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Introduction

	Categorical cutpoints
Increased waist circumference*	Population-specific and country-specific definitions
Increased triglycerides (drug treatment for elevated TG is alternate indicator†)	≥150 mg/dL (1·7mmol/L)
Reduced HDL cholesterol (drug treatment for reduced HDL cholesterol is alternate indicator†)	<40 mg/dL (1·0 mmol/L) in men; <50 mg/dL (1·3 mmol/L) in women
Increased blood pressure (antihypertensive drug treatment in patient with history of hypertension is alternate indicator)	Systolic ≥130 and/or diastolic ≥85 mm Hg
Increased fasting glucose‡ (drug treatment of increased glucose is alternate indicator)	> 100 mg/dL (5·5 mmol/L)

*It is recommended that the IDF cutpoints be used for non-Europeans and either the IDF or AHA/NHLBI cutpoints used for people of European origin until more data are available. †Most commonly used drugs for increased triglycerides and reduced HDL cholesterol are fibrates and nicotinic acid. A patient on one of these drugs can be presumed to have high triglycerides and low HDL. Use of high-dose ω-3 fatty acids presumes high triglycerides. ‡Most patients with type 2 diabetes will have the metabolic syndrome by the proposed criteria.

Table: **Criteria for clinical diagnosis of metabolic syndrome**

The Metabolic Syndrome, Lancet 2010; 375: 181–183

Why metabolic syndrome?

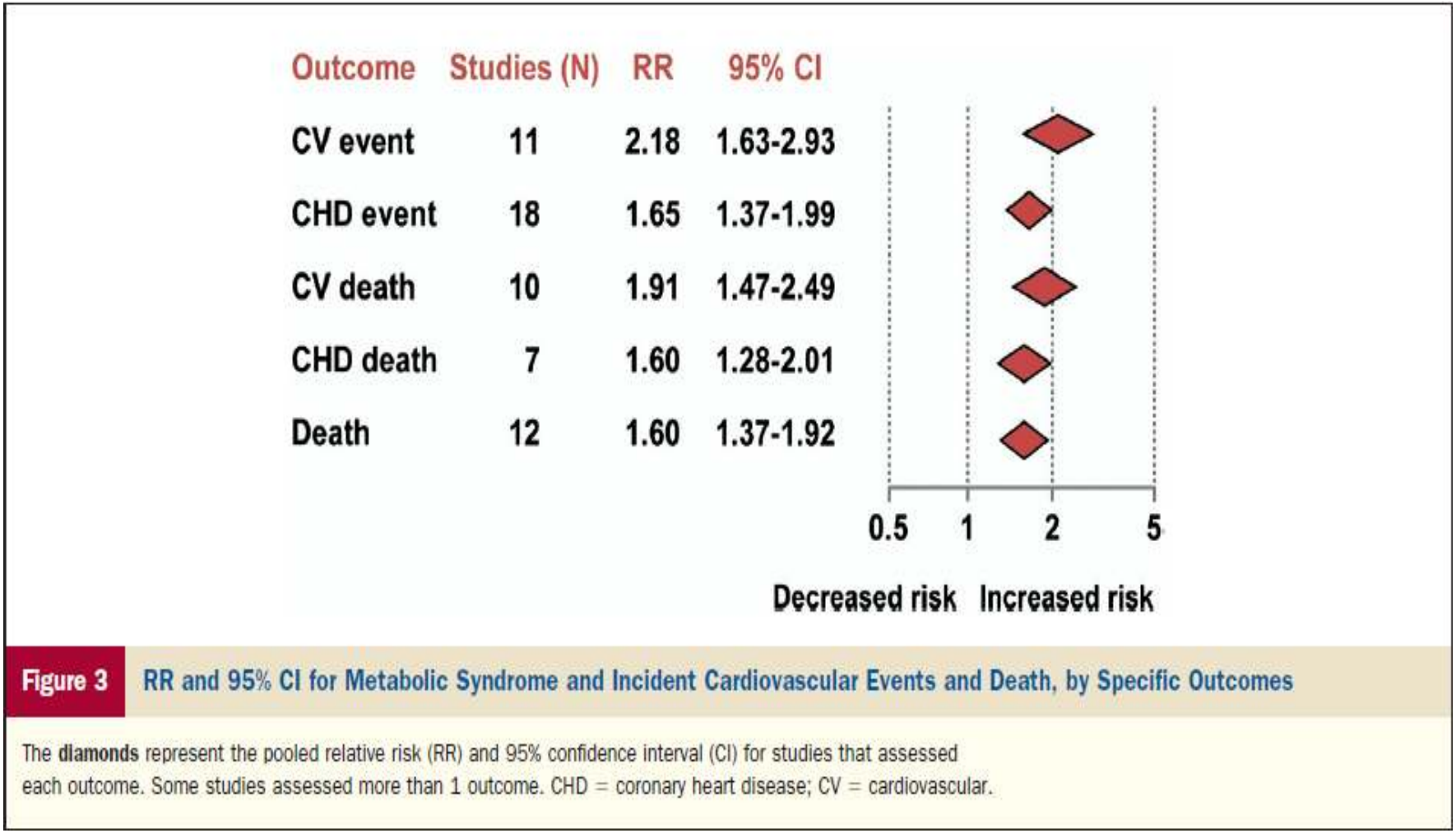
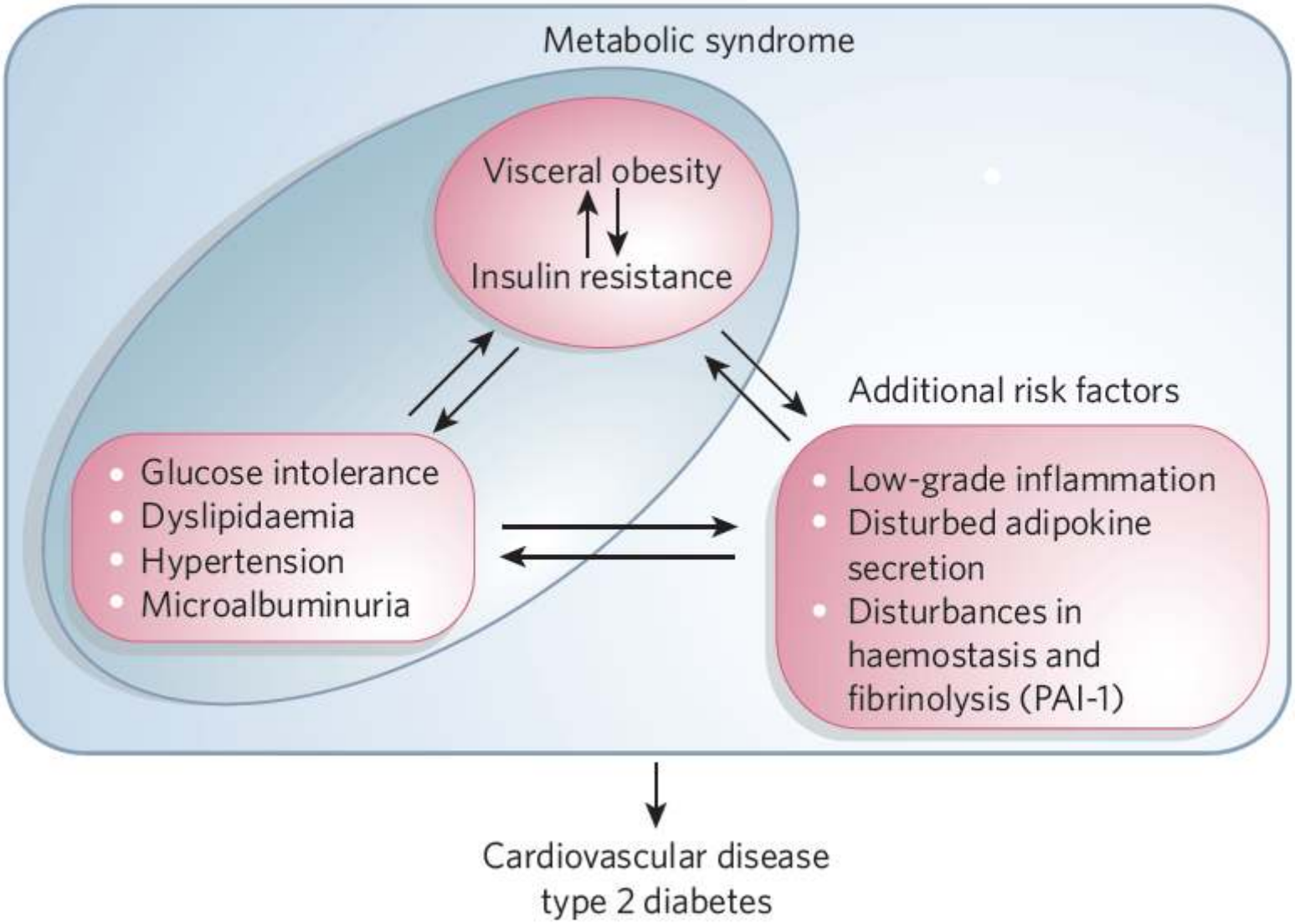


Figure 3 RR and 95% CI for Metabolic Syndrome and Incident Cardiovascular Events and Death, by Specific Outcomes

The **diamonds** represent the pooled relative risk (RR) and 95% confidence interval (CI) for studies that assessed each outcome. Some studies assessed more than 1 outcome. CHD = coronary heart disease; CV = cardiovascular.

J Am Coll Cardiol. 2007;49:403– 414.



Nature 2006; 444: 875–880.

Today's talk

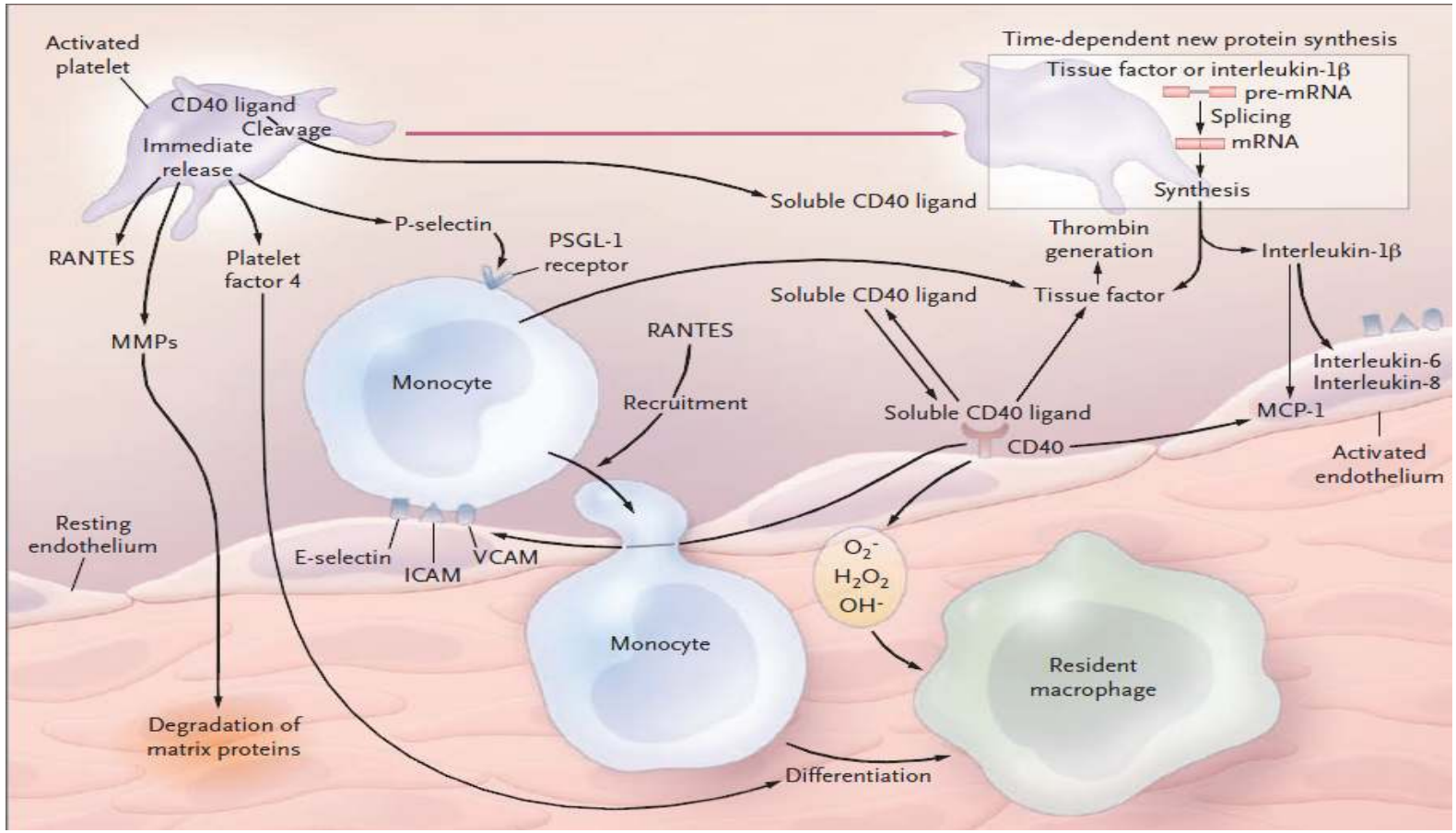
Evidence and markers of platelet hyperactivity

Factors associated platelet hyperactivity in obesity and MS

Influences of anti-obesity therapy on platelet function

Anti-platelet agent use for metabolic syndrome

Evidence and markers of platelet hyperactivity



N Engl J Med 2007; 357: 2482–2494

Mean platelet volume(MPV)

: a parameter mirroring in vivo platelet activation

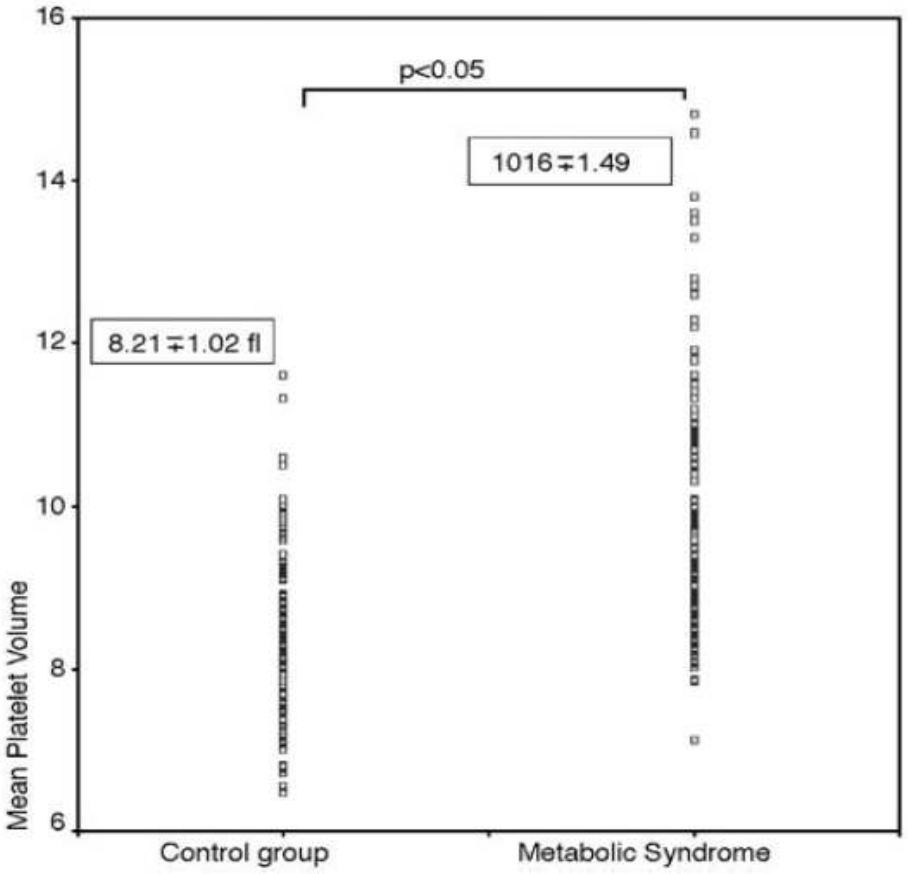


Figure 1 Comparison of patients with MS and control values for mean platelet volume (MPV).

Table 2 Correlation between MPV and antropometric, blood pressure, and laboratory measurements

	Mean platelet volume	
	Correlation coefficient (*r*)	*p*
Waist circumference	0.316	<0.01
Body mass index	0.411	<0.01
Systolic blood pressure	0.243	<0.01
Diastolic blood pressure	0.255	<0.01
Total cholesterol	0.155	0.17
LDL-cholesterol	0.128	0.24
HDL-cholesterol	−0.037	0.53
Triglyceride	0.150	0.12
Fasting plasma glucose	0.307	<0.01
Number of components of metabolic syndrome	0.315	<0.01

Thromb Res 2007; ***120:***245–250

Clin Invest Med 2011;34:330-335

Mean platelet volume(MPV)

: a parameter mirroring in vivo platelet activation

Table I. Clinical and biochemical characteristics by glucose tolerance status.

	Total	Normal glucose tolerance (HbA1c < 5.7% and FPG < 100 mg/dl)	Intermediate hyperglycemia (5.7% ≤ HbA1c < 6.5% or 100 mg/dl ≤ FPG < 126 mg/dl)	Diabetes (HbA1c ≥ 6.5% or FPG ≥ 126 mg/dl)	*P*-value
n	3098	1785	1192	121	
Sex					<0.0001
Men	1728 (55.8%)	940 (52.7%)	700 (58.7%)	88 (72.7%)	
Women	1370 (44.2%)	845 (47.3%)	492 (41.3%)	33 (27.3%)	
Age (years)	46.29 ± 10.61	43.62 ± 9.79[a]	49.68 ± 10.57[b]	52.31 ± 10.69[c]	<0.0001
BMI (kg/m^2)	23.63 ± 3.02	23.09 ± 2.95[a]	24.22 ± 2.91[b]	25.38 ± 3.36[c]	<0.0001
WC (cm)	82.73 ± 8.30	80.94 ± 8.13[a]	84.83 ± 7.77[b]	88.40 ± 8.41[c]	<0.0001
SBP (mmHg)	121.51 ± 13.53	119.63 ± 13.45[a]	123.53 ± 13.05[b]	129.40 ± 13.72[c]	<0.0001
DBP (mmHg)	73.64 ± 10.44	72.32 ± 10.34[a]	75.14 ± 10.32[b]	78.25 ± 9.73[c]	<0.0001
WBC (10^{3}cells/μl)	6.00 ± 1.39	5.87 ± 1.37[a]	6.11 ± 1.39[a]	6.76 ± 1.34[b]	
Hemoglobin (g/dl)	14.48 ± 1.35	14.44 ± 1.35[a]	14.51 ± 1.36[a]	14.96 ± 1.22[b]	
Plt (count/mm^3)	256.46 ± 50.34	251.94 ± 49.04[a]	262.49 ± 51.37[b]	263.88 ± 52.27[b]	<0.0001
MPV (fl)	8.13 ± 0.77	8.15 ± 0.81	8.12 ± 0.73	8.12 ± 0.56	0.633
FPG (mg/dl)	88.67 ± 16.35	83.87 ± 7.31[a]	90.89 ± 10.40[b]	137.78 ± 46.99[c]	<0.0001
HbA1c (%)	5.64 ± 0.59	5.36 ± 0.20[a]	5.85 ± 0.20[b]	7.63 ± 1.59[c]	<0.0001
LDLc (mg/dl)	119.75 ± 30.52	114.18 ± 29.42[a]	126.69 ± 30.44[b]	133.62 ± 28.94[c]	<0.0001
HDLc (mg/dl)	53.26 ± 13.33	54.05 ± 12.21[a]	52.56 ± 14.77[a]	48.67 ± 13.05[b]	<0.0001
Smoking					0.001
Nonsmoker	1898 (61.3%)	1131 (63.4%)	708 (59.4%)	59 (48.8%)	
Current smoker	365 (11.8%)	207 (11.6%)	134 (11.2%)	24 (19.8%)	
Ex-smoker	835 (27.0%)	447 (25.0%)	350 (29.4%)	38 (31.4%)	

Table II. Multiple linear regression analyses of the relationship between MPV (as dependent variable) and FPG (as independent variable) according to glucose tolerance status in men and women.

	NG (n = 1,785)			IH (n = 1,192)			Diabetes (n = 121)		
	Coefficient			Coefficient			Coefficient		
	$\beta \pm$ SE	*P*	R^2	$\beta \pm$ SE	*P*	R^2	$\beta \pm$ SE	*P*	R^2
Men									
Model 1	−0.127 ± 0.034	<0.0001	0.014	−0.067 ± 0.028	0.015	0.015	0.012 ± 0.027	0.671	0.022
Model 2	−0.125 ± 0.035	<0.0001	0.018	−0.068 ± 0.028	0.017	0.030	0.012 ± 0.028	0.664	0.122
Model 3	−0.112 ± 0.033	<0.0001	0.109	−0.072 ± 0.027	0.007	0.130	0.013 ± 0.029	0.665	0.145
Women									
Model 1	−0.141 ± 0.035	<0.0001	0.019	−0.121 ± 0.036	0.001	0.029	0.109 ± 0.032	0.002	0.279
Model 2	−0.129 ± 0.035	<0.0001	0.026	−0.125 ± 0.036	0.001	0.032	0.112 ± 0.034	0.003	0.296
Model 3	−0.102 ± 0.034	0.003	0.132	−0.111 ± 0.035	0.002	0.100	0.097 ± 0.037	0.016	0.442

Notes: Model 1: adjusted by age. Model 2: adjusted by age, body mass index, systolic and diastolic blood pressure, smoking. Model 3: adjusted by age, body mass index, systolic and diastolic blood pressure, smoking, LDL cholesterol, HDL cholesterol, and platelet count. All of the continuous variables were logarithmic transformed for analysis.

NG, HbA1c < 5.7% and FPG < 100 mg/dl; IH, 5.7% ≤ HbA1c < 6.5% or 100 mg/dl ≤ FPG < 126 mg/dl; diabetes, HbA1c ≥ 6.5% or FPG ≥ 126 mg/dl.

FPG, fasting plasma glucose; IH, intermediate hyperglycemia; MPV, mean platelet volume; NG, normal glucose tolerance; SE, standard error.

Mean platelet volume(MPV)

: a parameter mirroring in vivo platelet activation

Table 1—*MPV levels (fL) according to the presence or absence of diabetes, the metabolic syndrome, and each component of the metabolic syndrome*

Characteristic	Present	Absent	*P*
Diabetes	8.20 (7.62–8.82)	8.06 (7.55–8.65)	0.0073
Metabolic syndrome	8.09 (7.58–8.74)	8.07 (7.55–8.69)	0.2372
Abdominal obesity	8.09 (7.58–8.71)	8.05 (7.54–8.63)	0.0262
High blood pressure	8.08 (7.57–8.73)	8.06 (7.55–8.63)	0.0665
Abnormal glucose metabolism	8.10 (7.58–8.75)	8.10 (7.63–8.72)	0.7063
Low HDL cholesterol	8.09 (7.58–8.70)	8.06 (7.55–8.68)	0.0435
Hypertriglyceridemia	8.06 (7.55–8.63)	8.07 (7.56–8.71)	0.4646

Data are presented as median (IQR). *P* values were obtained by linear regression.

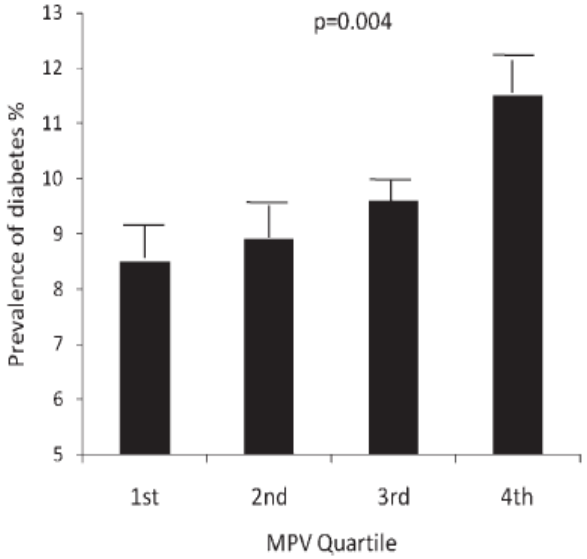


Figure 1—*Prevalence of diabetes is shown stratified by mean MPV quartiles. The SE for the prevalence of diabetes is 0.7 in the 1st MPV quartile, 0.7 for the 2nd MPV quartile, 0.5 for the 3rd MPV quartile, and 0.7 for the 4th MPV quartile.*

Diabetes Care 2012;35:1074–1078

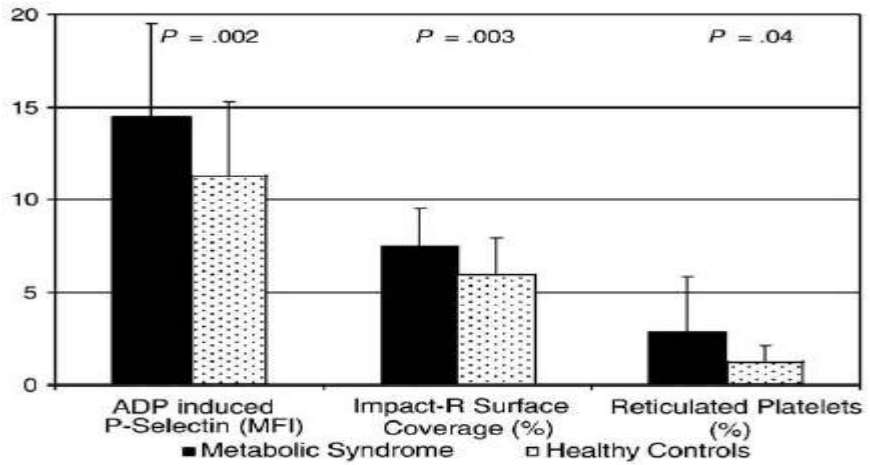
Proportion of reticulated platelets

Table I. Clinical characteristics

	MS subjects (n = 50)	Control subjects (n = 50)	P
Age (y)	44.1 ± 9	39.7 ± 7	.003
Female (%)	40 (80%)	40 (80%)	NS
BMI (kg/m^2)	34.5 ± 8	24.1 ± 3	≤.0001
Waist girth (in)	41.0 ± 6	27.1 ± 5	≤.0001
HDL (mg/dL)	46.5 ± 15	52.9 ± 7	.05
LDL (mg/dL)	130.8 ± 38	111.9 ± 11	.04
Cholesterol (mg/dL)	210.0 ± 45	163.1 ± 20	.002
TG (mg/dL)	161.7 ± 81	95.6 ± 26	.04
Fasting glucose (mg/dL)	114.7 ± 46	89.3 ± 6	.04
hs-CRP (mg/L)	4.4 ± 4	1.4 ± 2	≤.0001
SBP (mm Hg)	138.1 ± 11	113.2 ± 15	≤.0001
DBP (mm Hg)	82. ± 11	70.6 ± 9	≤.0001
Current smokers (%)	3 (6%)	3 (6%)	NS
Alcohol consumption * (%)	3 (6%)	3 (6%)	NS

BMI, Body mass index; *LDL*, low-density lipoprotein; *TG*, triglycerides; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure.
*Alcohol consumption >1 drink per week.

Figure 1



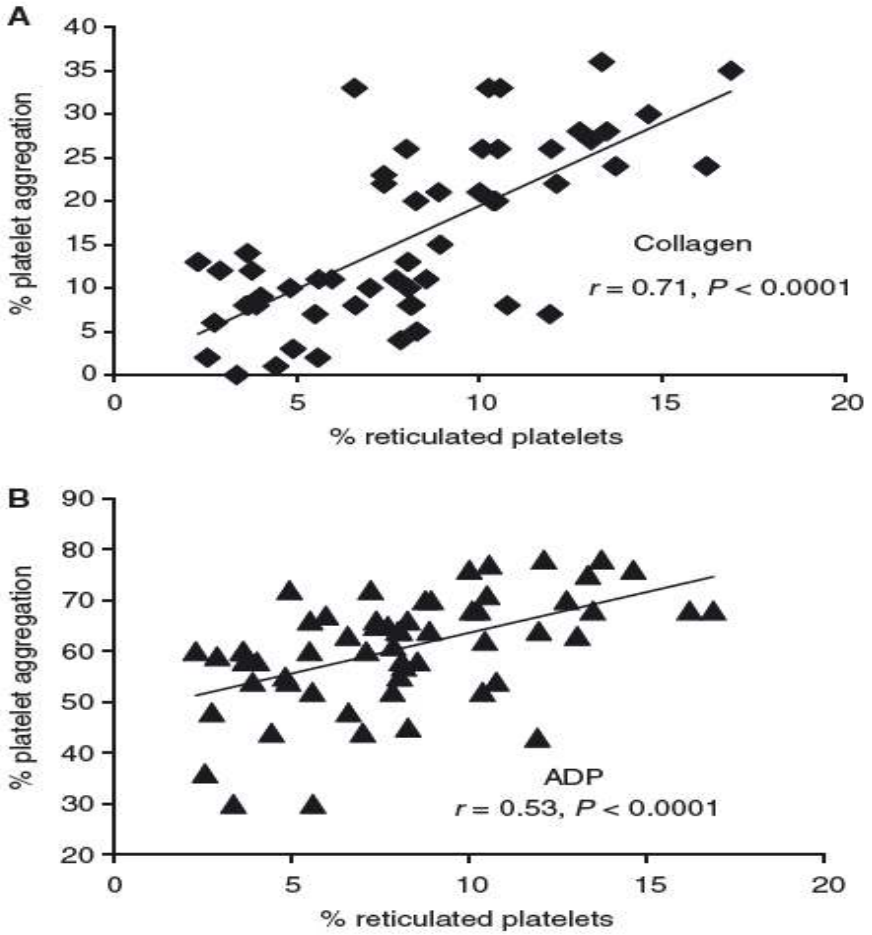


Fig. 2. Correlation of 1 μg mL^{-1} collagen-induced (A) and 5 μM ADP-induced (B) platelet aggregation to % reticulated platelets.

Am Heart J 2008; 156: 1002 e1-7

Platelet derived microparticles(PMP)

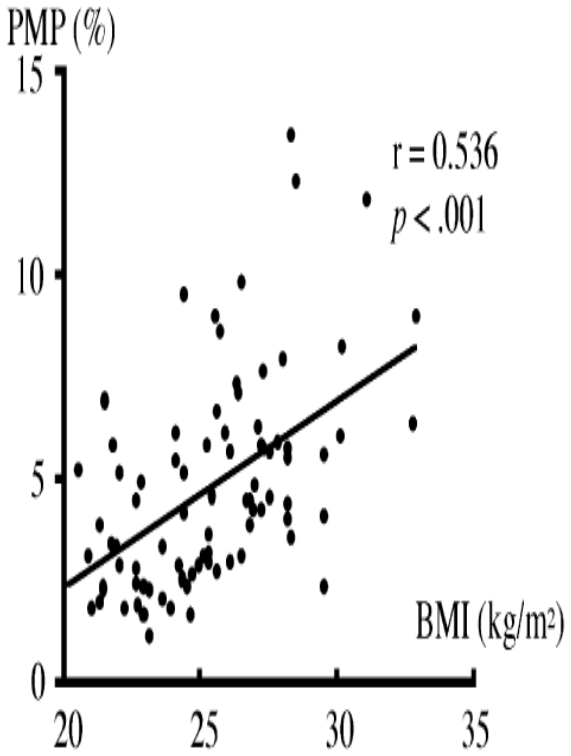
: a membrane vesicle released from activated platelet

Table 1 Baseline clinical characteristics

	Control group	Obese non-diabetic group	
n (F:M)	37 (21:16)	49 (24:25)	*p*
Age, year	49.2 ± 1.8	50.6 ± 1.4	.534
BMI, kg/cm^2	22.8 ± 0.2	27.4 ± 0.3	<.001
Waist circumference, cm	87.9 ± 0.8	96.6 ± 0.8	<.001
Fat tissue mass, kg	15.7 ± 0.6	22.1 ± 0.5	<.001
Visceral fat area, cm^2	78.0 ± 8.7	122.8 (77.3–162.9)	<.001
Subcutaneous fat area, cm^2	137.6 ± 10.8	217.6 ± 10.2	<.001
Systolic blood pressure, mm Hg	122.3 ± 1.8	131.9 ± 2.6	.003
Diastolic blood pressure, mm Hg	78.7 ± 1.4	85.0 ± 1.6	.004
Fibrinogen, mg/dl	242.7 ± 8.0	302.2 ± 8.9	<.001
Total cholesterol, mg/dl	214.4 ± 5.6	215.9 ± 5.4	.851
Triglycerides, mg/dl	78.0 (57.0–136.0)	106.0 (67.0–143.0)	.098
HDL-cholesterol, mg/dl	61.0 (52.0–75.0)	55.3 ± 1.7	.026
LDL-cholesterol, mg/dl	131.5 ± 6.1	136.1 ± 4.8	.551
Fasting glucose, mg/dl	88.9 ± 1.4	96.3 ± 1.5	.001
Hemoglobin A1c, %	4.89 ± 0.1	5.00 (4.80–5.60)	.033
PAI-1 activity, ng/ml	0.42 (0.18–0.57)	0.54 (0.34–1.05)	<.001
t-PA antigen, ng/ml	5.47 ± 0.3	6.73 (5.34–7.78)	.009
PMP, %	2.89 (2.16–4.73)	5.70 (4.07–7.22)	<.001

Data are mean ± SEM or median (p25–p75).

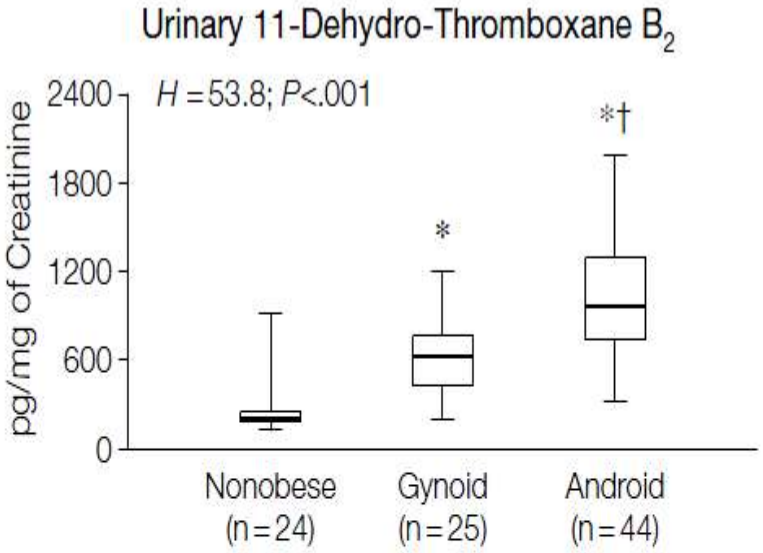
HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAI-1, plasminogen activator inhibitor; t-PA, tissue-type plasminogen activator; PMP, platelet derived microparticle.



Thromb Res 2007; 119: 45–53

11-dehydro-TXB_2 excretion

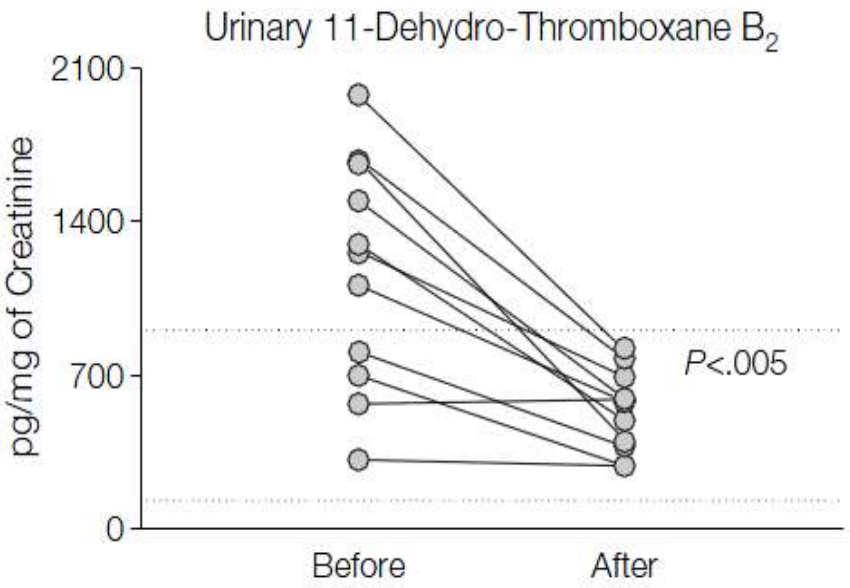
: a major enzymatic metabolite of TX



The *H* statistic was calculated by the Kruskal-Wallis test. The error bars represent minimum and maximum values, the heavy horizontal rules indicate median values, and the ends of the boxes indicate interquartile range.

*$P<.001$, gynoid and android vs nonobese.

†$P<.001$, android vs gynoid.



Circles and lines connecting circles represent metabolite measurements performed in each participant; dotted lines indicate the range of metabolite excretion in nonobese women.

Differences between before and after weight loss program were analyzed by Wilcoxon signed-rank test.

JAMA 2002; 288: 2008–2014

Other markers

: sP-selectin, sCD40L, prothrombin fragment 1+2

Table 1 Characteristics of normal weight and overweight and obese study subjects

	Normal weight ($n = 17$)	Overweight and obese ($n = 33$)	*P*-value
Age (years)	34.5 ± 9.78	36.2 ± 10.3	ns
Body mass index ($kg \cdot m^{-2}$)	22.4 ± 1.41	33.8 ± 4.84	<0.001
Waist circumference (cm)	79.9 ± 5.31	106.3 ± 11.6	<0.001
Fasting plasma glucose (mg/dl)	82.6 ± 5.44	89.3 ± 10.5	<0.05
Fasting plasma insulin (μUI/ml)	12.1 ± 4.18	21.6 ± 10.7	<0.001
$HOMA_{IR}$	2.46 ± 0.90	4.70 ± 2.23	<0.001
Triglycerides (mg/dL)	65.16 ± 25.7	81.6 ± 28.5	ns
Total cholesterol (mg/dL)	172.5 ± 29.5	182.6 ± 30.5	ns
HDL-cholesterol (mg/dL)	51.7 ± 10.0	49.1 ± 11.6	ns
Systolic blood pressure (mmHg)	108.8 ± 6.96	118.2 ± 10.5	<0.01
Diastolic blood pressure (mmHg)	69.1 ± 7.12	77.9 ± 5.47	<0.001
sP-selectin (ng/ml)	63.1 ± 16.4	77.9 ± 21.7	<0.05
PAI-1 antigen (ng/ml)	12.9 ± 10.2	31.9 ± 17.1	<0.001
vonWillebrand factor antigen (%)	96.9 ± 25.9	113.3 ± 24.8	<0.05
Fibrinogen (mg/dL)	280.7 ± 31.2	362.2 ± 68.2	<0.001

Abbreviations: HOMA-IR, homeostasis model assessment; HDL, high-density lipoprotein; PAI-1, plasminogen activator inhibitor-1.

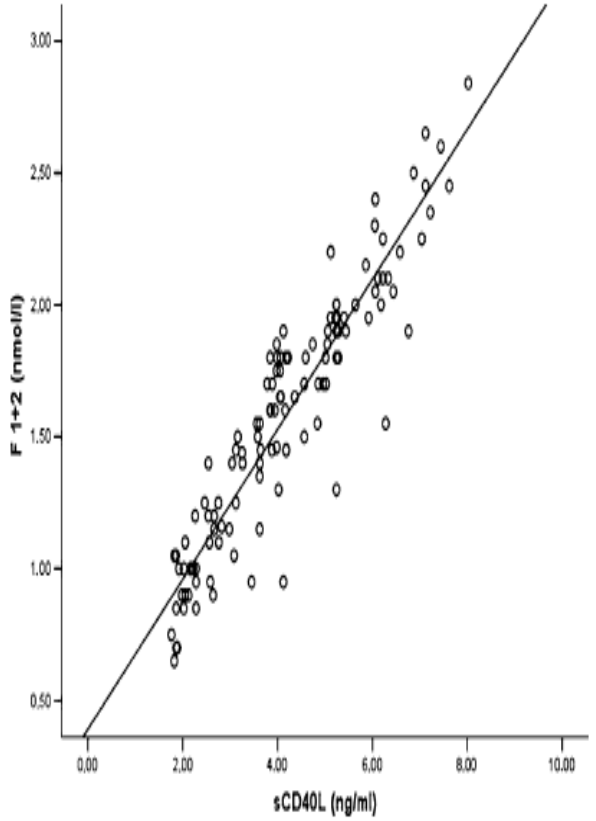


Fig. 1 Correlation between sCD40L and F_{1+2} in metabolic syndrome patients (n=106)

Nutr Metab Cardiovasc Dis 2008; 18: 227–232

Diabetologia 2006; 49: 1169–1174.

Factors associated platelet hyperactivity in obesity and MS

Inflammation

Insulin resistance

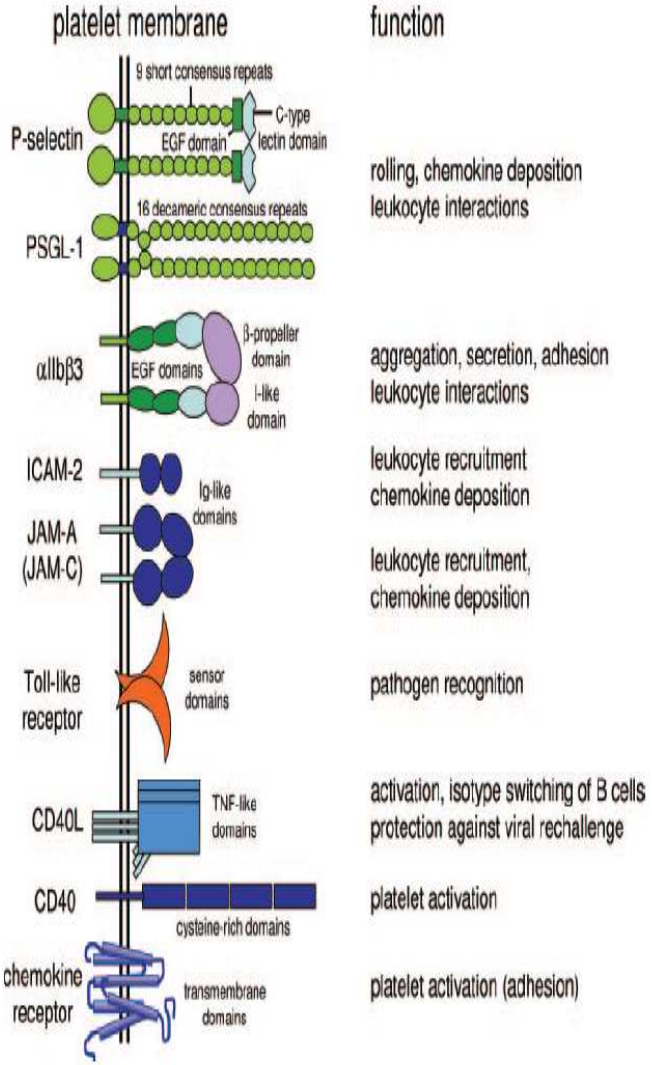
Adipokines

Oxidative stress

Inflammation

- Platelet activation is a common feature in inflammatory diseases and the activation of platelets by inflammatory triggers may be a critical component of atherothrombosis.

- Numerous receptors of proinflammatory molecules are expressed on platelet surface, constitutively or after platelet activation.

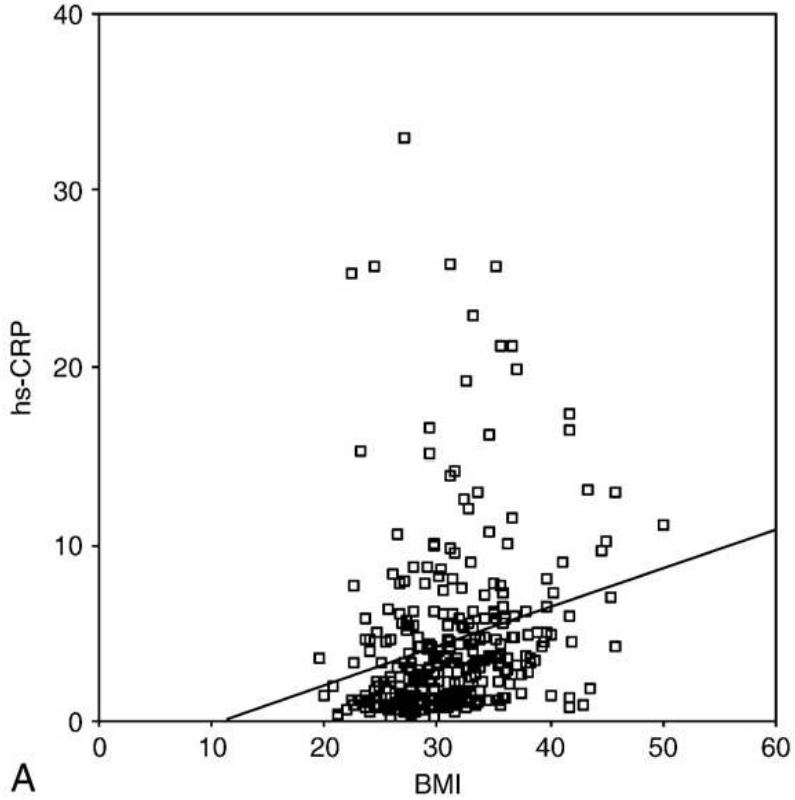


Circ Res 2007; 100: 27–40

Hs-CRP and sCD40L are directly related to BMI in MS patients

Table 2
Pearson correlation test between hs-CRP/sCD40L and all other parameters evaluated in MS patients

Variable	hs-CRP		sCD40L	
	r	*P*	*r*	*P*
Age (y)	0.00	.932	−0.04	.414
BMI (kg/m^2)	0.23	**.000**	0.14	**.017**
Waist (cm)	0.19	**.001**	0.06	.296
WHR	−0.03	.599	−0.05	.415
SBP (mm Hg)	0.03	.658	0.02	.737
DBP (mm Hg)	0.005	.402	−0.05	.345
FG (mg/dL)	0.13	**.026**	0.04	.523
PPG (mg/dL)	0.14	**.018**	0.05	.362
TC (mg/dL)	0.02	.688	0.04	.529
TG (mg/dL)	0.09	.127	−0.30	.641
LDL-C (mg/dL)	0.03	.573	0.04	.462
HDL-C (mg/dL)	−0.14	**.016**	0.00	.963
HbA_{1c} (%)	0.20	**.001**	0.02	.695
WBC (×1000/mm^3)	0.15	**.011**	0.13	**.034**
Platelets	0.09	.099	0.19	**.001**



Metabolism 2010; ***59: 305–313***

Insulin resistance

- The finding that human platelets have insulin receptors that modulate platelet function led to the hypothesis that platelets were sites of insulin resistance.

- Physiologic actions exerted by insulin on platelet function

1) reduction of pro-aggregatory properties of agonist
2) activation of endothelial NO synthase
3) increased NO formation and intra-platelet cAMP concentration
4) sensitization of platelets to the inhibitory action of NO synthase

*Biochem Biophys Res Commun 1988; 157: 1190–*1196
Diabetes 1988; 37:780–786.
Diabetes 1997; 46: 742–749, Diabetes 1995; 44: 1318–1322

Anti-aggregating effect is blunted in obesity

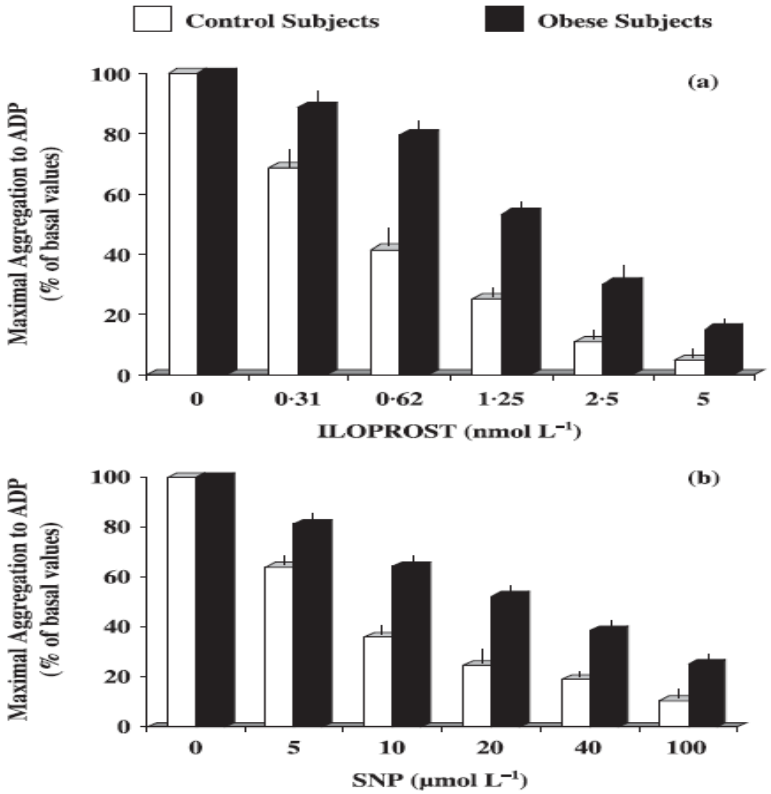


Figure 1 (a) Concentration-dependent effect of a 3-min incubation with the stable prostacyclin (PGI_2) analogue Iloprost (0·31–5 nmol L^{-1}) on Adenosine-5-diphosphate sodium salt (ADP)-induced platelet aggregation in controls (n = 15) and obese subjects (n = 16). Data are expressed as percent of the aggregation in the absence of Iloprost. Significance is described in Results. (b) Concentration-dependent effect of a 3-min incubation with sodium nitroprusside (SNP; 5–100 μmol L^{-1}) on ADP-induced platelet aggregation in controls (n = 15) and obese subjects (n = 16). Data are expressed as percent of the aggregation in the absence of SNP. Significance is described in Results.

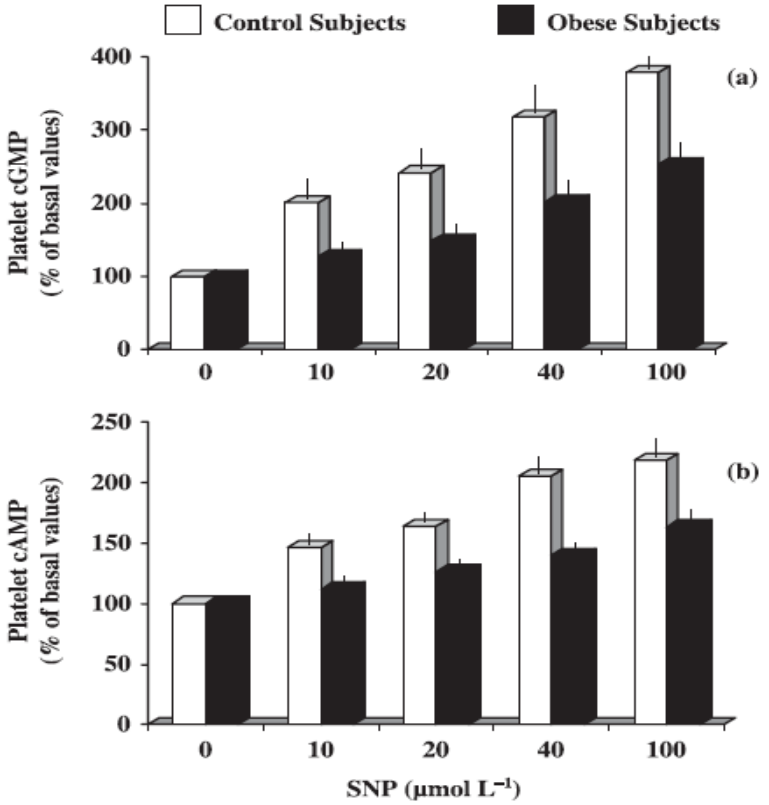


Figure 3 Concentration-dependent effect a 3-min incubation with of sodium nitroprusside (SNP) (10–100 μmol L^{-1}) on intraplatelet guanosine 3′,5′-cyclic monophosphate (cGMP) levels (a) and cyclic nucleotides adenosine 3′,5′-cyclic monophosphate (cAMP) levels (b) in controls (n = 15) and obese subjects (n = 16). Data are expressed as percent of the values in the absence of SNP. Significance is described in Results.

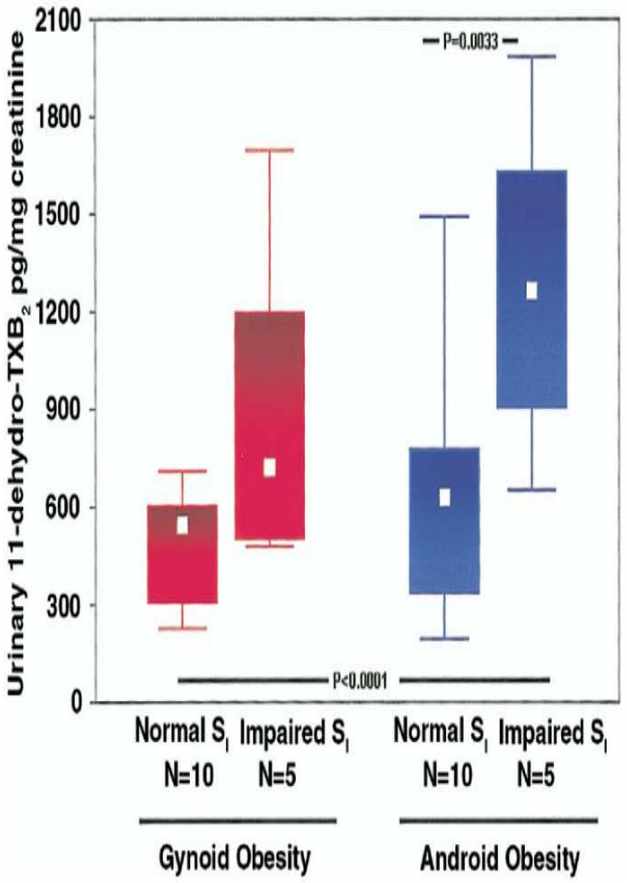
Eur J Clin Invest 2004; 34: 482–489

Insulin resistance as a determinant of platelet activation in Obese patients

Table 2. Spearman's Correlation Coefficients Among the Various Parameters Analyzed in 40 Obese Women

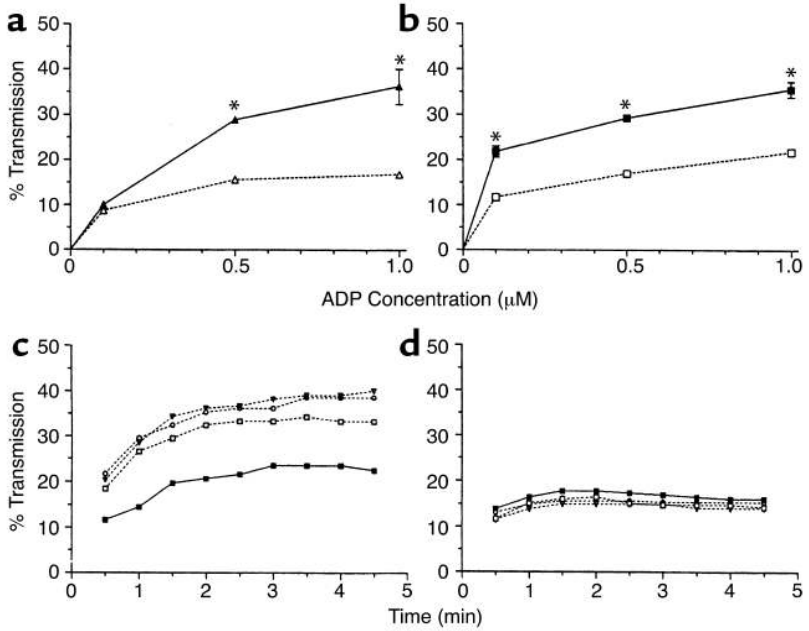
	CD40L	CRP	BMI	WHR	Adiponectin	ΔAIR_G	DI	S_I
U-11-dehydro-TXB_2	0.66 p < 0.0001	0.67 p < 0.0001	0.20 p = 0.206	0.32 p = 0.043	−0.56 p < 0.0002	0.16 p = 0.315	−0.37 p = 0.017	−0.72 p < 0.0001
CD40L	—	0.55 p < 0.0003	0.26 p = 0.109	0.21 p = 0.188	−0.47 p < 0.003	0.41 p = 0.0085	−0.18 p = 0.257	−0.73 p < 0.0001
CRP	—	—	0.11 p = 0.489	0.16 p = 0.326	−0.64 p < 0.0001	0.09 p = 0.555	−0.39 p = 0.012	−0.65 p < 0.0001
BMI	—	—	—	0.55 p < 0.0003	−0.02 p = 0.874	0.19 p = 0.240	0.11 p = 0.487	−0.02 p = 0.904
WHR	—	—	—	—	−0.03 p = 0.837	0.01 p = 0.964	0.01 p = 0.937	−0.04 p = 0.799
Adiponectin	—	—	—	—	—	−0.016 p = 0.316	0.48 p < 0.002	0.83 p < 0.0001
ΔAIR_G	—	—	—	—	—	—	0.64 p < 0.0001	−0.28 p = 0.0833
DI index	—	—	—	—	—	—	—	0.50 p < 0.001

ΔAIR_G = incremental acute insulin response; BMI = body mass index; CD40L = CD40 ligand; CRP = C-reactive protein; DI = disposition index; S_I = insulin-sensitivity index; U-11-dehydro-TXB_2 = urinary 11-dehydro-thromboxane B_2; WHR = waist-to-hip ratio.



Am Coll Cardiol 2006; 48: 2531–2538

Adipokines - Leptin



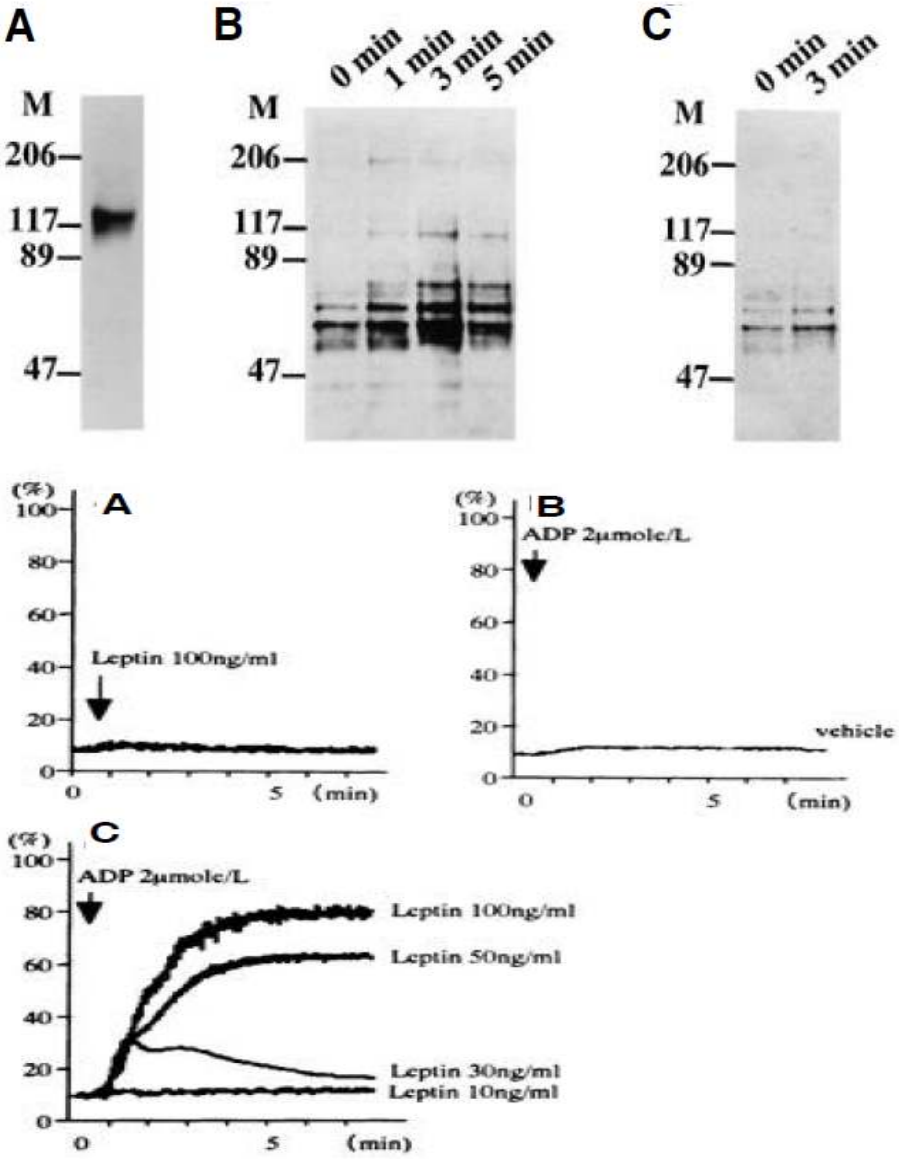


Figure 4
Leptin promotes murine platelet aggregation in response to ADP. In vitro aggregation studies of mouse PRP (3×10^8 platelets/ml) were performed using a microplate reader. Displayed are the mean values ± 1 SD from measurements performed in triplicate. PRP from *ob/ob* (**a**) and WT (**b**) mice was stimulated by the addition of increasing concentrations of ADP in the absence (dashed lines) and presence (continuous lines) of 100 ng/ml leptin, respectively. $*P < 0.001$ for the aggregation in the presence versus absence of leptin. (**c** and **d**) Effects of leptin on the aggregation of platelets from *ob/ob* (**c**) and *db/db* (**d**) mice stimulated with 0.5 μM ADP. The continuous lines represent the aggregation trace of PRP in response to 0.5 μM ADP alone (filled squares). The dashed lines represent platelet aggregation induced by the same concentration of ADP after preincubation with 10 (open squares), 100 (triangles), and 500 (circles) ng/ml leptin, respectively.

J Clin Invest 2001;108: 1533–1540

Diabetes 1999; 48: 426–429

Adipokines - Adiponectin

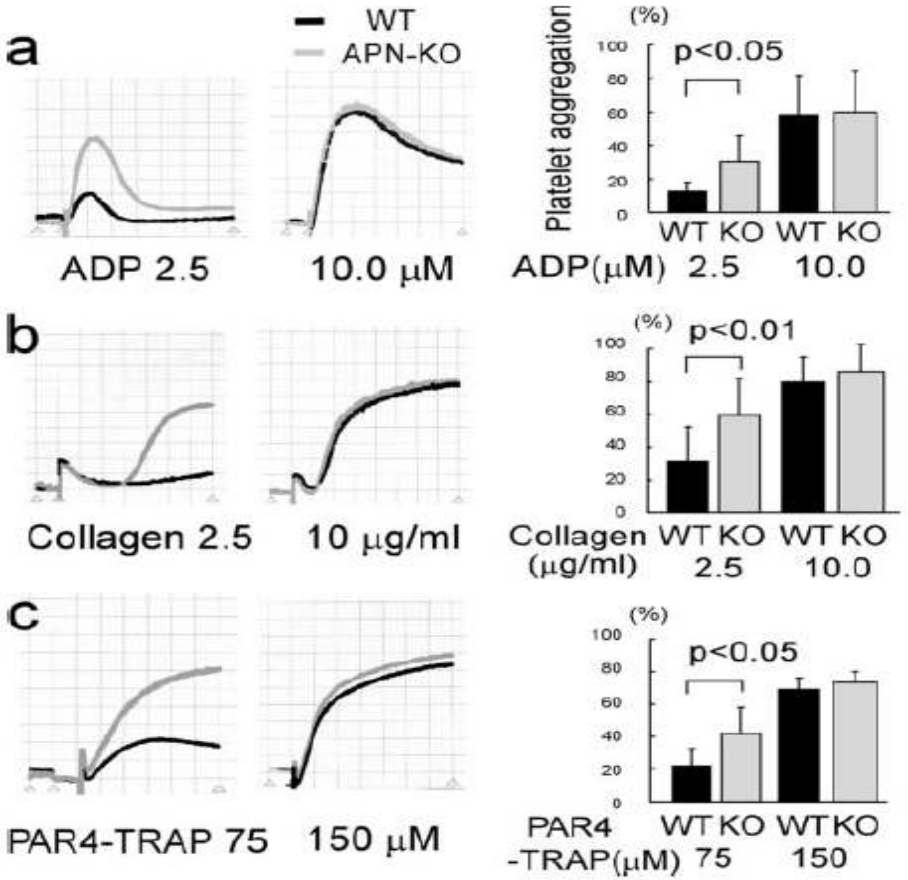


Figure 3. Enhanced platelet aggregation in APN-KO mice. Platelet aggregation in PRP obtained from WT or APN-KO mice. PRP ($300\times10^3/\mu L$) obtained from WT (black line) or APN-KO mice (gray line) was stimulated with ADP (a; n=4), collagen (b; n=4), or PAR4-TRAP (c; n=3). As compared with WT mice, platelet aggregation was enhanced in APN-KO mice at low concentrations of agonists.

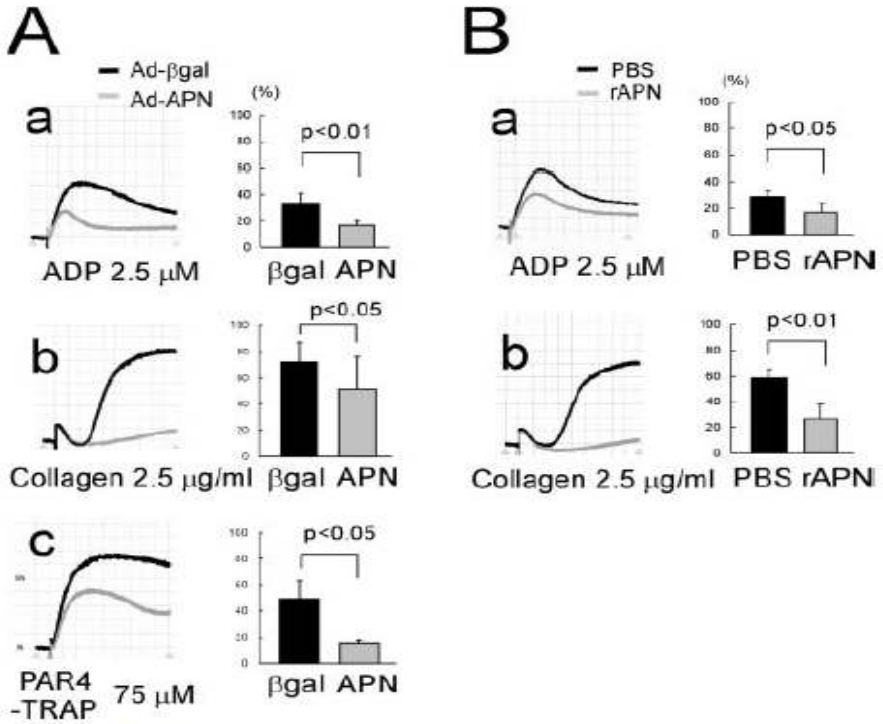


Figure 4. Effects of in vitro supplementation of adiponectin or recombinant adiponectin on the enhanced platelet aggregation in APN-KO mice. (A) One volume of PRP from APN-KO mice was mixed with ≈4 volumes of PPP from APN-KO mice injected with Ad-βgal (black line) or Ad-APN (gray line) to obtain a platelet concentration of $300\times10^3/\mu L$. Platelets were stimulated with indicated agonists (n=4). (B) Mouse recombinant adiponectin (40 μg/mL, gray line) or PBS (black line) was added to PRP from APN-KO mice. Platelets were adjusted to 300×10^3 platelets/μL and stimulated with indicated agonists (n=4).

Arterioscler Thromb Vasc Biol 2006; 26: 224–230.

Adipokines - Adiponectin

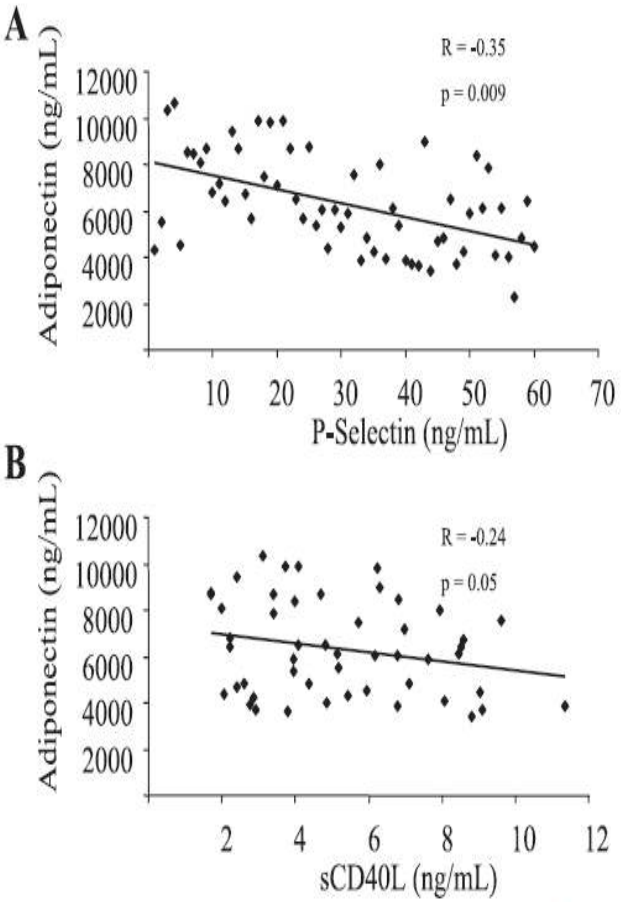
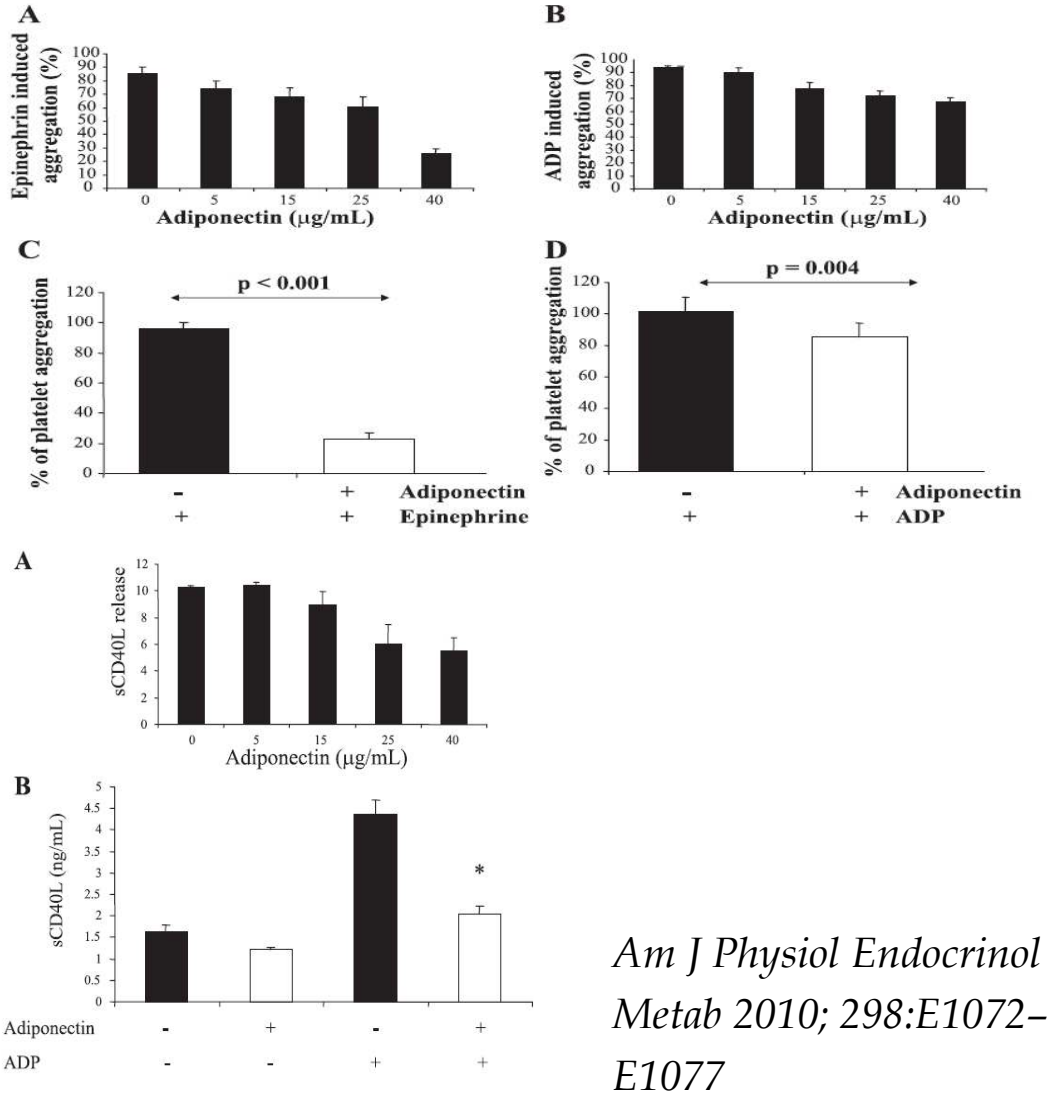


Fig. 2. Correlations of circulating adiponectin with P-selectin and sCD40L. Serum P-selectin, sCD40L, and adiponectin were measured in patients with and without MS (both $n = 30$). Scatter plots show correlations of circulating adiponectin with P-selectin (*A*) and sCD40L (*B*) in patients with and without MS.

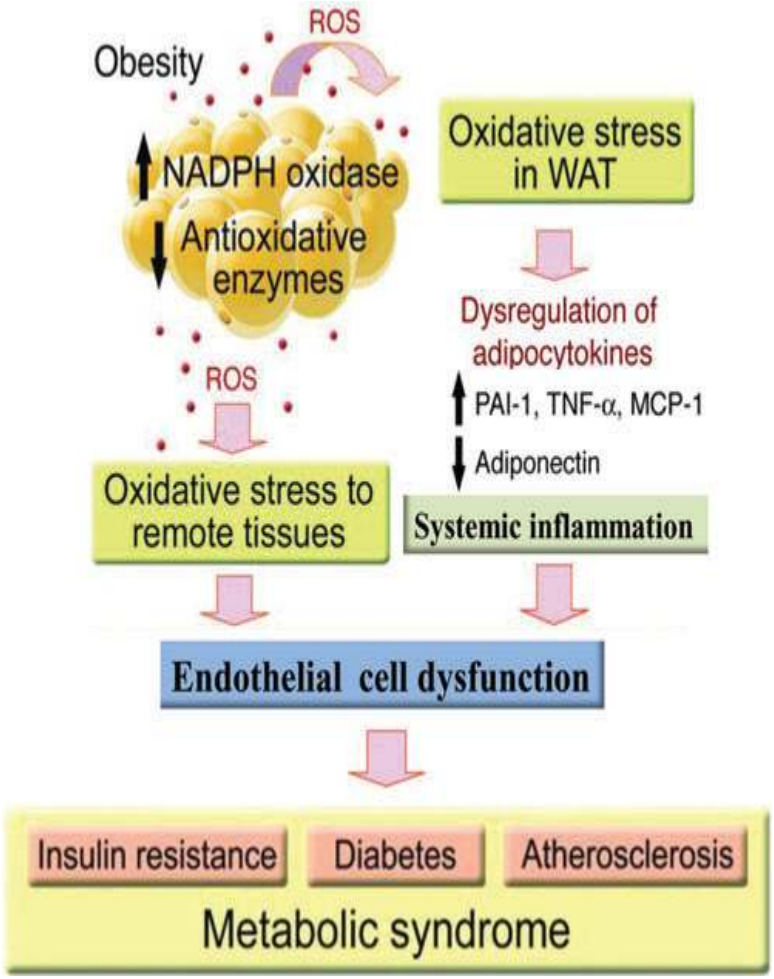


Am J Physiol Endocrinol Metab 2010; 298:E1072–E1077

Oxidative stress

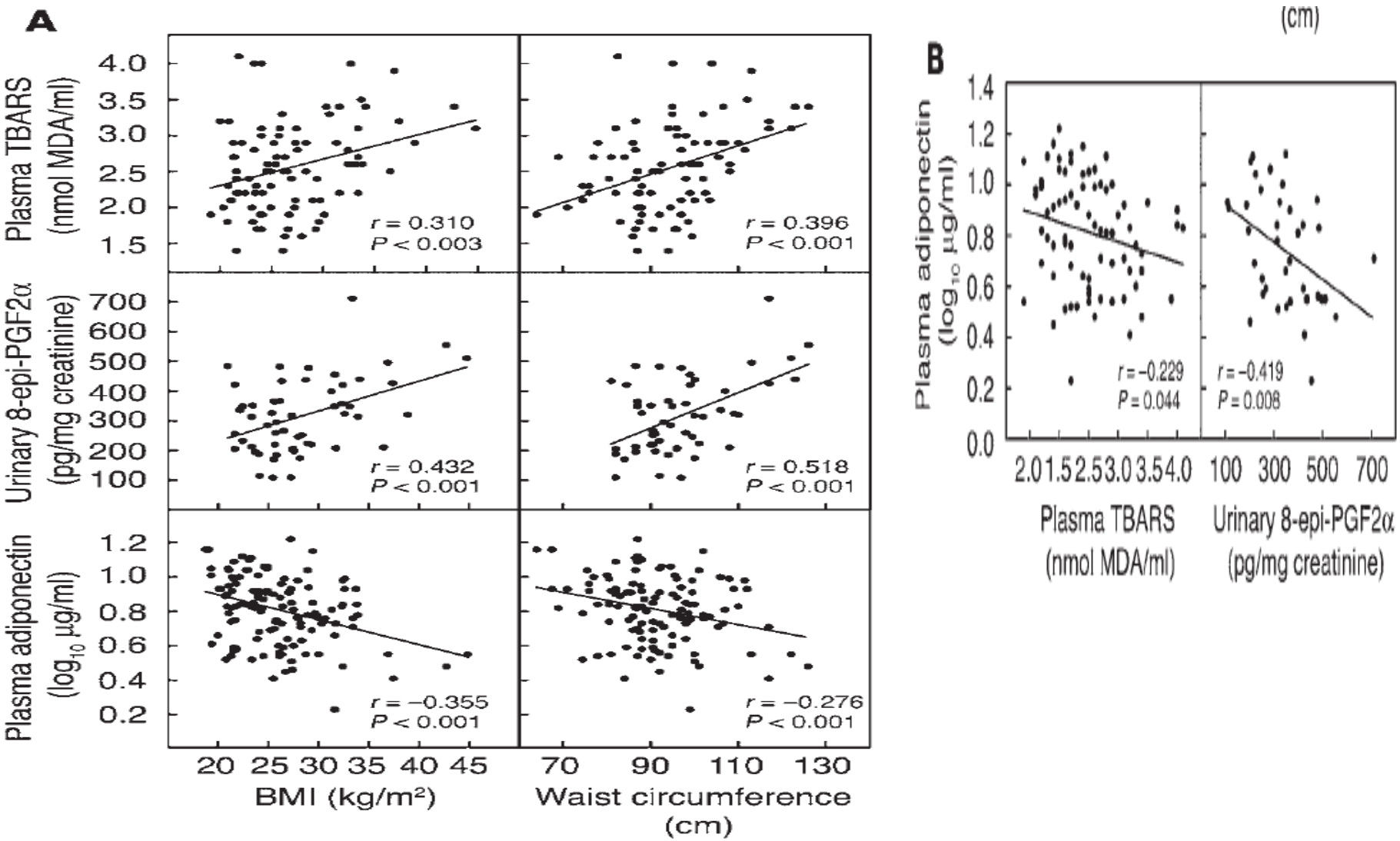
A growing body of evidence suggests that increased oxidative stress in white adipose tissue is central to the pathogenesis of cardiovascular disease in MS.

The molecular mechanism of oxidative stress to adipocytes remains unclear and appears to be multifactorial.



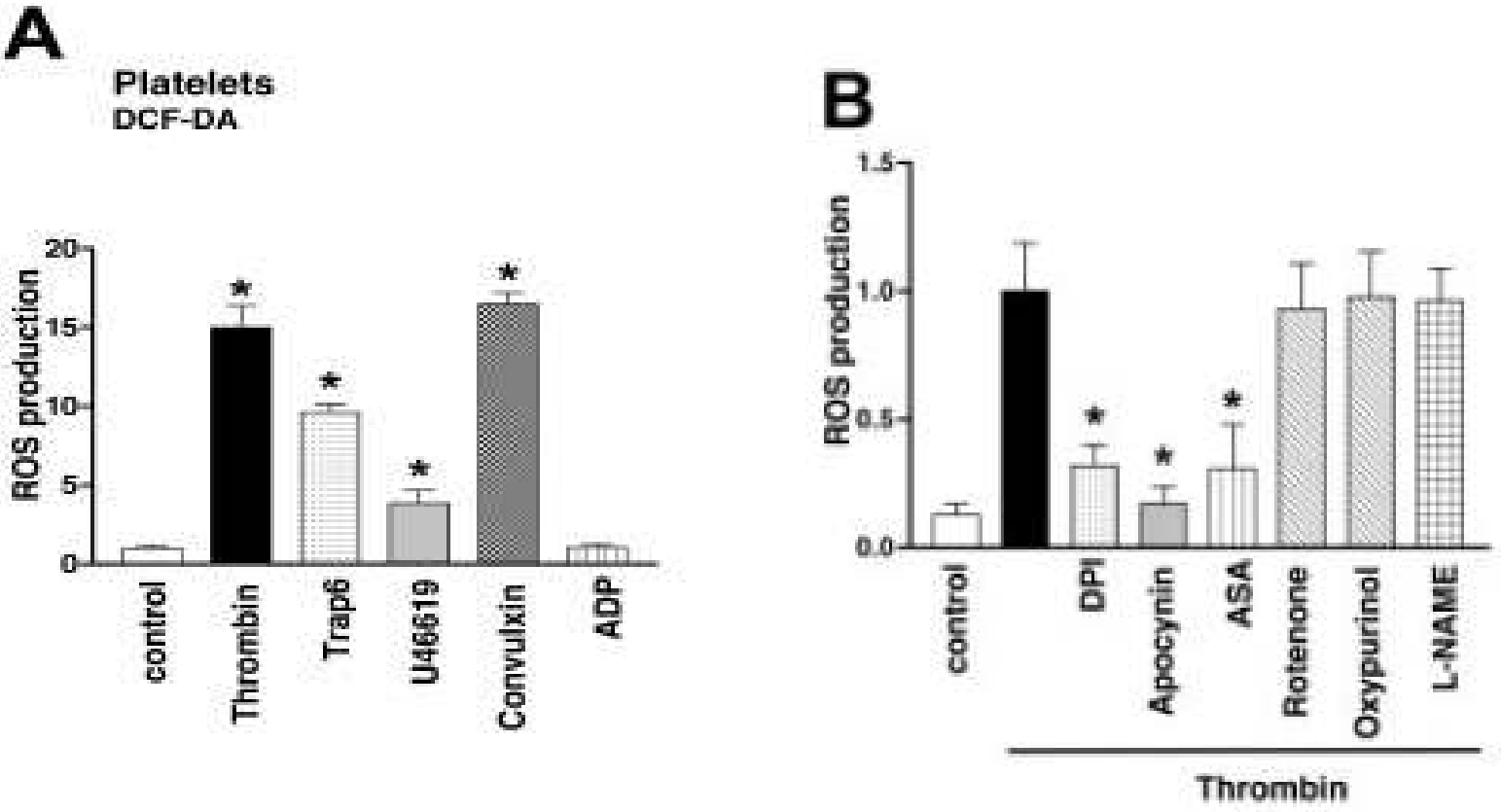
Antioxid Redox Signal 2011; 15: 1911–1926

Oxidative stress



J Clin Invest 2004; 114: 1752–1761

Activated platelet produce intracellular ROS



Blood 2005; 106: 2757–2760

Interventional study with antioxidants

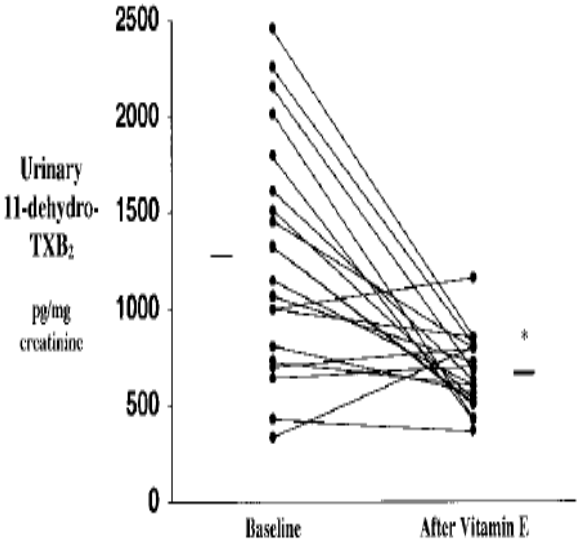


Figure 5. Effect of vitamin E supplementation on urinary excretion of 11-dehydro-TXB_2. Dots depict data points from duplicate determinations made either before treatment (baseline) or after vitamin E administration (600 mg/d for 2 weeks). Horizontal lines represent the mean values for the whole group of patients. *P=.0015.

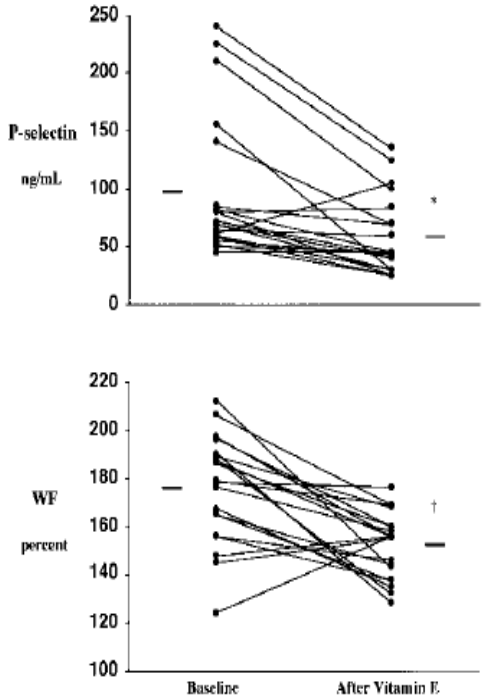


Figure 3. Impact of vitamin E supplementation on soluble P-selectin (top) and plasma vWF (bottom). Dots depict data points from duplicate determinations made either before treatment (baseline) or after vitamin E administration (600 mg/d for 2 weeks). Horizontal lines represent the mean values for the whole group of patients. *P=.001; †P=.001.

Circulation 1998; 97: 953–957

Effects of anti-platelet therapy in metabolic syndrome

Anti-obesity therapy

- Lifestyle modification
- Anti-obesity drug
- Bariatric surgery

Insulin sensitizer

- Anti-diabetic drug

Anti-platelet agent

Lifestyle modification

Table 4. Cardiovascular Risk Factors at Baseline and at 2 Years*

	Intervention Group (n = 60)				Control Group (n = 60)					
Risk Factors	Baseline	2 Years	Mean Change	*P* Value	Baseline	2 Years	Mean Change	*P* Value	Corrected Difference (95% CI)†	*P* Value at 2 Years
Weight, kg	95 (9.4)	81 (7.5)	−14	<.001	94 (9.2)	91 (9.0)	−3	.01	−11 (−14 to −8)	<.001
Body mass index‡	35 (2.3)	30 (2.1)	−5.2	<.001	34 (2.4)	34 (2.4)	−1	.04	−4.2 (−6.4 to −2)	<.001
Waist-hip ratio	0.86 (0.07)	0.78 (0.07)	−0.08	<.001	0.87 (0.07)	0.85 (0.07)	−0.02	.03	−0.06 (−0.09 to −0.03)	.008
SBP, mm Hg	124 (8.5)	121 (8.4)	−3	.01	124 (7.9)	122 (7.8)	−1.0	.15	−2 (−3.5 to −0.5)	.009
DBP, mm Hg	85 (4.7)	82 (4.6)	−3	.01	84.5 (4.9)	83.2 (4.5)	−1.3	.27	−1.7 (−3 to −0.4)	<.001
Glucose, mg/dL	106 (14)	97 (13)	−9	.01	105 (13)	103 (11)	−2	.16	−7 (−9 to −5)	<.001
Insulin, µU/mL	14 (4)	9 (3)	−5	.02	14 (4)	12 (3)	−2	.02	−3 (−5 to −1)	.009
HOMA‡	3.6 (0.4)	2.3 (0.3)	−1.3	.02	3.7 (0.5)	3.3 (0.4)	−0.4	.02	−0.9 (−1.3 to −0.5)	.008
TC, mg/dL	197 (62)	193 (58)	−4	.04	193 (23)	193 (23)	0	.50	−4 (−12 to 4)	.13
HDL-C, mg/dL	46 (12)	54 (12)	+8	.03	46 (12)	46 (12)	0	.40	+4 (2 to 6)	.02
Triglycerides, mg/dL	142 (44)	123 (35)	−19	.04	150 (53)	142 (44)	−8	.30	−12 (−18 to −5)	.04
FFA, mmol/L	581 (102)	419 (63)	−162	.01	562 (98)	523 (85)	−39	.11	−123 (−200 to −53)	.01
IL-6, pg/mL§	4.3 (1.9-9.0)	2.9 (1.1-6.5)	−1.4	.01	4.1 (2.0-9.0)	3.8 (2.1-8.9)	−0.3	.15	−1.1 (−1.7 to −0.6)	.009
IL-18, pg/mL§	225 (185-291)	157 (112-212)	−68	.02	217 (183-289)	206 (165-274)	−11	.24	−57 (−100 to −12)	.02
Adiponectin, µg/mL	5.6 (2.2)	8.3 (2.9)	+2.7	.02	5.4 (2.1)	5.9 (2.1)	+0.5	.13	+2.2 (1.0 to 3.5)	.01
CRP, mg/L§	3.2 (1.5-8.4)	2.1 (0.9-7.1)	−1.1	.01	3.4 (1.4-8.3)	3.1 (1.3-8.2)	−0.3	.19	−0.8 (−2.0 to −0.4)	.008

Abbreviations: CI, confidence interval; CRP, C-reactive protein; DBP, diastolic blood pressure; FFA, free fatty acids; HDL-C, high-density lipoprotein cholesterol; HOMA, homeostatic model assessment of insulin sensitivity; IL-6, interleukin 6; IL-18, interleukin 18; SBP, systolic blood pressure; TC, total cholesterol.
SI conversion factors: see Table 1.
*Data are presented as mean (SD) unless otherwise indicated; †Intervention group minus control group; ‡For definitions, see Table 1 footnotes; §Data are presented as median (interquartile range).

JAMA 2003; 289: 1799–1804

Orlistat

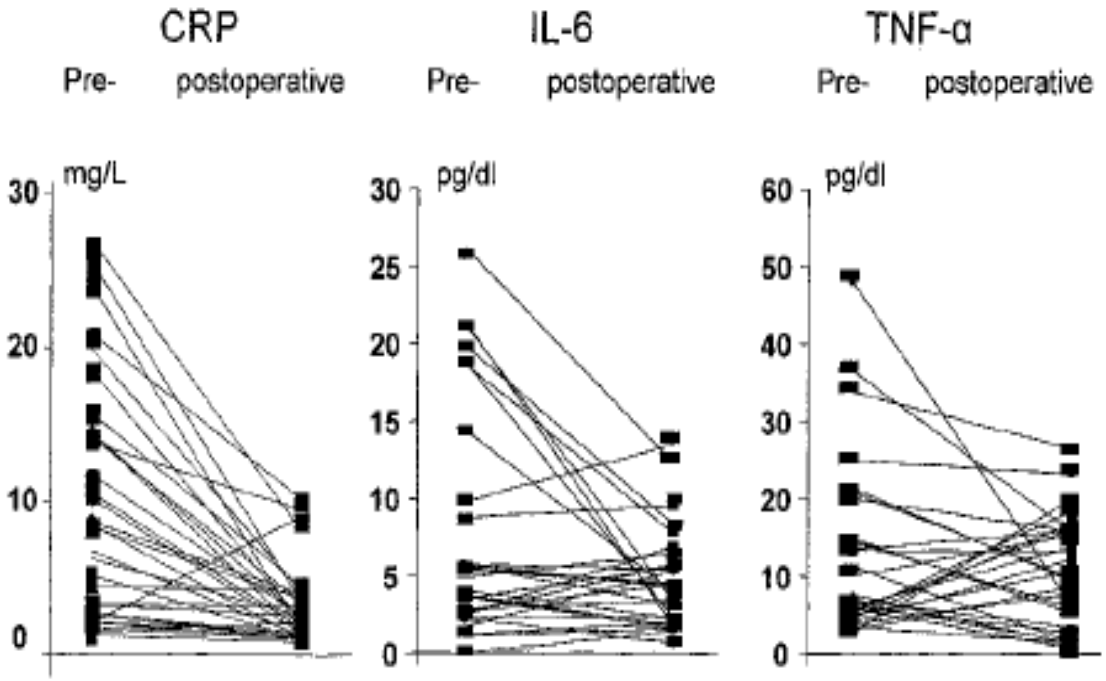
Table 3. Anthropometric indices, biochemical, and hormonal levels in groups A1 and A2, before and after intervention

	Group A1 (Diet plus orlistat)			Group A2 (Only Diet)		
Parameter	**Before**	**After**	**P value**	**Before**	**After**	**P value**
Weight (Kg)	98.6±14.9	75.4±12.7	<0.001	102.1±18.7	82.5 ±14.8	<0.001
BMI(Kg/m²)	37.2±5.3	28.42±4	<0.001	38.5±7	30.9±5.7	<0.001
W/H ratio	0.9	0.8	<0.001	0.9	0,8	<0.001
Waist circumference(cm)	109.3±12.7	97.4±12.7	<0.001	108.5±10.6	94.1±9.4	0.028
%body fat	43.3±5.4	31.4±4.8	<0.001	42.5±8.1	34.7±7.3	<0.001
%free fat mass	56.7±5	66.9±4.7	<0.001	57.9±8.2	64.68±6.9	<0.001
Chol (mg/dl)	197.6±38.2	176.4±32.2	0.002	209.5±43.7	169.7±27.2	<0.001
Trigl. (mg/dl)	127.7±46.8	89.9±23.1	<0.001	141.5±42.9	125±40	0.002
HDL (mg/dl)	40.8±10.7	44.3±8.3	NS	42.1±10.3	33.9±8.2	<0.001
LDL (mg/dl)	127.4±32.8	93.5±21.8	<0.001	131.2±43.9	116.9±28.5	0.034
hsCRP (mg/l)	9.3±5.5	4.1±2.8	<0.001	8.5±3.9	6.6±3.3	0.007
Insulin (IU/ml)	39.2±31.5	23.8±18.8	<0.001	41±30	26.9±18.3	<0.001
HOMA-IR	9.4±8.2	5.3±4.1	<0.001	10.1±8.2	6.5±4.6	<0.001
Leptin (ng/ml)	90.1±30	51.6±19.5	0.03	88.7±29.3	60.8±22.4	<0.001
IL-6 (pg/ml)	82.3±17	10.4±2	<0.001	83±17	11.7±3.1	<0.001
IGF-I (ng/ml)	102.9±55.4	230.3±53.3	<0.001	97±42.7	287.6±83.3	<0.001
TNF-α (pg/ml)	43±15.9	22.3±7.5	<0.001	41.1±12.7	32.5±10.3	<0.001
Isoprostane (pg/ml)	5298.2±1778.7	1127.5±467.1	<0.001	5166.4±1787.2	1472.2±506.4	<0.001
Peroxidase of glutathione (ng/ml)	22±9.8	52.3±15.2	<0.001	22.3±9.5	48.9±14.1	<0.001
Resistin (ng/ml)	22.30±8.1	16.7±5.9	<0.001	23.7±9.1	17±5.4	<0.001
Adiponectin (ng/ml)	17.29±4.9	39.8±13.4	<0.001	20.5±6.2	35.3±21.8	<0.001

Chol: cholesterol; Trig: triglycerides; HDL: high density lipoprotein; IL-6: interleukin 6; hsCRP: C reactive protein; IGF-1: insulin like growth factor 1; TNF-α: Tumor necrosis factor α; HOMA-IR: homeostasis model assessment index; NS: Non significant.
For SI units multiply for insulin by 7.175, for cholesterol, LDL and HDL by 0.02586, for triglycerides by 0.01536. Normal values (range): resistin; 7-16ng/ml, TNF-α; 1.2-7.8pg/ml, adiponectin 28.2-110ng/ml

Hormones (Athens) 2006; 5: 259–269

Bariatric surgery



Markers of inflammation in morbidly obese subjects before and after weight loss as a result of gastric surgery.

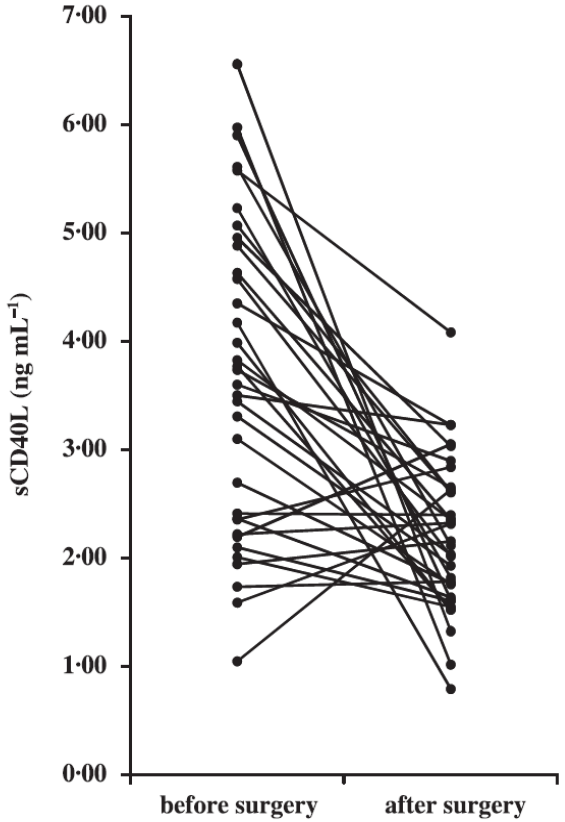


Figure 1 Decline of sCD40L levels after mean weight loss of 33·1 ± 18·4 kg, achieved by bariatric surgery.

Arterioscler Thromb Vasc Biol 2003; 23: 1042–1047
Obes Surg 2006; 16: 709–715

Metformin

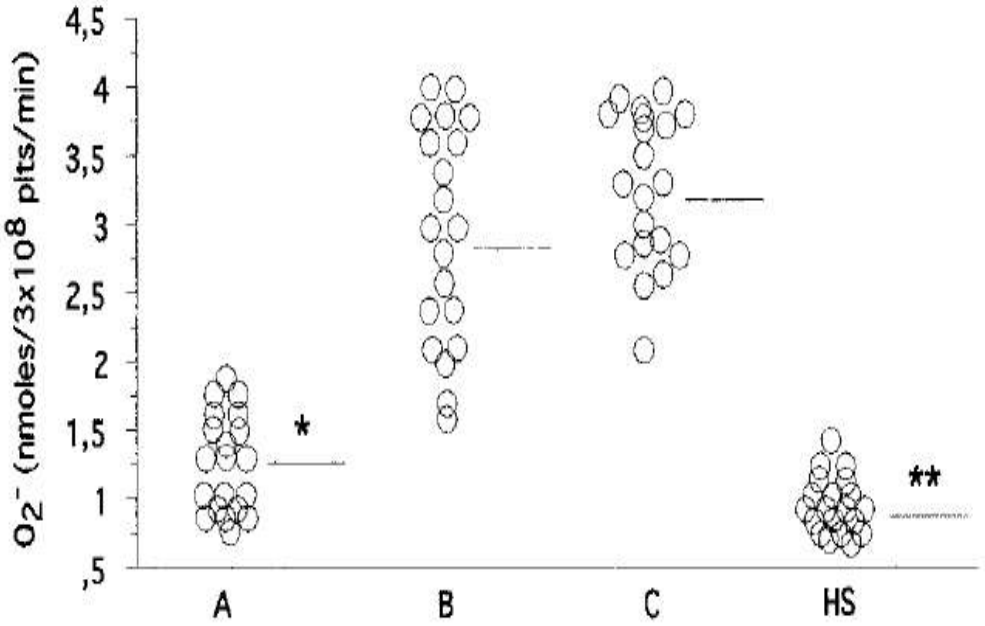


Figure 1. Platelet superoxide anion (O_2^-) production in treated patients (Group A: metformin, Group B: glibenclamide, Group C: diet) and healthy subjects (HS). *$p<0.001$ Group A vs Group B and Group C. **$p<0.001$ HS vs Group B and Group C

Table 1. Clinical and metabolic data for the diabetic patients and healthy subjects (controls)

	Patient group			
	A	B	C	Controls
Age (years)	57.4±9.8	62.9±10.6	60.7±7.5	59.2±8.5
Disease duration (years)	7.3±5.9	9.7±7.4	8.1±6.1	-
BMI (kg/m)	29.97±3.37	23.78±2.25	28.35±2.71	22.2±3.7
HbA_{1c} (%)	7.29±2.1	7.04±2.1	6.99±0.5	4.55±0.3
Total cholesterol (mg/dl)	213.26±39.9	195±40.5	210.5±18.1	181.76±18.1
Triglycerides (mg/dl)	168±96.6	134.4±94.7	106.8±33.4	87.7±37.9
Glycaemia (mg/dl)	165.2±44.3	134.7±42.8	127.47±15.7	83.3±6.5
C-peptide (ng/ml)	2.6±0.8	2.5±1.2	2.28±0.4	1.8±0.3

BMI, body mass index; HbA_{1c}, glycosylated haemoglobin.

Diabetes Metab Res Rev 2002; 18: 156–159

Metformin

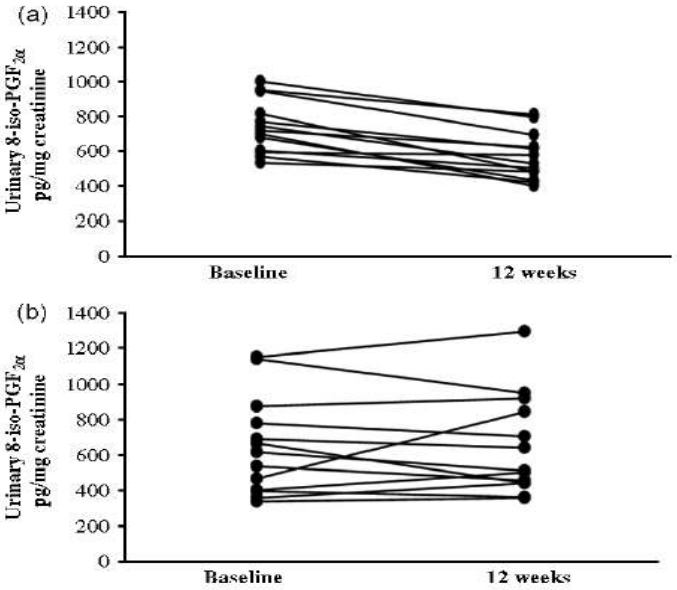


Figure 1. Urinary excretion of 8-iso-$PGF_{2\alpha}$ before and after 12 weeks metformin treatment (a) or gliclazide treatment. (b) Individual measurements of 8-iso-$PGF_{2\alpha}$ excretion are represented for patients who achieved comparable metabolic control after metformin or gliclazide.

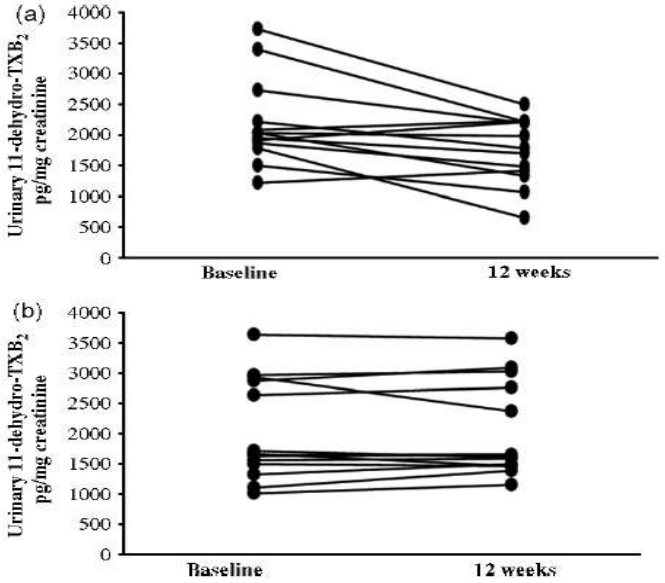


Figure 2. Urinary excretion of 11-dehydro-TXB_2 before and after 12 weeks metformin treatment (a) or 12 weeks gliclazide treatment. (b) Individual measurements of urinary 11-dehydro-TXB_2 excretion are represented for patients who achieved comparable metabolic control after metformin or gliclazide.

Table 3. Delta after-before treatment with metformin or gliclazide for vitamins A and E plasma concentration and urinary excretion of 11-dehydro-TXB_2 and 8-iso-$PGF_{2\alpha}$

	Metformin delta	Gliclazide delta	*p* (metformin *vs* gliclazide)*	*p* (metformin *vs* gliclazide)**
Plasma vitamin A (µmol/L)	0.4 ± 0.03	0.0 ± 0.4	0.008	0.031
Plasma vitamin E (µmol/L)	5.5 ± 7.9	0.6 ± 2.5	0.008	0.027
Urinary 8-iso-$PGF_{2\alpha}$ (pg/mg creatinine)	−119 ± 113	0.6 ± 156	0.030	0.048
Urinary 11-dehydro-TXB_2 (pg/mg creatinine)	−437 ± 517	3.2 ± 216	0.010	0.008

*Multiple regression with stepwise variable selection (baseline HbA_{1c}, HbA_{1c} change, baseline BMI, BMI change, and QUICKI change tested as covariates).
**Multiple regression analysis with baseline HbA_{1c} levels and change in HbA_{1c} levels forced in. Vitamins A and E were log transformed.

Diabetes Metab Res Rev 2008; 24: 231–237

Anti-platelet agent in metabolic syndrome

- The platelet alterations described in central obesity and in the other insulin resistant states provide a rationale for antiplatelet therapy
- Obese patients have ‘angrier’ platelets whose consequences are higher rates of ischemic complications.
- This finding is further enhanced by the evidence for an impaired response to antiplatelet therapy in association with obesity.
- And also, insufficient suppression of platelet activation by aspirin is a predictor of cardiovascular events in high-risk patients.

Blunted aspirin action in obese patients

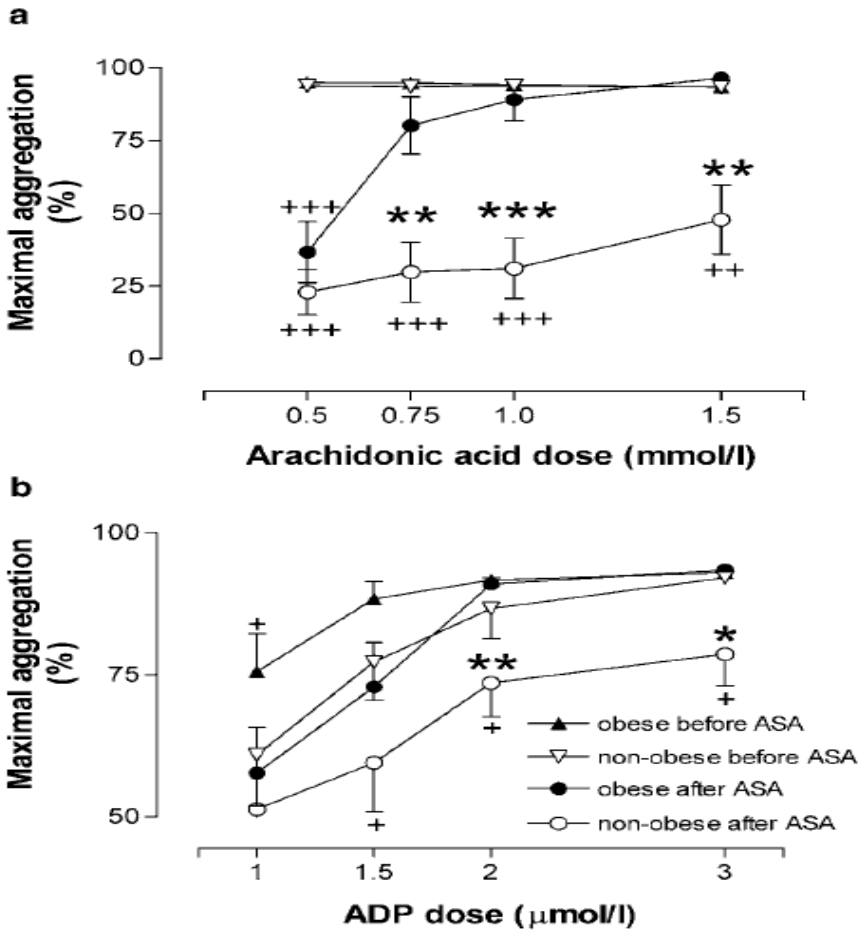


Figure 1 Maximal aggregation at four concentrations of AA (a) and ADP (b) at baseline and after ASA 50 mg. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ for obese *vs* nonobese after ASA 50 mg. $^{+}P<0.05$, $^{++}P<0.01$, $^{+++}P<0.001$ for difference between aggregation at baseline and after ASA.

Table 2 Correlations between insulin sensitivity (mg/kg · min) determined by the euglycemic clamp technique and maximal aggregation with different concentrations of AA and ADP in the whole study group

	r	P
AA 0.75 mmol/l after ASA	−0.67	<0.001
AA 1 mmol/l after ASA	−0.68	<0.001
AA 1.5 mmol/l after ASA	−0.63	<0.001
ADP 1 μmol/l at baseline	−0.48	<0.05
ADP 1.5 μmol/l at baseline	−0.48	<0.05
ADP 1.5 μmol/l after ASA	−0.52	<0.05
ADP 3 μmol/l after ASA	−0.45	<0.05

Int J Obes Relat Metab Disord 2003; 27: 907–911

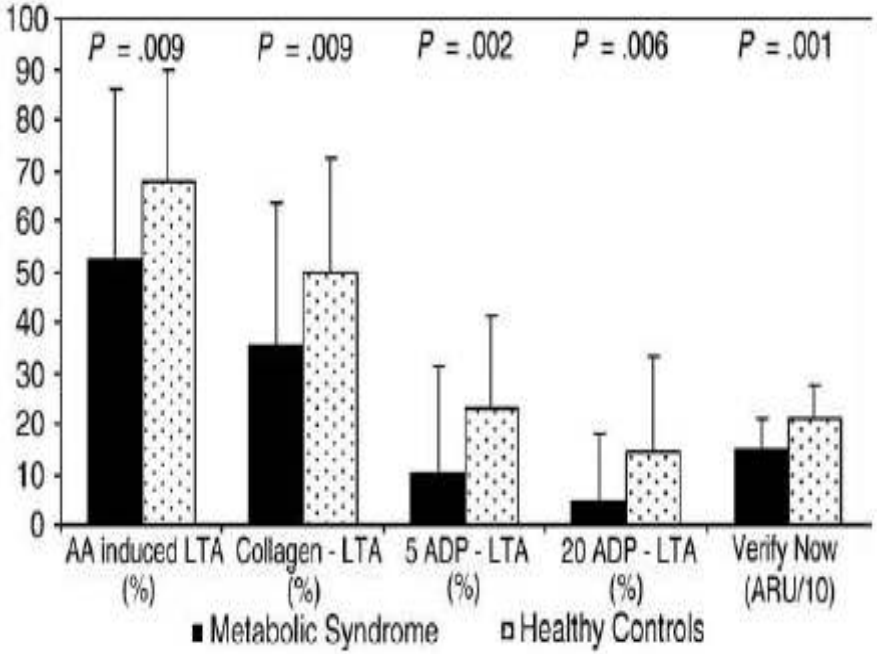
Blunted aspirin action in metabolic syndrome

Table II. Platelet function in subjects with MS and healthy controls before and after aspirin

	Baseline		Post-aspirin	
	MS	Controls	MS	Controls
LTA—AA (%)	69.9 ± 29	77.2 ± 21	16.3 ± 13	9.6 ± 8*
LTA—collagen (%)	59.3 ± 27	62.3 ± 24	21.8 ± 15	12.7 ± 12†
LTA—5 ADP (%)	79.7 ± 18	84.5 ± 14	67.6 ± 13	61.4 ± 18‡
LTA—20 ADP (%)	85.4 ± 12	89.8 ± 8	79.6 ± 10	75.6 ± 19
VerifyNow (ARU)	623.5 ± 53	627.4 ± 42	470.9 ± 54	414.2 ± 46†
P-Selectin ADP (MFI)	14.5 ± 5	11.3 ± 4*	13.2 ± 5	10.6 ± 4§
GP IIb/IIIa activation (MFI)	6.3 ± 2	7.0 ± 3	6.4 ± 2	6.3 ± 3

*P = .002.
†$P \leq .001$.
‡P = .06.
§P = .006 for the comparison of subjects with MS vs controls.

Figure 2



Am Heart J 2008; 156: 1002 e1-7

Mechanism linking metabolic syndrome to impaired response to aspirin

Underdosing of drugs

Reduced bioavailability

Enhanced platelet turnover

Significant association between BMI and platelet function

Table II. Platelet Function at Baseline and After Aspirin Among Nonobese and Obese Individuals

Phenotype	Nonobese BMI <30 kg/m^2 (N=1184)	Obese BMI ≥30 kg/m^2 (N=830)	*P* Value[a]
Aggregation to collagen 1 µg/mL, ohms			
Baseline	19.6 (5.5)	20.2 (6.0)	.02
After aspirin	6.1 (5.2)	6.7 (5.5)	.008
Change	−13.4 (6.5)	−13.5 (7.0)	.87
Aggregation to ADP 10 µmol/L, ohms			
Baseline	12.4 (5.8)	13.0 (6.03)	.01
After aspirin	11.8 (6.0)	13.1 (6.0)	<.0001
Change	−0.538 (5.3)	0.130 (4.8)	.003
Aggregation to arachidonic acid 0.5 mmol/L, ohms			
Baseline	15.5 (6.5)	16.5 (6.5)	.0003
After aspirin (nonzero aggregation)	4.9%	8.3%	.002
Urinary thromboxane B2, ng/mmol creatinine			
Baseline	235.5 (581.5)	254.6 (530.2)	.002
After aspirin	49.9 (97.3)	54.4 (102.0)	.003
Change	−183.0 (579)	−207.6 (552)	.013
Aspirin resistance[b] (%)	20.5	26.4	.002

Abbreviations: ADP, adenosine diphosphate; BMI, body mass index. All results are mean (SD) unless otherwise noted.
[a] *t* tests or χ^2 on log-transformed variables. [b] Upper quartile of urinary thromboxane metabolite.[9]

Table III. Residual Platelet Function After Aspirin 81 mg and After 325 mg/d in a Subset of Obese and Nonobese Individuals (n=106)

	After Aspirin 81 mg/d	After Aspirin 325 mg/d	*P* Value
Nonzero aggregation to arachidonic acid 0.5 mmol/L			
Nonobese	9.38%	8.47%	.8612
Obese	19.05%	10.00%	.2466
Aggregation to collagen 1 µg/ml, ohms			
Nonobese	4.27 (3.90)	4.53 (5.13)	.7542
Obese	4.17 (3.93)	4.85 (4.97)	.4722
Aggregation to ADP 10 µmol/L, ohms			
Nonobese	11.16 (5.89)	11.54 (4.33)	.6439
Obese	11.60 (4.52)	11.73 (4.61)	.8607
Urinary thromboxane metabolite (adjusted for creatinine)			
Nonobese	67.86 (73.2)	56.22 (82.5)	.0399
Obese	46.67 (24.4)	47.76 (42.33)	.9798

Abbreviation: ADP, adenosine diphosphate.

Table V. Multiple Linear Regression Models for Urinary Thromboxane Metabolites (TxM) Before and After Aspirin Therapy (N=2014)

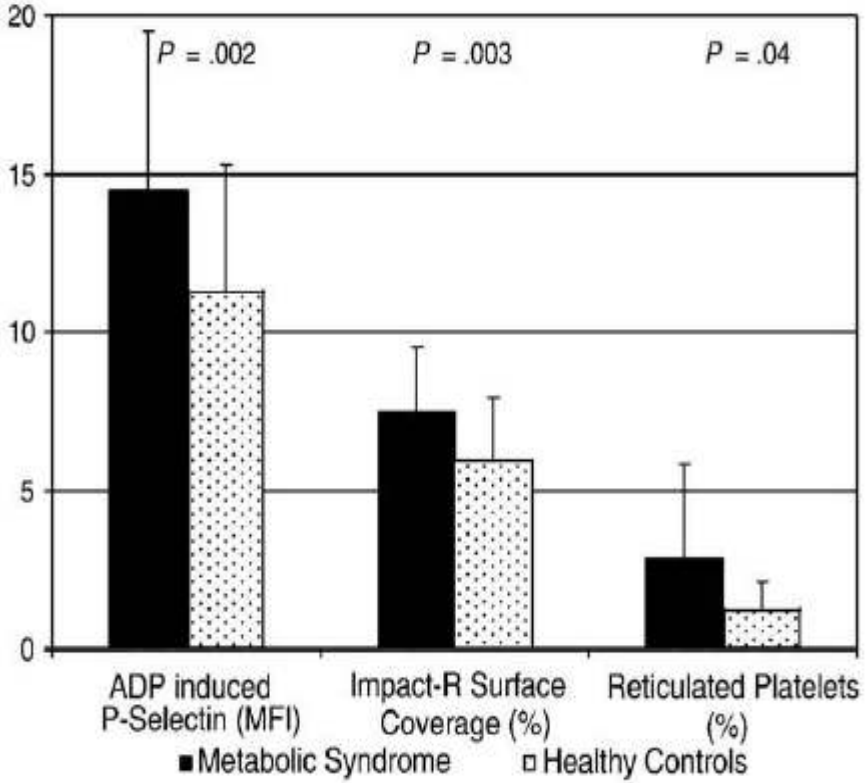
	Baseline		After Aspirin	
	β (SE)	*P* Value[a]	β (SE)	*P* Value[a]
Body mass index, kg/m^2	0.02 (0.004)	<.0001	0.01 (0.004)	.0009
Female sex	0.2 (0.06)	.001	0.1 (0.05)	.006
Age, y	0.007 (0.002)	.003	0.005 (0.002)	.02
White race	0.07 (0.06)	.3	0.03 (0.06)	.6
Current smoker	0.3 (0.07)	<.0001	0.3 (0.06)	<.0001
Systolic blood pressure, mm Hg	−0.0006 (0.002)	.8	−0.0007 (0.002)	.7
Glucose, mg/dL	0.0006 (0.001)	.6	0.001 (0.0009)	.3
Total cholesterol, mg/dL	−0.0004 (0.0007)	.5	−0.0006 (0.0006)	.3
Fibrinogen mg/dL	0.00004 (0.0003)	.9	−0.0005 (0.0002)	.8

[a] Adjusted for nonindependence of families using the generalized estimating equation method.

Prev Cardiol 2010; 13: 56–62

Increased platelet turnover

Figure 1



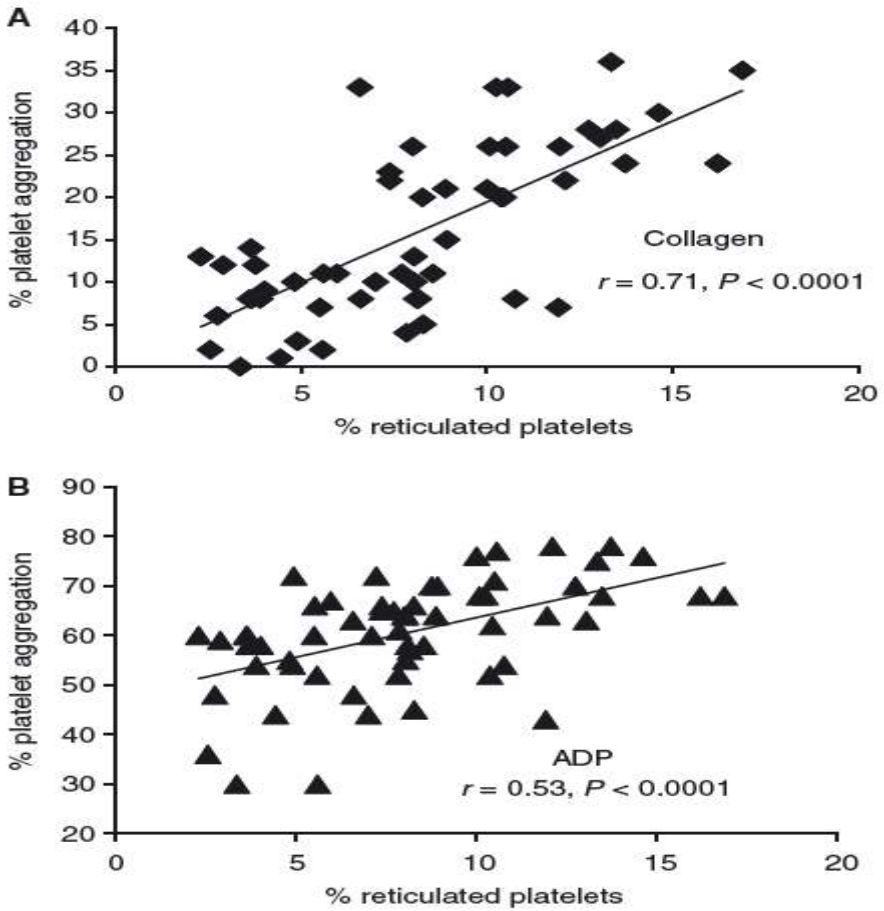


Fig. 2. Correlation of 1 μg mL^{-1} collagen-induced (A) and 5 μM ADP-induced (B) platelet aggregation to % reticulated platelets.

J Thromb Haemost 2007; 5: 490–496

Increased platelet turnover

Table 2 Platelet aggregation measured by light transmittance aggregometry in tertiles of % reticulated platelets

	Baseline platelet aggregation (%)				Postaspirin platelet aggregation (%)			
	Upper tertile	Middle tertile	Lower tertile	*P*-value*	Upper tertile	Middle tertile	Lower tertile	*P*-value*
ADP 5 μM	83 ± 14	84 ± 12	72 ± 20	0.06	67 ± 9	60 ± 8	54 ± 11	0.0002
ADP 20 μM	90 ± 4	91 ± 4	86 ± 10	0.14	81 ± 6	80 ± 7	75 ± 7	0.008
Arachidonic acid 1.5 mM	72 ± 28	64 ± 32	67 ± 29	0.57	8 ± 7	7 ± 5	5 ± 4	0.1
Collagen 1.0 μg mL^{-1}	80 ± 7	77 ± 16	69 ± 22	0.03	24 ± 8	15 ± 8	8 ± 4	< 0.0001

*Upper vs. lower tertile, Student's *t*-test.

Table 4 Serum thromboxane B_2 (TxB_2, ng mL^{-1}) synthesis in tertiles of % reticulated platelets

	Upper tertile	Middle tertile	Lower tertile	*P*-value*
Baseline TxB_2	417 ± 157	387 ± 206	351 ± 195	0.15
Postaspirin TxB_2	5.5 ± 4	4.8 ± 2.7	3.2 ± 2.5	0.03
Postaspirin TxB_2 with *ex vivo* SC-560	0.49 ± 0.46	0.49 ± 0.52	0.35 ± 0.30	0.35
Postaspirin TxB_2 with *ex vivo* NS-398	1.18 ± 1.46	0.43 ± 0.27	0.65 ± 0.69	0.2

*Upper vs. lower tertile, Mann–Whitney test.

J Thromb Haemost 2007; 5: 490–496

Cox-1 and Cox-2

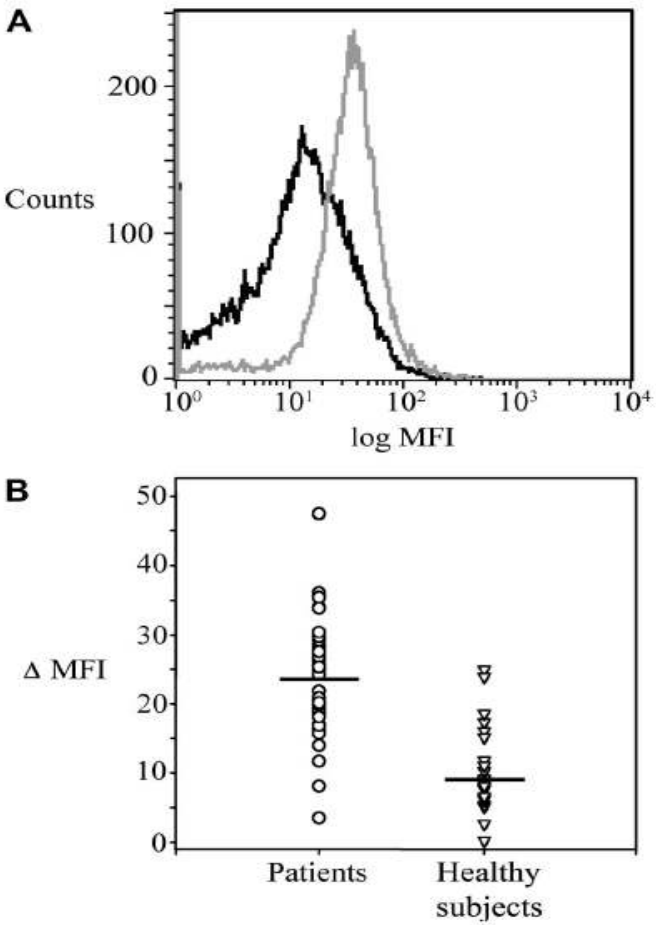


Figure 1. Platelet COX-2 expression in ET patients and healthy subjects. (A) Flow cytometric histograms of fluorescence intensity on platelets stained for COX-2 in a patient (gray) and a control subject (black). The plot of the patient is shifted to the right, indicating a higher expression of COX-2. (B) Individual values of ΔMFI (see "Platelet immunophenotyping and reticulated platelets" for details) for COX-2 in platelets from patients (n = 41) and controls (n = 22). Horizontal lines indicate medians.

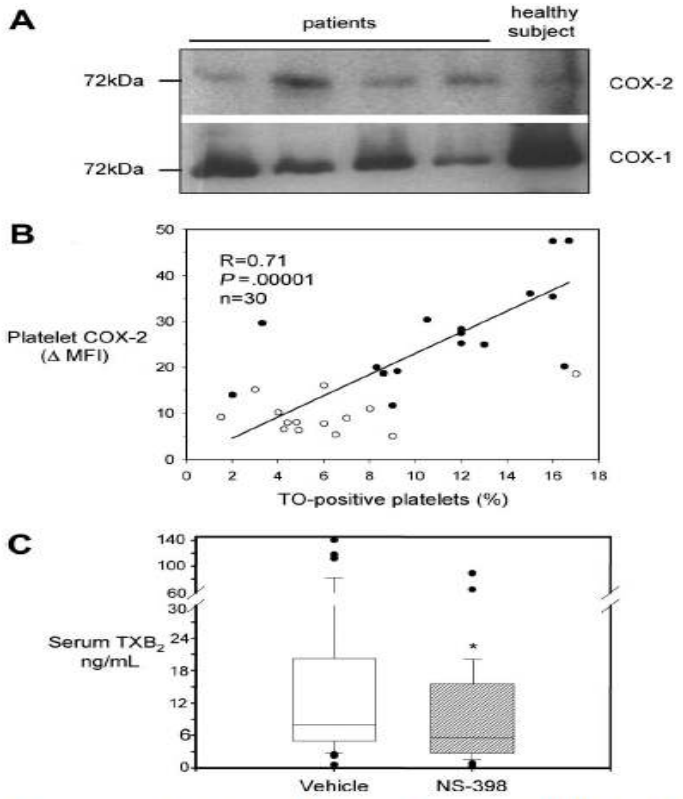


Figure 3. Characterization of COX-2 expression and activity in platelets from ET patients. (A) Western blot analysis of platelet protein extracts for COX-1 and COX-2 in 4 patients and 1 healthy subject. Proteins were extracted from washed platelets and electrophoresed in 10% SDS polyacrylamide gel under reducing conditions. Gels were blotted onto nitrocellulose membranes, which were incubated with monoclonal antibodies against COX-1 or COX-2. Positivity was revealed by anti–mouse horseradish peroxidase–conjugated antibodies and ECL detection reagent. Protein bands were visualized using Kodak Biomax light film. (B) Correlation between COX-2 expression in platelets, expressed as ΔMFI, and the percentage of TO-positive platelets in 16 patients (●) and 14 healthy subjects (○). (C) Box-whisker plots representing whole blood TXB_2 production in vitro, as reflected by serum TXB_2, in samples from 41 ET patients incubated with vehicle (open box) or NS-398 (striped box) added in vitro, at V0. *$P < .001$ versus vehicle.

Blood 2010; 115: 1054–1061

Other proposed mechanism

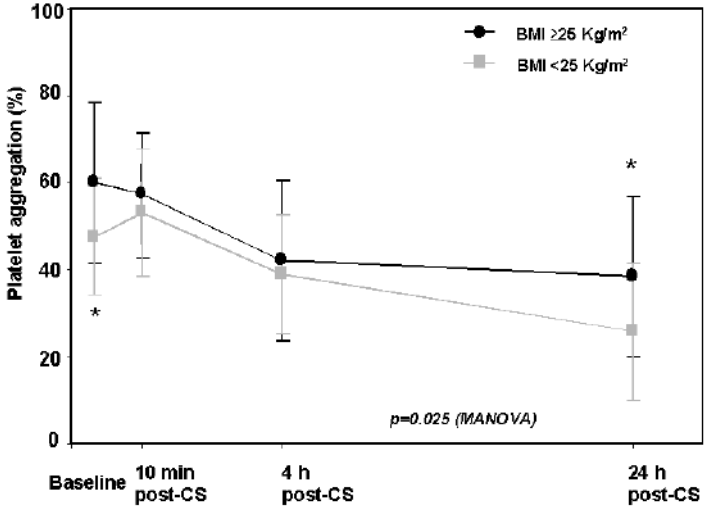
Extraplatelet TXA2 generation

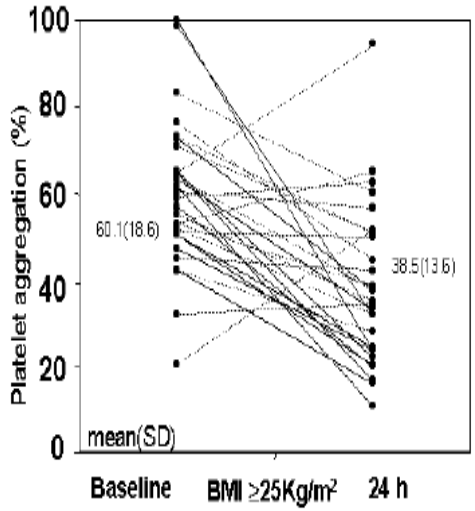
Aspirin-insensitive eicosanoid biosynthesis

Reduced platelet sensitivity to anti-aggregating effect of NO

Enhanced formation of lipid hydroperoxides limiting COX isoenzyme acetylation by aspirin

Blunted clopidogrel effect in obese patients





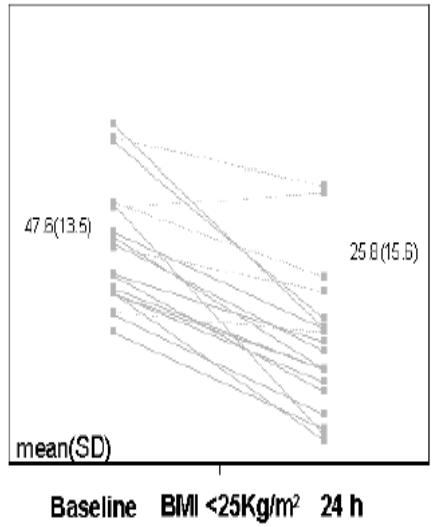


Table 3. Univariate analysis of inadequate inhibition of platelet aggregation following clopidogrel loading- dose

	p-value	Odds Ratio	95% CI
BMI ≥ 25 kg/m²	0.03	0.25	0.07–0.90
Clinical status	0.58	1.41	0.41–4.81
Diabetes	0.19	0.42	0.11–1.53
Hypercholesterolemia	0.67	0.78	0.24–2.50
Smoking habit	0.47	1.60	0.50–5.10
Hypertension	0.75	1.20	0.38–3.75
Gender	0.29	2.70	0.44–16.20
Age (years)	0.60	1.02	0.96–1.08

BMI = body mass index

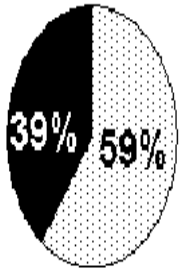


Figure 2. *Individual values of 6 μM adenosine diphosphate-induced platelet aggregation at baseline and 24 hours following clopidogrel loading-dose in overweight (upper left) and normal weight (upper right) patients (adequate inhibition: solid line; suboptimal inhibition: plotted line). A suboptimal degree of platelet inhibition was observed in 59% of overweight (bottom left) and 26% of normal weight (bottom right) patients (p = 0.04). Values are expressed as means and standard deviations.*

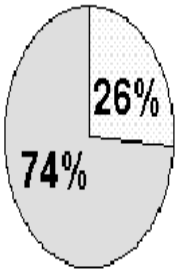


Image 5 of 5

J Invasive Cardiol 2004;16(4):169-74

Selective thromboxane receptor antagonist

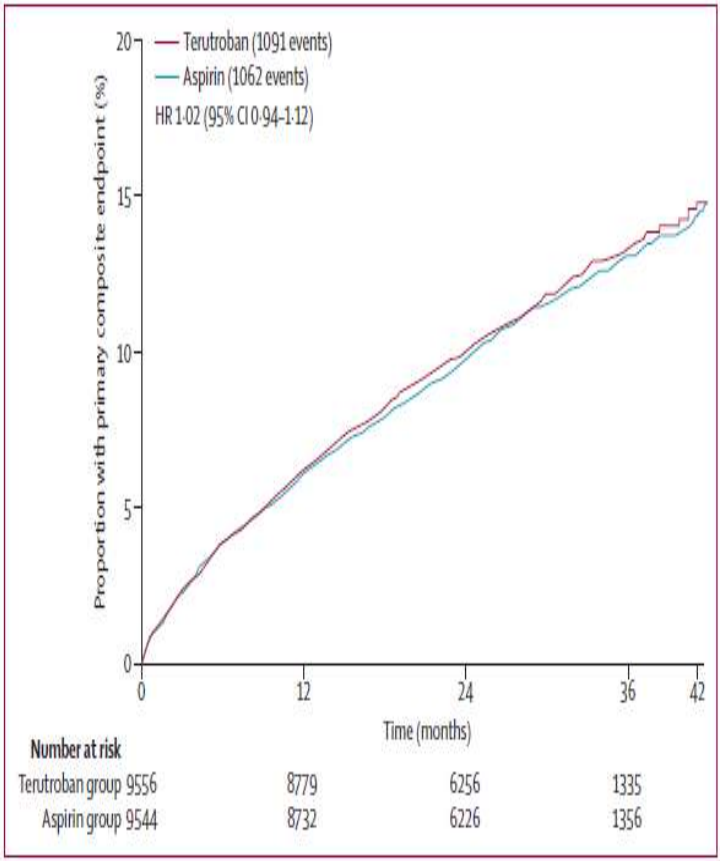


Figure 2: Kaplan-Meier cumulative event curves for the primary composite endpoint of fatal or non-fatal ischaemic stroke, fatal or non-fatal myocardial infarction, and other vascular death (excluding haemorrhagic death)
HR=hazard ratio.

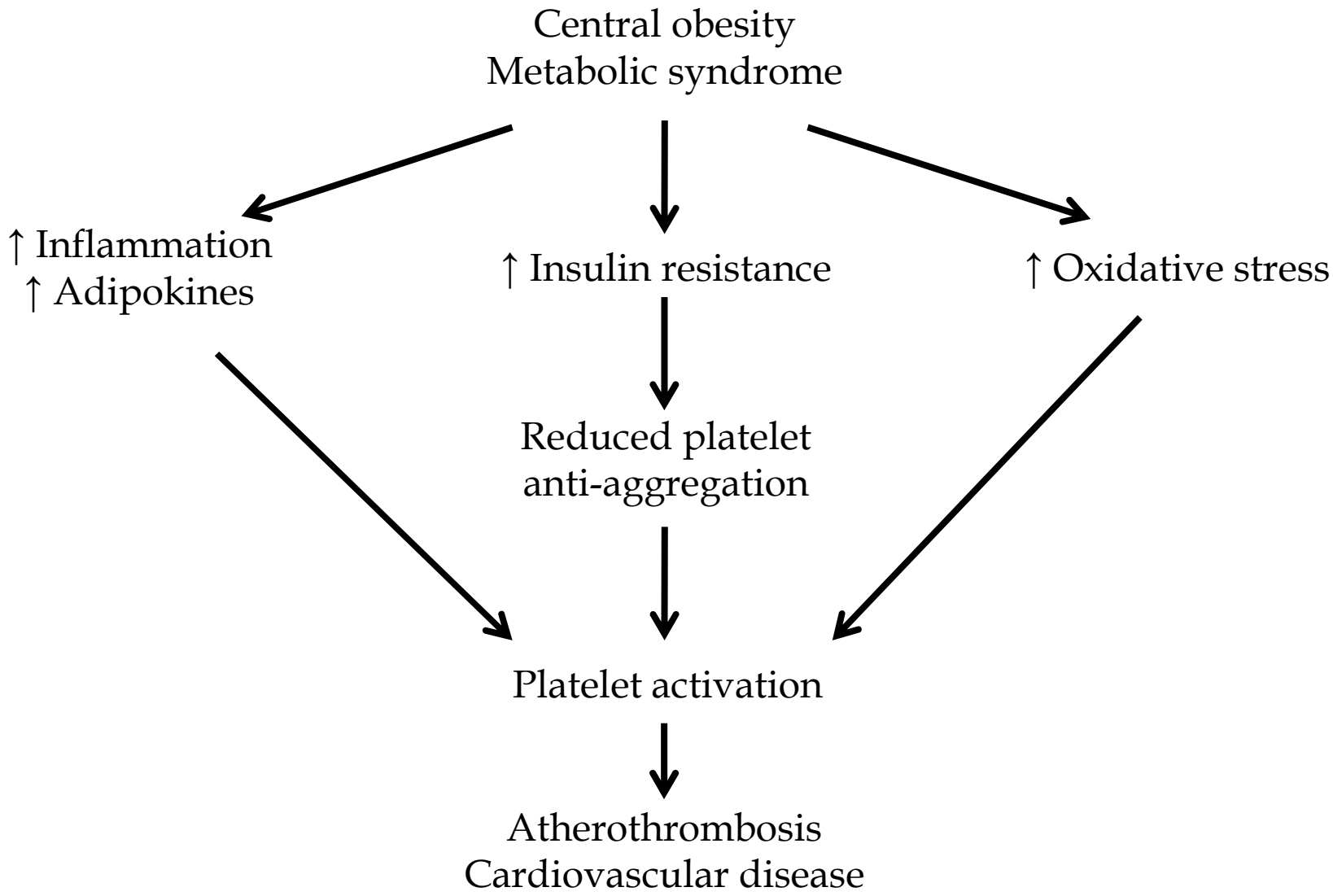
	Terutroban (n=9556)	Aspirin (n=9544)	HR* (95% CI)
Primary composite endpoint			
Fatal or non-fatal ischaemic stroke, fatal or non-fatal MI, and other vascular death†	1091 (11%)	1062 (11%)	1·02 (0·94–1·12)
Secondary endpoints			
Secondary composite endpoint			
Any stroke (fatal or non-fatal), fatal or non-fatal MI, and other vascular death†	1151 (12%)	1122 (12%)	1·02 (0·94–1·11)
Stroke-related endpoints			
Fatal or non-fatal ischaemic stroke	781 (8%)	763 (8%)	1·02 (0·92–1·13)
Non-fatal ischaemic stroke	728 (8%)	724 (8%)	1·00 (0·90–1·11)
Fatal ischaemic stroke	64 (1%)	49 (1%)	1·30 (0·90–1·89)
Any stroke	842 (9%)	828 (9%)	1·01 (0·92–1·12)
Any fatal stroke	98 (1%)	78 (1%)	1·25 (0·93–1·69)
Number of patients with more than one stroke	104 (1%)	93 (1%)	--
MI-related endpoints			
Fatal or non-fatal MI	159 (2%)	129 (1%)	1·23 (0·98–1·56)
Non-fatal MI	140 (1%)	114 (1%)	1·23 (0·96–1·58)
Fatal MI	26 (<1%)	21 (<1%)	1·24 (0·70–2·20)
Mortality-related endpoints			
Other vascular death†	215 (2%)	224 (2%)	0·95 (0·79–1·15)
All-cause mortality	594 (6%)	587 (6%)	1·01 (0·90–1·13)
Cognition-related endpoints			
Incident dementia‡	162 (2%)	155 (2%)	1·05 (0·84–1·31)
Cognitive decline§	3301 (38%)	3392 (39%)	0·96 (0·90–1·02)
Tertiary endpoints			
Hospitalisation due to cardiac causes	464 (5%)	435 (5%)	1·07 (0·94–1·22)
Cardiac death	52 (1%)	54 (1%)	0·96 (0·66–1·41)
Disabling or fatal stroke	688 (7%)	698 (7%)	0·98 (0·88–1·09)
Revascularisation	313 (3%)	324 (3%)	0·97 (0·83–1·13)
Carotid revascularisation	22 (<1%)	26 (<1%)	0·84 (0·48–1·49)
Major lower limb amputation	33 (<1%)	21 (<1%)	1·57 (0·91–2·71)

Data are number of first events (%) and HR (95% CI). HR=hazard ratio. MI=myocardial infarction. *Odds ratio for cognition-related endpoints. †Vascular death excludes haemorrhagic death of any origin. ‡Number of patients without dementia at baseline: 9424 terutroban, 9428 aspirin. §Number of patients without dementia at baseline and with available scores: 8761 terutroban, 8762 aspirin.

Table 2: **Efficacy for primary, secondary, and tertiary endpoints**

Lancet 2011; 377: 2013–22

Summarization



Thanks for your attention!!