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Suboptimal inhibition of platelet cyclo-oxygenase-1 (COX-1) by aspirin in lupus erythematosus: Association with metabolic syndrome

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Abstract

Objectives—Low-dose aspirin prevents platelet aggregation by suppressing thromboxane A₂ synthesis. However, in some individuals thromboxane A₂ suppression by aspirin is impaired, indicating suboptimal inhibition of platelet COX-1 by aspirin. Because patients with systemic lupus erythematosus (SLE) have increased risk of thrombotic events, many receive aspirin; however, the efficacy of aspirin in SLE has not been determined. We examined the hypothesis that aspirin response is impaired in SLE.

Methods—We assessed the effect of aspirin by measuring concentrations of the stable metabolite of thromboxane A₂ - serum thromboxane B₂ (sTxB₂), before and after treatment with 81 mg daily aspirin for 7 days in 34 patients with SLE and 36 control subjects. The inability to suppress sTxB₂ synthesis to <10 ng/ml represents suboptimal inhibition of platelet COX-1 by aspirin.

Results—Aspirin almost completely suppressed sTxB₂ in control subjects to 1.5, [0.8–2.7] ng/ml (median and interquartile ranges [IQR]), but had less effect in patients with SLE (3.1, [2.2–5.3] ng/ml) (P=0.002). A suboptimal effect of aspirin was present in 15% (5/34) of the patients with SLE but not in control subjects (0/36) (P=0.023). Incomplete responders were more likely to have metabolic syndrome (P=0.048), obesity (P=0.048) and higher concentrations of CRP (P=0.018).

Conclusion—The pharmacologic effect of aspirin is suboptimal in 15% of patients with SLE but in none of the control subjects, and the suboptimal response was associated with metabolic syndrome, obesity, and higher CRP concentrations.

Keywords

Aspirin response; lupus erythematosus

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INTRODUCTION

Patients with systemic lupus erythematosus (SLE) have a marked increased risk of thrombotic events compared to the general population (1–3). For example, the risk of myocardial infarction is increased between 2 to 50-fold, depending on age, in women with SLE (1,2). The underlying mechanisms for this increased risk are not clear, but involve both severity of atherosclerosis (4,5) and propensity for thrombosis (6). Consequently, in addition to interventions to decrease atherosclerosis, many patients with SLE also receive aspirin to prevent thrombosis.

In the general population, the efficacy of aspirin is well defined (7,8) and it is widely used for primary and secondary prevention of thrombosis (9). The major mechanism for the antithrombotic effect of aspirin is suppression of platelet reactivity by irreversible inhibition of the cyclo-oxygenase activity of prostaglandin H synthase – 1 (also termed COX-1), and thus inhibition of platelet thromboxane A₂ (TxA₂) synthesis (10).

Low doses of aspirin suppress production of platelet TxA₂ almost completely in normal individuals (11,12) and a dose of 81–100 mg/day is almost universally recommended for the prophylaxis of myocardial infarction (9). However, not all patients respond adequately to aspirin, and such interindividual variability resulting in suboptimal response to aspirin has been reported in patients after coronary artery bypass (13), in essential thrombocythemia (14), in coronary artery disease (15), and in metabolic syndrome (16).

Measurement of serum thromboxane B₂ (sTxB₂), a stable metabolic product of TxA₂, is the only test that specifically measures the effect of aspirin on platelet COX-1 activity - its pharmacological mechanism of action (17). Measurement of sTxB₂ in whole blood allowed to clot represents maximal platelet TxA₂ production (12,18). Suppression of sTxB₂ concentrations to below 10ng/ml are uniformly associated with 95% suppression of platelet aggregation induced by arachidonic acid *ex vivo* (15). Consequently, concentrations of sTxB₂ 10ng/ml after aspirin treatment are often considered a threshold to define a suboptimal effect of aspirin (18,19).

Although many patients with SLE are treated with aspirin to prevent thrombosis, little is known about their response to aspirin (20–22). In other populations aspirin resistance has been associated with factors such as metabolic syndrome, increased oxidative stress, and obesity (16,23,24), many of which are more prevalent in SLE (25,26). Thus, we examined the hypothesis that the response to low-dose aspirin is impaired in patients with SLE.

MATERIALS AND METHODS

Study design

The study compared the effect of low-dose aspirin between patients with SLE and subject controls. The study protocol included two visits, one at baseline and another after 7 days of aspirin treatment. Participants did not take NSAIDs for at least 7 days before the baseline visit and during the study. At the baseline visit, participants were evaluated with a standardized clinical interview, physical examination, laboratory tests, and review of medical records. Subjects were asked not to take any aspirin for 7 days before the baseline visit, unless they were receiving aspirin for prophylaxis of thrombosis. We considered any subject that reported use of aspirin, or had a sTxB₂ concentration <10 ng/ml at baseline, to be currently receiving aspirin. The study was approved by the Institutional Review Boards of Vanderbilt University and Harvard University and all participants provided written informed consent.

Setting and Participants

We prospectively studied 34 patients with SLE and 36 healthy control subjects. All study participants were 18 years old. The groups were frequency-matched for age, race and sex. Patients met the classification criteria for SLE (27) with disease duration 6 months. Controls had no inflammatory rheumatic disease. Exclusion criteria were: concurrent use of anticoagulants and/or antiplatelet drugs (except for aspirin), history of allergy to aspirin or non-steroidal anti-inflammatory drugs (NSAIDs), peptic ulcer disease, gastrointestinal bleeding, renal impairment (serum creatinine >1.8 mg/dL, proteinuria +2 on dipstick, or receiving dialysis), thrombocytopenia (platelet count < 135,000/ μ L), or pregnancy. The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (28) and the Systemic Lupus International Collaborating Clinics (SLICC) (29) scores, measures of disease activity and damage respectively, were recorded for patients with SLE. Metabolic syndrome (MetS) was defined using the International Diabetes Federation definition (30) that requires the presence of central obesity (waist circumference above ethnicity specific value or BMI >30 kg/m²) and at least two of the following: a) raised triglycerides >150mg/dL or specific treatment for this abnormality, b) reduced HDL <40 mg/dL in men or <50 mg/dL in women or specific treatment for this abnormality, c) raised systolic blood pressure 130 mmHg or diastolic blood pressure 85 mmHg or treatment of previously diagnosed hypertension, d) raised fasting plasma glucose 100 mg/dL, or previously diagnosed type 2 diabetes (30). We used BMI in the MetS definition.

Intervention

After the baseline visit participants received 81 mg daily of immediate release aspirin for 7 days with adherence to treatment monitored by pill count. Those participants who were already taking aspirin continued taking their regular prescribed aspirin up to the baseline visit and then took the study aspirin for the next 7 days. Participants were instructed to take the last dose of aspirin early in the morning before coming to the follow-up visit. Participants (SLE and control subjects) did not take NSAIDs for at least 7 days before the baseline visit and during the study.

Outcomes

We collected samples of urine and venous blood at baseline and after 7 days of aspirin treatment to evaluate the effect of aspirin by measuring sTxB₂, platelet aggregation and the concentration of the metabolite of TxA₂, 11-dehydro thromboxane (Tx-M), in urine. Routine laboratory assessments were performed at baseline and included a full blood count, high-density and low-density lipoprotein cholesterol, triglycerides and C-reactive protein (CRP). Interleukin 6 (IL6) and tumor necrosis factor alpha (TNF α) concentrations were measured using ELISA (Millipore) with a lower limit of sensitivity of 1.6 pg/ml and 0.14 pg/ml respectively.

Ex vivo synthesis of sTxB₂ was measured as previously described (16). Briefly, immediately after phlebotomy whole blood was allowed to clot at 37° C for 1 hour (12), centrifuged at 3000 rpm for 15 minutes, and the extracted serum was stored at -80° C for later analysis. sTxB₂ was assayed by stable isotope dilution gas chromatography/mass spectrometry with selective ion monitoring (31).

Platelet aggregation was measured using the VerifyNow™ Aspirin Assay (Accumetrics, San Diego, CA, USA) according to the manufacturer's recommendations. The results are expressed as aspirin reaction units (ARU) and a value of 550 ARU in an individual receiving aspirin is considered to represent aspirin resistance. Platelet aggregation tests were not performed in three blood samples due to technical difficulties: one sample from an SLE

patient at baseline, and in two samples after aspirin treatment (one from a different SLE patient and another from a control subject).

Urine samples for determination of Tx-M and F₂-isoprostanes (a measure of oxidative stress) excretion were collected and stored at -80° C until analyzed. Urinary Tx-M and urinary F₂-isoprostanes were measured by negative ion chemical ionization gas chromatography/mass spectrometry as previously described (32,33) and expressed as ng/mg creatinine. Urinary F₂-isoprostanes could not be measured in one SLE patient at baseline due to technical difficulties.

Sample size

Our initial sample size projection was 45 SLE patients and 90 control subjects based on the expected difference on urinary Tx-M excretion after aspirin treatment between SLE patients and control subjects. However, as emerging evidence pointed sTxB₂ to be the best marker of the effect of aspirin in platelet COX-1 enzyme, we recalculated our sample size using the mean±SD (6.30±2.38 ng/ml) of sTxB₂ concentration of the control subjects already on aspirin when enrolled in the study. We estimated that 34 SLE patients and 34 controls provided approximately 95% power to detect a difference of 2ng/ml in the mean concentration of sTxB₂ between groups with type error I of 0.05. Our primary outcomes of interest were comparison of sTxB₂, urine Tx-M and platelet aggregation after aspirin therapy in patients with SLE and controls. Other comparisons were exploratory and hypothesis generating. Because our primary outcomes were not independent and were prespecified we did not adjust for multiple comparisons but reported all comparisons (34,35).

Statistical analysis

Data are expressed as frequency and percentage (%) for categorical variables and as median [interquartile ranges] for continuous variables. We used chi-square or Fisher's exact test to compare categorical variables. Continuous variables were analyzed with Wilcoxon rank-sum test. A two-sided 5% significance level was considered significant. Statistical analyses were performed using Stata/SE® version 12.1 StataCorp LP, TX.

RESULTS

Subject characteristics

We studied 34 patients with SLE and 36 control subjects; the two groups did not differ with regard to age, race, sex, or BMI (Table 1). Patients with SLE were more likely to have a history of smoking, hypertension, and kidney disease compared to controls (Table 1). Concentrations of IL6 (P=0.002) and TNFα (P<0.001) were higher in SLE patients than in control subjects. Twenty nine percent (10/34) of SLE patients and 8% (3/36) of control subjects were taking aspirin at baseline. Participants who were taking aspirin at baseline were on 81 mg/d of aspirin except for one SLE patient who was on 325 mg/d of aspirin. There were no differences in sTxB₂, urinary Tx-M and F₂-isoprostanes excretion at baseline between patients with SLE and control subjects (Table 1).

Response to aspirin

Aspirin 81 mg/day for 7 days suppressed sTxB₂ synthesis in control subjects (69.4 [36.2–132.1] ng/ml to 1.5 [0.8–2.7] ng/ml, p<0.001), and in patients with SLE (43.6 [10.3–121.9] ng/ml to 3.1 [2.2–5.3] ng/ml, p<0.001), but the effect of aspirin was smaller in patients with SLE (Figure 1, P=0.002). Aspirin failed to suppress sTxB₂ concentrations to <10 ng/ml in 5 patients with SLE (15%) and in none of the control subjects (P=0.023). Aspirin suppressed platelet aggregation similarly in control subjects and in patients with SLE (409 [399–434]

ARU and 421 [398–441] ARU respectively, $P=0.308$). However, platelet aggregation after aspirin remained >550 ARU (the threshold for “aspirin resistance”) in 2/33 (6%) patients with SLE (both of whom failed to suppress sTxB₂ concentrations to <10 ng/ml), and in none of the control subjects. Urinary Tx-M excretion after aspirin therapy did not differ significantly among control subjects and patients with SLE (0.098 [0.078–0.149] ng/ml Cr and 0.103 [0.087–0.147] ng/ml Cr respectively, $P=0.800$). Two control subjects had the highest concentrations of urinary Tx-M after aspirin therapy.

Aspirin sensitive vs. insensitive SLE patients

The five SLE patients that failed to suppress sTxB₂ concentrations to less than 10 ng/ml after aspirin treatment were more likely to have metabolic syndrome and obesity than aspirin sensitive patients. They also had higher concentrations of CRP (Table 2). Excretion of urinary F₂ isoprostanes before and after treatment with aspirin was similar in patients who were sensitive to aspirin and those with suboptimal responses (Table 2). Screening for the presence of lupus anticoagulant, a potential risk factor for aspirin resistance, was not performed as part of the study but four of the five patients with suboptimal response to aspirin had a previous negative test for lupus anticoagulant.

Although treatment with aspirin suppressed excretion of urinary Tx-M significantly in aspirin sensitive ($P<0.001$) but not in the 5 patients with incomplete response to aspirin ($P=0.080$), there was considerable overlap in the excretion of urinary Tx-M in responders (0.10 [0.08–0.13] ng/mg Cr) and non-responders to aspirin (0.22 [0.11–0.24] ng/mg Cr) and it was not possible to define a threshold value for urinary Tx-M excretion that defined incomplete responses to aspirin. The two patients with SLE that had platelet aggregation >550 ARU after aspirin treatment had higher concentrations of sTxB₂ (58.9 [12.8–105.0] ng/ml) and higher excretion of urinary Tx-M (0.30 [0.22–0.38] ng/mg Cr) after aspirin compared to those that suppressed platelet aggregation to <550 ARU (3.1 [2.1–5.0] ng/ml and 0.10 [0.09–0.13] ng/mg Cr respectively).

DISCUSSION

The major new finding of this study is that aspirin failed to suppress platelet synthesis of sTxB₂ to <10 ng/ml, which indicates a suboptimal pharmacologic response to this antiplatelet agent (15,18) in 15% of patients with relatively well controlled SLE, but in none of the control subjects. In SLE, an inadequate effect of aspirin was associated with metabolic syndrome, and with one of its components - obesity, and CRP concentrations.

To our knowledge this is the first systematic study comparing aspirin response in patient with SLE and control subjects. Previous studies using urinary Tx-M have suggested that response to aspirin may be impaired in SLE (20–22). Ferro *et al* (21) reported that administration of aspirin (50 mg/d for 7 days) suppressed urinary Tx-M excretion by 80% in SLE. However, in that study several SLE patients had urinary Tx-M concentrations after aspirin treatment that were higher than the median value for controls that were not taking aspirin (21). In a cross-sectional study that did not measure adherence to aspirin, we previously reported that urinary Tx-M did not differ significantly among SLE patients who reported taking or not taking aspirin (20) – suggesting that responses to aspirin could be impaired. However, urinary TxM is not a reliable indicator of the magnitude of aspirin effect on platelets (16,36).

Only the determination of sTxB₂ concentration in whole blood allowed to clot measures the capacity of maximally activated platelets to generate thromboxane through COX-1 activation. Therefore, sTxB₂ test is the most accurate and appropriate method to assess the pharmacological effects of aspirin (37), and is also the most stable and reproducible test to

define response to aspirin (38,39). The 10 ng/ml threshold has often been selected to define adequate response to aspirin since concentrations of sTxB₂ below this level were associated with >98% inhibition of platelet COX1 activity in healthy individuals taking 100 mg of daily aspirin (15,18). A lower threshold as proposed by Frelinger et al (sTxB₂<3.1 ng/ml) (40) would result in even higher rates of inadequate response to aspirin (17% in controls and 47% in SLE). The imperfect concordance observed among sTxB₂, urinary Tx-M, and platelet aggregation tests of aspirin response has been reported before in other populations (38,41,42). A likely explanation is that the different tests measure different aspects of the response to aspirin (18,39) such as thromboxane synthesis from extra-platelet and COX-1 independent sources (18,22,43), or residual platelet reactivity (41,44). The VerifyNow aspirin assay is a functional test that uses a turbidimetric optical system to detect platelet aggregation in whole blood. Platelet aggregation detected by the VerifyNow assay is mediated by several mechanisms and only partially reflects the ability aspirin to inhibit platelet COX-1 (44). In contrast, inhibition of sTxB₂ by aspirin is the most specific test of its pharmacological action (38,39).

The causes of impaired response to aspirin are unclear but it has been reported in patients with various conditions such as coronary disease (15), after coronary artery bypass (13), essential thrombocythemia (14), metabolic syndrome (16), and obesity (36,45). Furthermore, suboptimal responses to aspirin, defined using a range of techniques, have been associated with worse cardiovascular outcomes in patients treated with aspirin (46). In SLE, we found that aspirin resistance was associated with metabolic syndrome and with one of its components - obesity. This finding is of clinical relevance since in a previous study we have reported that patients with SLE had higher prevalence of metabolic syndrome (32%) compared to control subjects (11%) (25). Several possible mechanisms have been postulated to explain impaired responses to aspirin in metabolic syndrome including a rapid turnover of platelets (47), reduced bioavailability of aspirin (36;45), increased biosynthesis of peroxides that results in COX-1 redox cycling and impaired COX-1 acetylation by aspirin (48), and increased formation of aspirin-insensitive isoprostanes through peroxidation (49).

Inflammation can activate platelets and induce oxidative stress (50), thus we postulated that impaired responses to aspirin in patients with SLE would be related to inflammation and oxidative stress. We found no association between F₂ isoprostane excretion (a measure of lipid peroxidation) and responses to aspirin. However, systemic measures of F₂ isoprostane production may not reflect exposure of platelets to lipid peroxides.

We also found that concentrations of CRP, but not other markers of inflammation (IL6 or TNF α), were associated with impaired responses to aspirin. It is possible that high levels of CRP, a stable protein with a relatively long half-life, may better reflect a state of sustained low-grade chronic inflammation than other inflammatory cytokines. Additionally, *in vitro* studies suggest that activated platelets in atherosclerotic lesions can dissociate pentameric CRP (which is the stable isoform that circulates) into its monomeric isoform that promotes platelet aggregation (51–53).

Our study has some limitations. We studied a relatively small number of patients with SLE, who because of the exclusion criteria for the study, had relatively well-controlled disease. Thus, our findings may under-represent the true prevalence of impaired responses to aspirin in patients with SLE. We did not measure platelet turnover, which has shown to be associated with a faster recovery of platelet COX-1 activity among patients with diabetes (36). Other potential factors that could affect aspirin responses such as pharmacokinetics were not assessed. However, it is difficult to obtain pharmacokinetic measures relevant to the response to aspirin because much of the effect of aspirin occurs in the portal circulation before aspirin reaches the liver. Thus, circulating concentrations of aspirin or its metabolites

will not reflect concentrations in the biologically relevant compartment. Additional studies that include patients with more severe disease are needed to establish whether aspirin response is dependent on lupus activity and whether increasing aspirin dose improves responses to aspirin (36). The secondary comparisons performed (metabolic syndrome, obesity and CRP) were exploratory. Although the findings are concordant with studies in the general population, and there are biological mechanisms that could explain these associations, the findings would not withstand adjustment for multiple statistical comparisons and larger studies of SLE patients with and without impaired response to aspirin are needed to replicate our findings.

In conclusion, we found that inhibition of platelet COX-1 by aspirin is suboptimal in 15% of SLE patients, and this is related in part to metabolic syndrome, obesity, and CRP concentrations.

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Significance and Innovation

- Suboptimal response to aspirin was present in 15% of patients with systemic lupus erythematosus.
- Suboptimal response to aspirin was associated with metabolic syndrome, obesity, and higher CRP concentrations.

Table 1

Baseline demographic and clinic characteristics of patients with lupus and controls

Characteristics	Controls N=36	Lupus N=34	P value
Demographics			
Age (years)	45 [33–50]	41 [29–47]	0.365
Female	26 (72%)	28 (82%)	0.313
Caucasian	27 (75%)	24 (71%)	0.678
Weight (kg)	74.3 [67.3–82.5]	70.3 [63.6–88.4]	0.738
BMI (kg/m ²)	25.5 [23.4–27.8]	25.3 [22.3–28.9]	0.855
Current smoker	3 (8%)	7 (21%)	0.182
Ever smoked	7 (19%)	14 (41%)	0.047
Co-morbidities & Medications			
Diabetes	0 (0%)	3 (9%)	0.109
Hypertension	4 (11%)	14 (41%)	0.004
History of kidney disease	0 (0%)	5 (15%)	0.023
Myocardial infarction/angina/stroke	0 (0%)	1 (3%)	0.486
Current aspirin users*	3 (8%)	10 (29%)	0.023
Laboratory parameters at baseline			
White blood cells (thousands/ul)	5.6 [4.7–6.4]	5.0 [3.9–6.3]	0.155
Platelet count (thousands/ul)	254.5 [220.5–297.5]	248.5 [213.0–281.0]	0.404
Hemoglobin (g/dl)	13.4 [12.5–14.6]	13.3 [12.1–14.2]	0.569
Serum creatinine (mg/dl)	0.8 [0.7–0.9]	0.8 [0.7–0.9]	0.957
Total cholesterol (mg/dl)	187.5 [166.5–212.5]	169.0 [148.0–191.0]	0.022
High-density lipoprotein cholesterol (mg/dl)	44.5 [36.5–52.5]	38.5 [34.0–49.0]	0.108
Low-density lipoprotein cholesterol (mg/dl)	113.5 [105.0–138.5]	101.5 [83.0–122.0]	0.007
Triglycerides (mg/dl)	86.5 [69.0–127.5]	104.5 [76.0–180.0]	0.157
C- reactive protein (mg/dl)	0.85 [0.50–1.75]	1.15 [0.60–4.50]	0.136
Interleukin 6 (pg/ml)	1.04 [0.60–1.72]	2.08 [1.13–5.03]	0.002
Tumor necrosis factor alpha (pg/ml)	5.71 [4.50–7.44]	11.40 [6.64–14.11]	<0.001
Baseline parameters in non aspirin users			
	N=33	N=24	
sTxB ₂ (ng/ml)	77.3 [45.0–134.8]	111.0 [38.1–132.3]	0.910
Platelet aggregation (ARU) [†]	654 [644–658]	640 [624–656]	0.030
Urinary Tx-M (ng/mg Cr)	0.291 [0.228–0.411]	0.363 [0.273–0.557]	0.293
Urinary F ₂ isoprostanes [‡]	2.11 [1.50–2.87]	1.98 [1.39–3.30]	0.934
Baseline parameters in current aspirin users*			
	N=3	N=10	
sTxB ₂ (ng/ml)	5.72 [4.26–8.91]	5.15 [1.58–10.27]	0.866
Platelet aggregation (ARU) [†]	406 [396–580]	459 [410–490]	0.498
Urinary Tx-M (ng/mg Cr)	0.094 [0.094–0.379]	0.145 [0.104–0.183]	0.735
Urinary F ₂ isoprostanes (ng/mg Cr)	2.39 [2.25–2.53]	1.87 [1.06–2.65]	0.612

* current users include participants that self-report using aspirin or with serum TBX<10 ng/ml at baseline.

[†]Platelet aggregation testing could not be performed in one lupus patient at baseline.

[‡]Urinary isoprostanes could not be measured in one lupus patient at baseline.

Abbreviations: BMI, body mass index; sTxB₂, serum thromboxane B₂; Tx-M, 11 dehydro-thromboxane B₂; ARU: aspirin reaction units; Cr, creatinine.

Table 2

Characteristics of aspirin sensitive and resistant patients with lupus

	Sensitive * (N=29)	Resistant * (N=5)	P value
Demographics			
Age (years)	40 [29–48]	45 [34–46]	0.922
Female	25 (86%)	3 (60%)	0.205
Caucasian	20 (69%)	4 (80%)	0.999
Weight (kg)	68.6 [63.6–78.1]	103.3 [88.6–132.7]	0.044
Body mass index (kg/m ²)	24.5 [22.3–27.7]	36.2 [28.9–36.6]	0.055
Current smoker	6 (21%)	1 (20%)	0.999
Ever smoke	10 (35%)	4 (80%)	0.135
Comorbidities/cotherapies			
Diabetes [†]	2 (7%)	1 (20%)	0.389
Hypertension [†]	10 (35%)	4 (80%)	0.135
Obesity (BMI ≥ 30 kg/m ²) [‡]	4 (14%)	3 (60%)	0.048
Metabolic syndrome [†]	4 (14%)	3 (60%)	0.048
SLEDAI	0 [0–4]	0 [0–4]	0.957
SLICC	0 [0–1]	1 [0–1]	0.429
Concomitant use of GC [§]	14 (48%)	2 (40%)	0.999
Laboratory parameters			
Platelet count (1,000/ul)	252 [213–281]	245 [198–252]	0.697
Serum creatinine (mg/dl)	0.8 [0.7–0.9]	0.8 [0.8–0.9]	0.473
HDL-cholesterol(mg/dl) [‡]	39 [34–49]	38 [34–41]	0.592
LDL-cholesterol (mg/dl)	98 [83–117]	117 [111–126]	0.108
Triglycerides (mg/dl) [‡]	101 [76–148]	212 [127–221]	0.206
C-reactive protein (mg/l)	0.9 [0.6–4.0]	17.2 [1.8–19.9]	0.018
Interleukin 6 (pg/ml)	2.2 [1.0–4.91]	1.9 [1.7–7.2]	0.436
TNF α (pg/ml)	11.0 [6.5–13.4]	14.7 [11.7–16.2]	0.166
Baseline//			
sTxB2 (ng/ml)	94.9 [34.0–127.6]	149.0 [114.5–190]	0.053
Urinary Tx-M (ng/mg Cr)	0.32 [0.22–0.49]	0.49 [0.40–0.87]	0.121
Platelet aggregation (ARU) [¶]	638 [622–656]	654 [646–659]	0.056
Urinary F ₂ isoprostanes (ng/mg Cr) [#]	1.96 [1.15–3.30]	2.43 [1.76–3.20]	0.626
After aspirin therapy			
sTxB2(ng/ml)	2.8[2.1–4.0]	12.8 [10.4–16.7]	<0.001
Urinary Tx-M (ng/mg Cr)	0.10 [0.08–0.13]	0.22 [0.11–0.24]	0.029
Platelet aggregation (ARU) [¶]	421 [402–435]	441 [396–552]	0.379

Urinary F ₂ isoprostanes (ng/mg Cr) [#]	1.56 [1.24–2.71]	1.48 [1.37–2.82]	0.903
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* Threshold for suboptimal response to aspirin is serum thromboxane >10 ng/ml.

[†] Metabolic syndrome per the International Diabetes Federation definition.

[‡] Elements of the metabolic syndrome (MetS) definition.

[§] GC: Glucocorticoids.

// Baseline analysis exclude patients that self-reported using aspirin or had serum thromboxane levels (TxB₂) <10 ng/ml at baseline.

[¶] Platelet aggregation was not performed in 2 different lupus patients: one at baseline and one after aspirin treatment.

[#] Urinary isoprostanes were not measured in one lupus patient at baseline.

Abbreviations: sTxB₂, serum thromboxane B₂; Tx-M, 11 dehydro-thromboxane B₂; BMI, Body mass index; TNF α, tumor necrosis factor α; ARU, Aspirin reaction units.