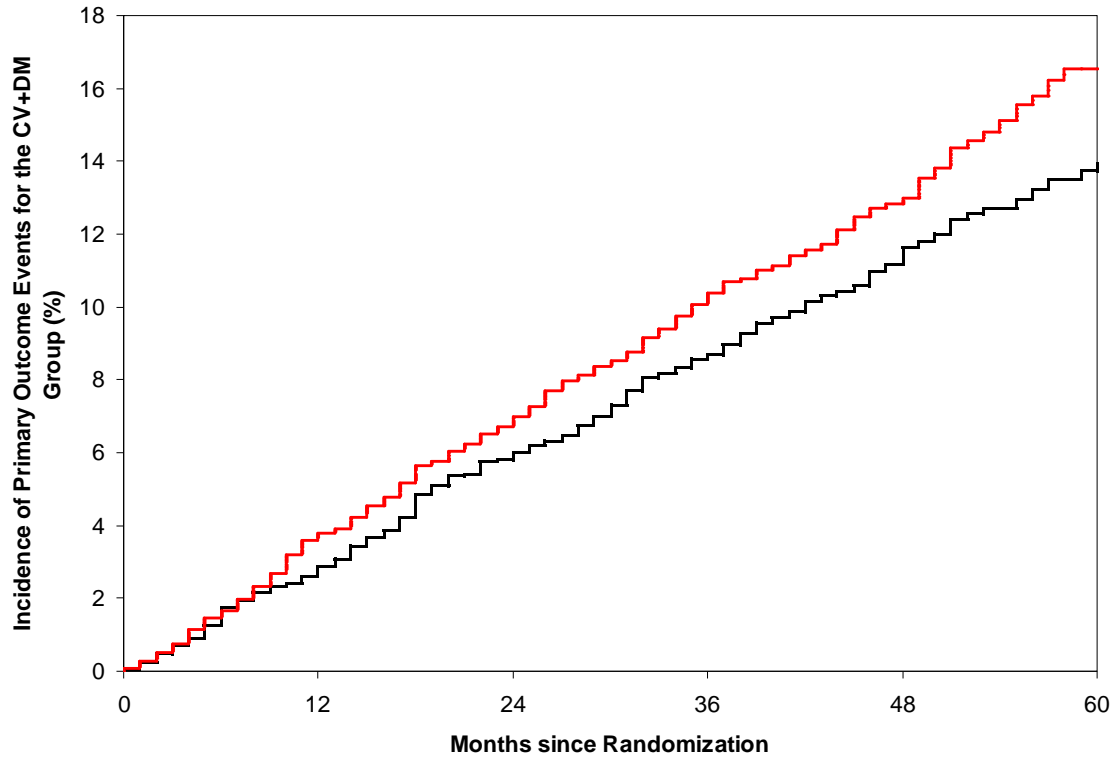


Figures adjusted for age (1.10 [1.07-1.13]), gender (0.68 [0.44-1.04]) and country ( $P=0.655$ )

**Numbers at risk:**

Time point	R	M12	M24	M36	M48	M60
PLA	793	786	775	763	738	501
SIB	759	753	741	726	709	476

**Figure E: Primary outcome events for the CV+DM group**

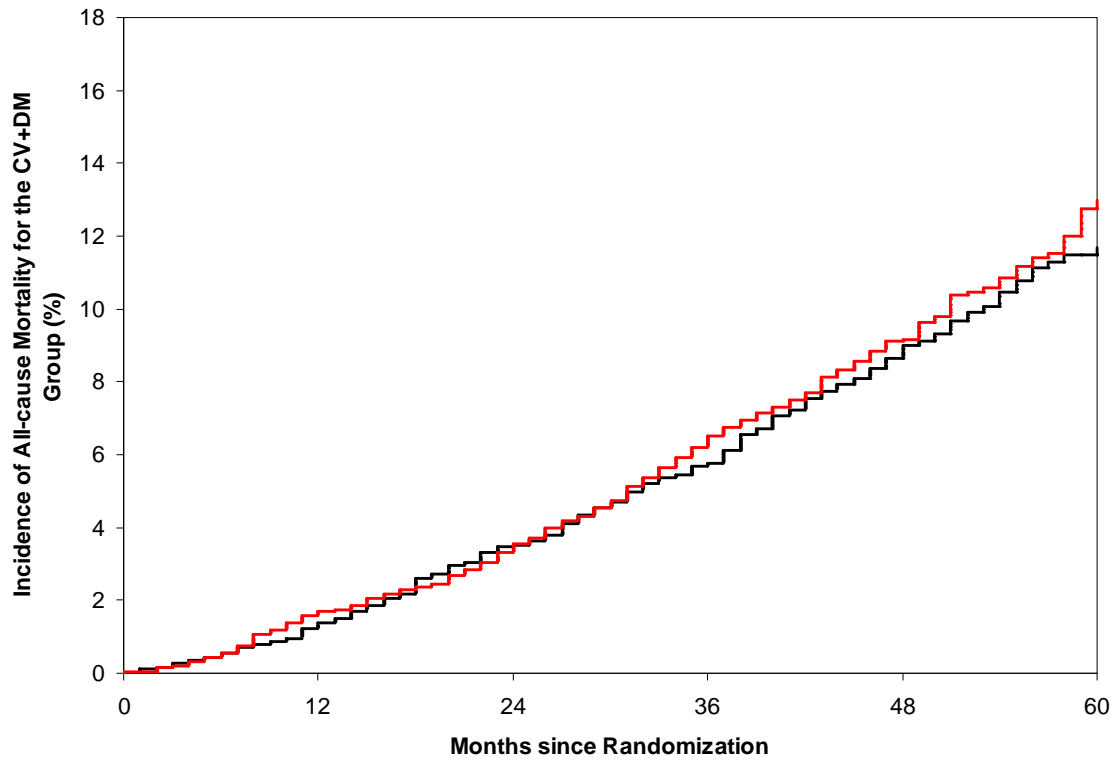


Figures adjusted for age (1.03 [1.02-1.04]), gender (0.71 [0.61-0.83]) and country ( $P=0.002$ )

**Numbers at risk:**

Time point	R	M12	M24	M36	M48	M60
PLA	2901	2815	2699	2598	1667	381
SIB	2906	2783	2674	2550	1622	388

**Figure F: All-cause mortality for the CV+DM group**



Figures adjusted for age (1.07 [1.06-1.08]), gender (0.63 [0.53-0.76]) and country ( $P=0.002$ )

**Numbers at risk:**

Time point	R	M12	M24	M36	M48	M60
<b>PLA</b>	2901	2862	2788	2718	1775	411
<b>SIB</b>	2906	2855	2802	2708	1742	427

**Cardiovascular risk groups:**

DM only: Subjects with a history of type 2 diabetes mellitus with at least one other risk factor (i.e., hypertension controlled on medication, dyslipidemia, current cigarette smoking, diabetic nephropathy with evidence of microalbuminuria), but no history of protocol-specified coronary artery disease, cerebrovascular disease, or peripheral arterial occlusive disease

CV only: Subjects with a history of protocol-specified coronary artery disease, cerebrovascular disease, or peripheral arterial occlusive disease, but no history of type 2 diabetes mellitus with at least one other risk factor

CV+DM: Subjects with a history of protocol-specified coronary artery disease, cerebrovascular disease, or peripheral arterial occlusive disease, and a history of type 2 diabetes mellitus with at least one other risk factor

R: Randomization

M: Month

PLA: placebo - - - - -

SIB: sibutramine - - - - -