

# **Higher Hydroxychloroquine Blood Levels Are Associated with Reduced Thrombosis Risk in Systemic Lupus Erythematosus**

Arthritis Rheumatol 2021. online ahead of print

**本論文のCQ: HCQ血中濃度測定は血栓症リスク予測に役立つか？**

# Introduction

- SLEにおいて血栓症はmortalityとmorbidityに関連する重要な因子
- HCQが血栓症のリスクを下げるという多くの報告がある
- 一方HCQは濃度依存性に網膜症のリスクが上昇することから、最近では5mg/kg/日で用いることが推奨されている（AAOガイドライン2016、EULAR Recommendations 2019）
- HCQ内服量と血中濃度の関係は調べてらておらず、血栓症との関連もみられていない

# PECO

- P: Hopkins Lupus CohortのSLE患者。  
HCQ内服歴があり、HCQ投与前に血栓症既往のない患者
- E: HCQ血中濃度測定
- C: HCQ血中濃度の高い患者と低い患者（3分位による）
- O: 血栓症の発症

# Methods

- 3カ月毎の外来で血栓症の有無をチェック（必要に応じ精査）
- HCQ血中濃度は全血で液体クロマトグラフィタンデム質量分析法（LC-MS/MS法）で測定
- 血栓症発症直前もしくは最終診察時のHCQ濃度、およびそれぞれ以前のHCQの平均濃度を算出
- 血栓症の発生は1000人年あたりで表記
- 平均HCQ濃度を血栓発症群と非発症群で比較（t-検定）
- 血栓症の頻度とHCQ血中濃度の関連はpooledロジスティック回帰で検定

# Results

739人の患者を解析。

対象期間中の2330人年において、38人に血栓症を発症（5.1%）。

ここから、血栓症発症率は16.3/1000人年と計算される。

静脈血栓が18人（DVT 15人、その他3人）、

動脈血栓症が20人（脳梗塞13人、心筋梗塞3人、指壊疽2人、  
その他5人）

Figure 1 HCQ投与量と血中濃度は無関係

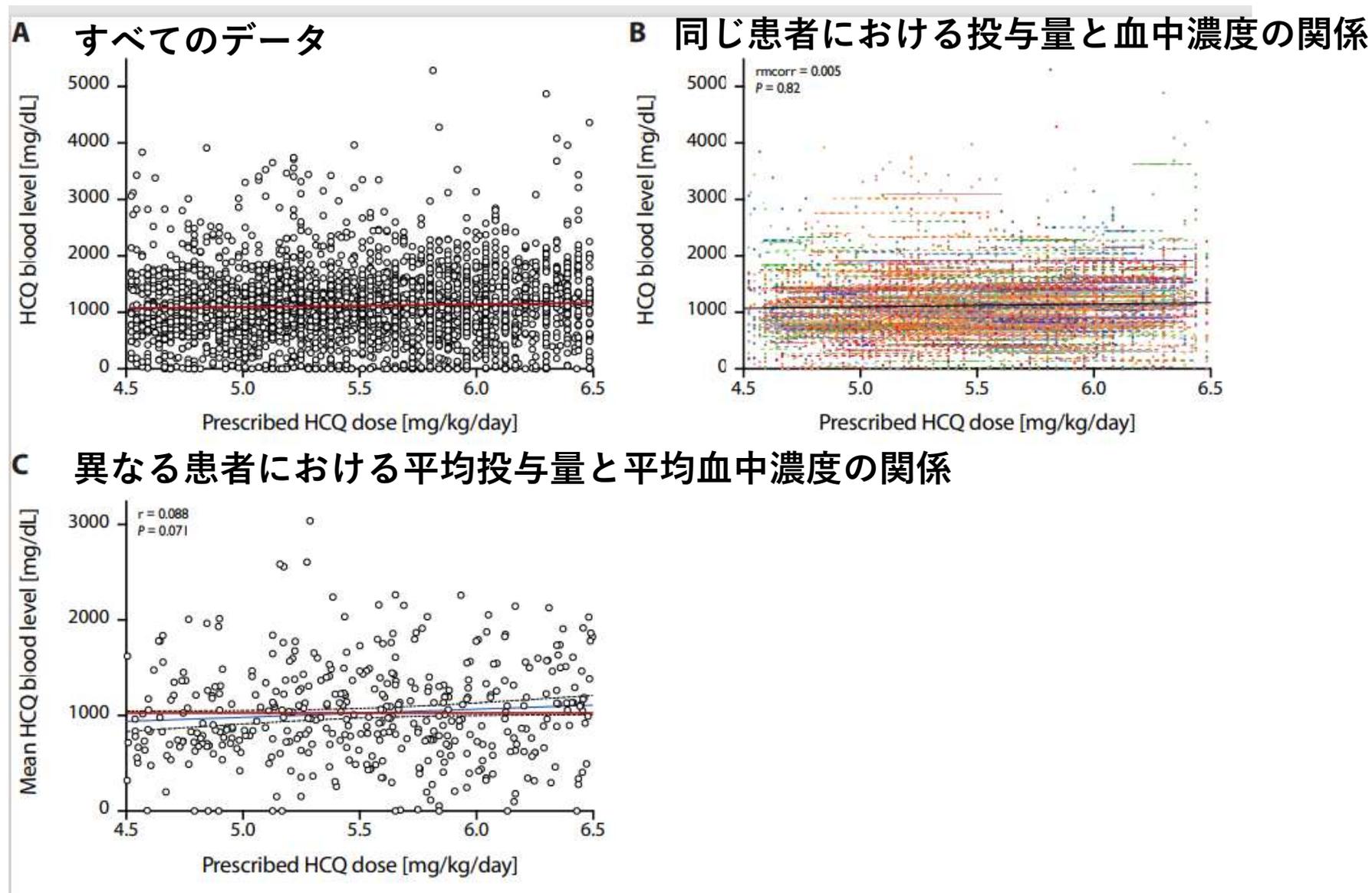


Table 1 – Association of Clinical Factors with Thrombosis

Subgroup	Observed No. of TEs	Person- years of follow up	Rate of events per 1000 person- years	Rate ratio	p- value
<b>All</b>	38	2330	16.3		
<b>Age at first HCQ</b>					
<40	17	990	17.2	1.00 (ref)	
40-49	9	488	18.4	1.07 (0.48, 2.41)	0.86
50-59	9	489	18.4	1.07 (0.48, 2.41)	0.87
>=60	3	363	8.3	0.48 (0.14, 1.64)	0.24
<b>Sex</b>					
Male	2	174	11.5	1.00 (ref)	
Female	36	2156	16.7	1.45 (0.35, 6.03)	0.61
<b>Ethnicity</b>					
Caucasian	11	1096	10.0	1.00 (ref)	
African American	23	998	23.0	2.3 (1.12, 4.72)	0.02
Other	4	236	17.0	1.69 (0.54, 5.32)	0.37
<b>Smoking</b>					
Never	24	1616	14.9	1.00 (ref)	
Ever	14	712	19.7	1.33 (0.69, 2.56)	0.40
<b>BMI</b>					
<20	3	193	15.5	1.96 (0.49, 7.84)	0.34
20-25	6	757	7.9	1.00 (ref)	
25-30	14	668	20.9	2.64 (1.02, 6.89)	0.046
>=30	15	710	21.1	2.67 (1.03, 6.87)	0.042

# 血栓症と関連する臨床因子の検索

➡ 黒人, low C3, HTNが血栓症と関連

## History of RVVT

No	27	1831	14.7	1.00 (ref)	
Yes	11	494	22.3	1.51 (0.75, 3.05)	0.25

## History of low C3

No	9	1013	8.9	1.00 (ref)	
Yes	29	1317	22.0	2.48 (1.17, 5.24)	0.017

## History of hypertension

No	11	1136	9.7	1.00 (ref)	
Yes	27	1194	22.6	2.34 (1.16, 4.72)	0.018

## History of hyperlipidemia

No	17	1229	13.8	1.00 (ref)	
Yes	21	1096	19.2	1.39 (0.73, 2.63)	0.32

RVVT:ラッセル蛇毒時間 (=LAC)

# 血栓群 vs 非血栓群におけるHCQ平均血中濃度の差

**Table 2 – Association of Thrombotic Events with Mean Hydroxychloroquine Whole Blood Level**

	Mean HCQ blood levels		
	Thrombotic event	No event	<i>p</i> -value
<b>Any thrombosis</b>	720±489	935±580	0.0247
<b>Any Venous</b>	688±389	931±580	0.0747
DVT/PE	623±399	931±578	0.0406
<b>Any arterial</b>	751±566	929±577	0.1735
Stroke	764±674	927±575	0.3113

DVT: Deep venous thrombosis; PE: pulmonary embolism

# HCQ血中濃度高値群 vs 低値群での血栓症発症率の差

**Table 3 – Event Rates, Unadjusted and Adjusted Rate Ratios for Thrombosis by Tertiles of Mean and Most Recent Hydroxychloroquine Whole Blood Level.** HCQ blood levels are measured in ng/mL. The *P* value for trend was *p*=0.0170 for most recent HCQ blood level and *p*=0.0062 for mean HCQ blood level.

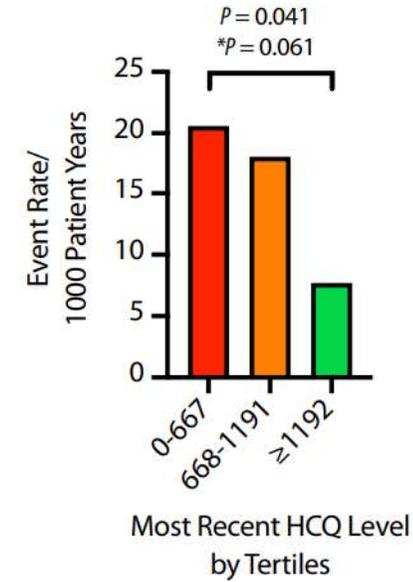
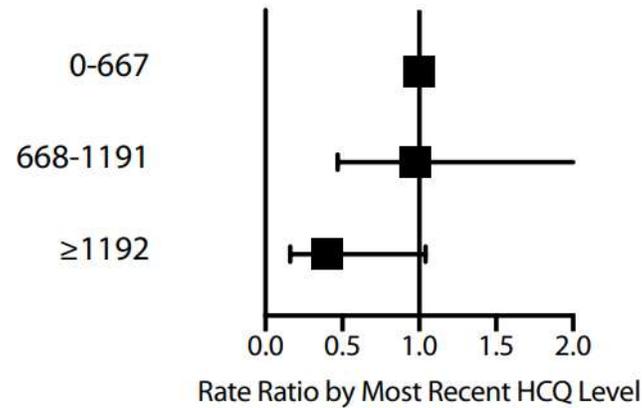
Subgroup	Observed No. of TEs	Person- years of follow up	Rate of events per 1000 pys	Rate ratio	<i>p</i> - value	Rate ratio adjusted for age, ethnicity, LAC	<i>p</i> -value adjusted
<b>All</b>	36	2326	15.5				
<b>Most recent HCQ blood level tertiles</b>							
0-667	16	776	20.6	1.00 (ref)		1.00 (ref)	
668-1191	14	775	18.1	0.88 (0.43, 1.8)	0.7196	0.97 (0.47, 2.01)	0.94
≥1192	6	775	7.7	0.38 (0.15, 0.96)	0.0408	0.4 (0.16, 1.04)	0.061
<b>Mean HCQ blood level tertiles</b>							
0-648	16	777	20.6	1.00 (ref)		1.00 (ref)	
648-1068	15	776	19.3	0.94 (0.46, 1.9)	0.8595	1.05 (0.52, 2.14)	0.89
≥1068	5	773	6.5	0.31 (0.11, 0.86)	0.0237	0.34 (0.12, 0.94)	0.037

Pys: person years

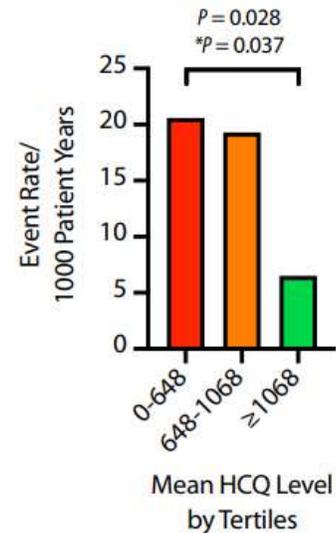
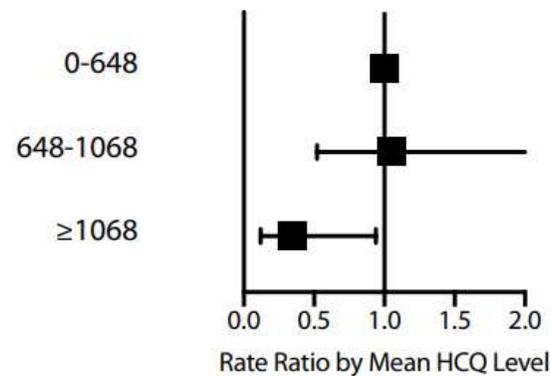
# Figure 2 HCQ血中濃度による血栓症リスク比

A

Table 3をグラフにしただけ



B



# HCQ血中濃度上昇による血栓症低下のリスク比

Table 4 – Rate Ratios for Risk of Prospective Thrombotic Events Based on Hydroxychloroquine Whole Blood Levels

	RR (95% CI)	<i>p</i> -value	Adjusted RR (95% CI) <sup>1</sup>	Adjusted <i>p</i> -value <sup>1</sup>	Adjusted RR (95% CI) <sup>2</sup>	Adjusted <i>p</i> -value <sup>2</sup>
<b>Mean HCQ blood level</b> (per 200 ng/ml increase)	0.86 (0.75, 0.99)	0.030	0.87 (0.76, 1.00)	0.051	0.87 (0.76, 1.00)	0.056
<b>Most recent HCQ blood level</b> (per 200 ng/ml increase)	0.86 (0.77, 0.97)	0.013	0.87 (0.78, 0.98)	0.023	0.87 (0.78, 0.98)	0.025

<sup>1</sup> Adjusted for age, ethnicity, and LAC

<sup>2</sup> Adjusted for age, ethnicity, LAC, C3, and HTN

RR: Rate ratio; LAC: lupus anticoagulant; C3: complement component C3; HTN: arterial hypertension

# Discussion

- HCQ 5mg/kgが推奨されているが、血中濃度でリスクアセスメントを行うのが理想的だ。
- HCQ血中濃度と血栓症リスク低下が示されたが、血栓症発症直前のHCQ血中濃度が平均血中濃度よりもより血栓症と関連したことは重要
- 同様の報告としてCostedoat-ChalumeauらはFlareしたSLE患者ではHCQ血中濃度が低かったと報告し、ROC解析から1000ng/mLが治療のTargetとしている
- HCQ全血濃度は血漿や血清中のHCQ濃度よりも、HCQ内服状況をしめし（参考文献引用なし）、内服アドヒアランスを反映。

# Limitation

- このモデルに含めていない未知の交絡因子の存在の可能性
- 1施設、1リウマチ専門医のスタディであり、血栓症イベントの数が少ないこと

# Conclusion

HCQ 5mg/kgへの減量はHCQの血栓症リスク低下のbenefitを損なう可能性があり、HCQ血中濃度1068 ng/mlを目標にしつつ網膜症と関連すると自分たちが以前証明したHCQ高値3分の1を避けることは可能だと考える

この論文の問題点は何だと思いますか？

私のClinical Question

HCQは本当にSLE血栓症の発症頻度を下げるのか？

# まずはIntroductionで引用された文献を検証

Multiple retrospective and a few prospective studies (3–13) have found that hydroxychloroquine (HCQ) reduces the risk of arterial and venous thrombosis.

3. Wallace DJ. *Arthritis Rheum* 1987;30:1435–1436.
4. Ho KT, Ahn CW, Alarcón GS, Baethge BA, Tan FK, Roseman J, et al. *Rheumatology* 2005;44:1303–1307.
5. Petri M, Lakatta C, Magder L, Goldman D. *Am J Med* 1994;96:254–9.
6. Kaiser R, Cleveland CM, Criswell LA. *Ann Rheum Dis* 2009;68:238–241.
7. Jung H, Bobba R, Su J, Shariati-Sarabi Z, Gladman DD, Urowitz M, et al. *Arthritis Rheum* 2010;62:863–868.
8. Hsu C-Y, Lin Y-S, Su Y-J, Lin H-F, Lin M-S, Syu Y-J, et al. *Rheumatology (Oxford)* 2017;56:2212–2221.
9. Tektonidou MG, Laskari K, Panagiotakos DB, Moutsopoulos HM. *Arthritis Rheum* 2009;61:29–36.
10. Erkan D, Yazici Y, Peterson MG, Sammaritano L, Lockshin MD. *Rheumatology (Oxford)* 2002;41:924–9.
11. Sisó A, Ramos-Casals M, Bové A, Brito-Zerón P, Soria N, Muñoz S, et al. *Lupus* 2008;17:281–8.
12. Petri M. *Scand J Rheumatol* 1996;25:191–3.
13. Petri M. *Curr Rheumatol Rep* 2011;13:77–80.

10. Erkan D, Yazici Y, Peterson MG, Sammaritano L, Lockshin MD. A cross-sectional study of clinical thrombotic risk factors and preventive treatments in antiphospholipid syndrome. *Rheumatology (Oxford)* 2002;41:924–9.

A群: 77人のAPS (血栓症+) vs B群: 56人の抗PL抗体(+) 血栓症(-)患者  
 血栓症発症前半年間 (A群) と最終診察前半年間 (B群) の背景を比較

(参考)

TABLE 2. Patients with additional thrombotic risk factors

Risk factor	Group A (%)	Group B (%)	P
Hypertension	14	20	0.4
Diabetes mellitus	0	5	0.07
Hypercholesterolaemia	5	7	0.4
Smoking	30	16	0.07
OC/HRT use	20 <sup>a</sup>	10*	0.12
Surgery	18	5	0.04
Pregnancy	14 <sup>a</sup>	0	0.005
Malignancy	1	2	1
Infection	14	16	0.8
Thrombocytopenia	17	5	0.06

<sup>a</sup>Percentage of female patients.

TABLE 6. Possible trigger factors for thrombosis

Age (yr)	Medical history	Event	Possible trigger factor	Other risk factors
16	n.s.	Stroke	Illicit drug use: marijuana	No
18	n.s.	Jugular vein thrombosis	Illicit drug use: ecstasy	Infection
37	n.s.	Stroke	'Long shift, high stress'	No
43	n.s.	DVT	'Long auto trip'	No
46	n.s.	DVT/PE	'Long auto trip'	No
49	SLE	Stroke	Blood transfusion	Smoking
52	n.s.	Stroke	Mother's death, 'stress'	Infection

n.s., not significant; PE, pulmonary embolism.

これだけの  
 リスク因子  
 を検討して  
 いる点は好  
 ましい

アスピリン内服とHCQ内服がB群に多かったが、妊娠、手術がA群に多かった (文章のみ)

Logistic解析でアスピリン **and/or** HCQは血栓抑制因子と記載があるが、結果のデータが載っていない

血栓リスク因子をしっかり挙げているが、HCQが独立した因子なのかデータから読み取れない

4. Ho KT, Ahn CW, Alarcón GS, Baethge BA, Tan FK, Roseman J, et al. Systemic lupus erythematosus in a multiethnic cohort (LUMINA): XXVIII. Factors predictive of thrombotic events. *Rheumatology* 2005;44:1303–1307.

LUMINAコホート442名のSLE患者で血栓症の有無を抗リン脂質抗体、HCQに絞って関連を解析

### 単変量解析

TABLE 1. Relationship between socioeconomic and clinical variables and thrombosis by univariable analyses among LUMINA patients

Variable	OR	95% CI	P <sup>a</sup>
Age (yr)	1.010	0.089–1.030	NS
Gender (% women)	0.756	0.279–2.048	NS
Ethnicity (%)			
Hispanic, Texas	0.997	0.509–1.952	NS
Hispanic, Puerto Rico	1.419	0.436–4.613	NS
African-American	1.382	0.715–2.672	NS
Caucasian	0.692	0.328–1.460	NS
Smoking	2.642	1.248–5.593	0.0112
Disease duration (months): mean (s.d.)	0.980	0.955–1.005	NS
Disease manifestations (%)			
Mucocutaneous	2.482	1.199–5.136	0.0143
Articular	1.554	0.664–3.639	NS
Serosal	3.423	1.938–6.047	<0.0001
Renal	1.564	0.872–2.803	NS
Neuropsychiatric	1.394	0.725–2.680	NS
SLAM <sup>b</sup> score: mean (s.d.)	1.112	1.068–1.158	<0.0001
SDI score <sup>c</sup> : mean (s.d.)	1.271	1.134–1.425	<0.0001
Cholesterol: mean (s.d.)	1.002	0.996–1.009	NS
High sensitivity-CRP: mean (s.d.)	1.004	0.999–1.010	NS
aPL <sup>d</sup> positivity (%)	0.747	0.408–1.368	NS
Anti-oxLDL <sup>e</sup> IgG: mean (s.d.)	0.999	0.997–1.003	NS
Anti-oxLDL <sup>e</sup> IgM: mean (s.d.)	1.001	0.998–1.005	NS
Hydroxychloroquine use (%)	0.536	0.304–0.946	0.0314
Glucocorticoid use (%)	2.016	1.044–3.891	0.0368
Azathioprine use (%)	2.070	0.968–4.422	0.0606

### 多変量解析

TABLE 2. Variables predictive of thrombotic events among LUMINA patients by generalized estimating equation analyses

Variable	OR*	95% CI <sup>†</sup>	P <sup>‡</sup>
Smoking	2.777	1.317–5.852	0.0073
SLAM score	1.099	1.053–1.147	<0.0001

\*Odds ratio; <sup>†</sup>Confidence interval.

<sup>‡</sup>Only variables with  $P \leq 0.05$  are shown.

単変量ではHCQ useが血栓低下と関連したが、  
多変量ではsmokingと疾患活動性のみが血栓と関連

抗リン脂質抗体もHCQも血栓とは関連ないという結果

11. Sisó A, Ramos-Casals M, Bové A, Brito-Zerón P, Soria N, Muñoz S, et al. Previous antimalarial therapy in patients diagnosed with lupus nephritis: influence on outcomes and survival. *Lupus* 2008;17:281–8.

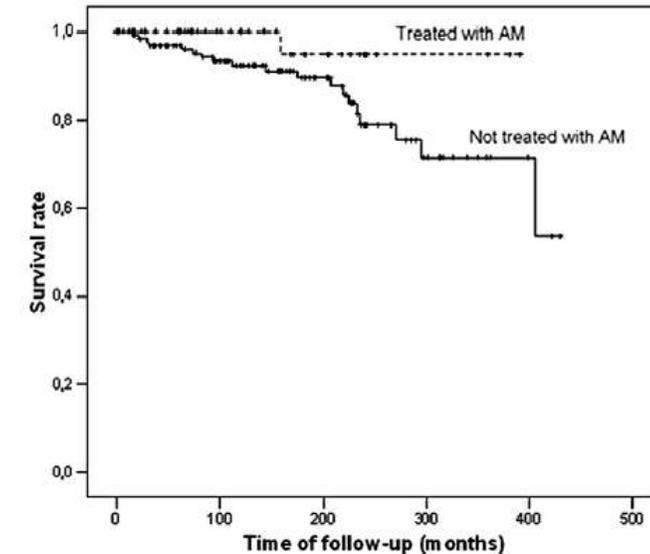
206名のループス腎炎(LN)患者でLN診断前にHCQをのんでいた56名 (27%)とのんでいなかった患者の腎症、死亡率、感染症、血栓症などをf/uした。

**Table 1** Baseline characteristics at diagnosis of lupus nephritis of patients treated or not with antimalarials

	<i>Antimalarial exposure before the diagnosis of LN</i>		<i>Univariate analysis</i>
	<i>No (n = 150)</i>	<i>Yes (n = 56)</i>	
<b>Epidemiologic features</b>			
Sex (female)	133 (89%)	52 (93%)	0.45
Age at SLE diagnosis (years)	29.03 ± 1.05	30.71 ± 1.05	0.932
Age at LN diagnosis (years)	28.86 ± 1.61	32.84 ± 1.65	0.289
Length of SLE evolution (months)	28.98 ± 0.88	31.29 ± 0.89	0.001
Previous treatment with corticosteroids	87 (58%)	18 (32%)	0.001*
Previous treatment with immunosuppressant	8 (5%)	1 (2%)	0.449
<b>Renal features</b>			
Raised creatinine	35 (23%)	6 (11%)	0.050
Mesangial glomerulonephritis	31 (21%)	12 (21%)	
Proliferative glomerulonephritis	95 (65%)	34 (61%)	0.803
Membranous glomerulonephritis	21 (14%)	10 (18%)	
<b>Immunological features</b>			
Antinuclear antibodies	136 (91%)	52/53 (98%)	0.120
Anti-dsDNA antibodies (>20 UI/L)	98/149 (66%)	41/53 (77%)	0.125
Anti-Sm antibodies	17/144 (12%)	6/52 (11%)	1.000
Anti-Ro/SS-A antibodies	38/144 (26%)	20/52 (38%)	0.113
Anti-La/SS-B antibodies	16/144 (11%)	7/52 (13%)	0.623
Rheumatoid factor	13/98 (13%)	6/38 (16%)	0.784
Low C3 levels	68/147 (46%)	30/53 (57%)	0.205
Low C4 levels	49/147 (33%)	25/53 (47%)	0.097
Lupus anticoagulant	26/144 (18%)	4/54 (7%)	0.076
IgG-aCL	33/144 (23%)	14/54 (26%)	0.709
IgM-aCL	16/144 (11%)	3/54 (6%)	0.290
<b>LN induction therapy</b>			
Oral prednisone 1 mg/kg	128 (85%)	46 (82%)	0.666
Intravenous cyclophosphamide	39 (26%)	19 (34%)	0.297

Abbreviations: LN: lupus nephritis; SLE: systemic lupus erythematosus; dsDNA: double stranded DNA.

\*Statistically significant in multivariate analysis.



HCQ(+)SLE患者は明らかに軽症であり、HCQ(-)SLEと比較すること自体がナンセンス。論外の内容である。

6. Kaiser R, Cleveland CM, Criswell LA. Risk and protective factors for thrombosis in systemic lupus erythematosus: results from a large, multi-ethnic cohort. *Ann Rheum Dis* 2009;68:238–241.

1930人のUCSF SLEコホート。血栓症のリスク因子を多変量解析。

**Table 3** Factors associated with one or more thrombosis events in multivariate analyses

Explanatory variable	≥1 Thrombosis OR (95% CI)	p Value	≥2 Thromboses OR (95% CI)	p Value	Test for trend p value
Female gender	–	–	–	–	–
Ethnicity	–	–	–	–	–
Ever smoker	1.26 (1.07 to 1.82)	0.011	1.90 (1.23 to 2.91)	0.004	0.012
History of nephritis*	1.35 (1.02 to 1.78)	0.036	1.65 (1.04 to 2.60)	0.033	0.000
Immunomodulator therapy†	1.40 (1.08 to 1.82)	0.011	1.95 (1.18 to 3.21)	0.009	0.000
Prednisone treatment	–	–	–	–	–
Hydroxychloroquine treatment	0.67 (0.50 to 0.90)	0.008	–	–	–
NSAID treatment	–	–	–	–	–
Age at SLE diagnosis					
≤ 20	0.52 (0.35 to 0.78)	0.001	–	–	–
>20–≤ 40	0.72 (0.54 to 0.97)	0.031	–	–	–
> 40	–	–	–	–	–
Disease duration (per 5 years)	1.26 (1.17 to 1.35)	0.027 × 10 <sup>-7</sup>	1.27 (1.12 to 1.43)	0.020 × 10 <sup>-2</sup>	n/a
aPL‡	3.22 (2.49 to 4.16)	< 10 <sup>-9</sup>	5.05 (3.28 to 7.78)	0.020 × 10 <sup>-11</sup>	0.000

ACL, anti-cardiolipin; aPL, antiphospholipid antibodies; LAC, lupus anticoagulant; NSAID, non-steroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus.

\*Nephritis was defined as meeting ACR renal criterion, confirmed by review of medical records and/or renal biopsy consistent with lupus nephritis.

†Cyclophosphamide, azathioprine, methotrexate, ciclosporin, mycophenolate mofetil, or chlorambucil. All medications were analysed as “ever” versus “never use”.

‡aPL (ACL IgM or IgG or LAC (measured by Russell Viper Venom Time with confirmatory and mixing studies), positive at least once documented in records).

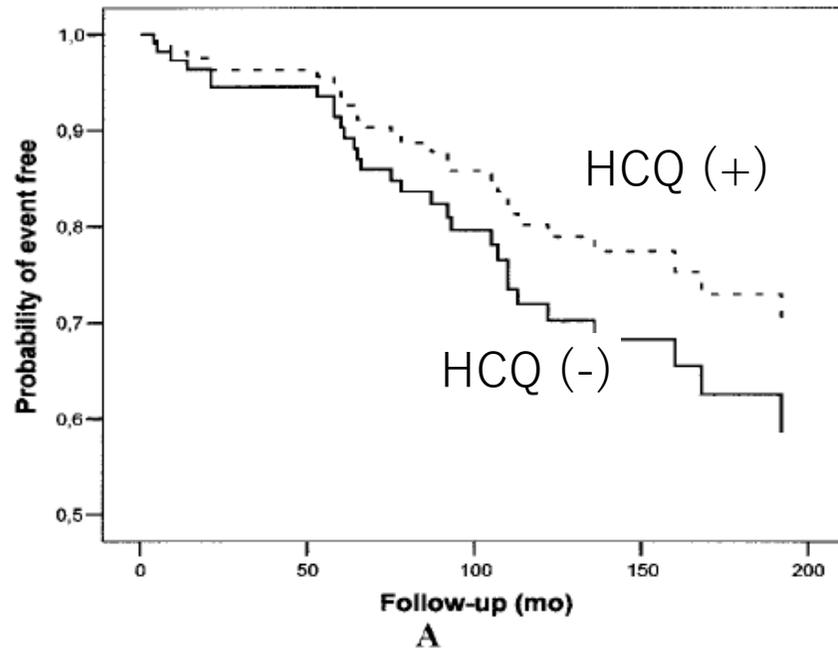
1930人のUCSF SLEコホート。血栓症のリスク因子を多変量解析。HCQを含む多くの因子が血栓症と関連。

信頼性が高そうなデータではあるが、HCQが80%の患者に入っているのに、逆に入っていない患者がどんな患者なのか気になる。

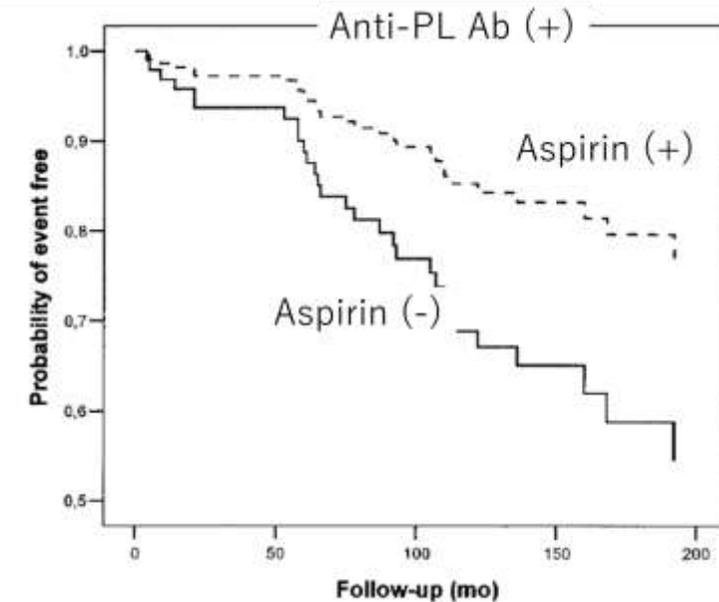
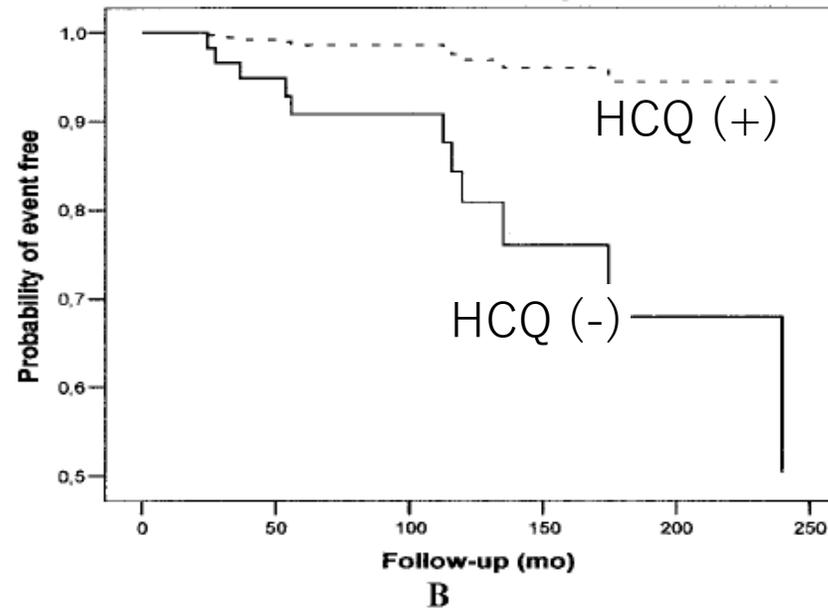
9. Tektonidou MG, Laskari K, Panagiotakos DB, Moutsopoulos HM. Risk factors for thrombosis and primary thrombosis prevention in patients with systemic lupus erythematosus with or without antiphospholipid antibodies. *Arthritis Rheum* 2009;61:29–36.

ギリシャのコホート。aPL Ab(+) SLE 144例と age, sex-matched aPL Ab(-) SLE144例。  
中央値約10年間のf/uで血栓症とHCQ, アスピリンの関連を検討

Anti-PL Ab (+)



Anti-PL Ab (-)



単変量解析でHCQはaPL Ab(-)では有意に血栓低下させるが、aPL Ab(+)では明らかではない。  
アスピリンによる血栓予防効果の方が強く、アスピリンによる交絡の可能性も。

7. Jung H, Bobba R, Su J, Shariati-Sarabi Z, Gladman DD, Urowitz M, et al. The protective effect of antimalarial drugs on thrombovascular events in systemic lupus erythematosus. *Arthritis Rheum* 2010;62:863–868.

トロントSLEコホート。血栓症(+)群54人と罹患時期、罹患期間、観察期間、重症度を調整した血栓症(-)群108人

**Table 2.** Univariate analysis for the risk factors associated with thrombovascular events during the 2-year followup in patients with systemic lupus erythematosus\*

Variable	Cases (n = 54)	Controls (n = 108)	Odds ratio (95% CI)	P
Ever user of antimalarial drugs	17 (32)	57 (53)	0.31 (0.13–0.71)	<0.01
Age >50 years	22 (41)	25 (23)	3.45 (1.39–8.59)	<0.01
Age, mean ± SD years	45.6 ± 14.6	40.2 ± 14.2	1.04 (1.01–1.07)	0.01
Female sex	43 (80)	93 (86)	0.62 (0.26–1.49)	0.28
aCL titer ever ≥40 PL units	15 (35)	22 (24)	1.52 (0.64–3.63)	0.34
Ever smoked	16 (30)	19 (18)	1.97 (0.91–4.28)	0.09
Ever had diabetes mellitus	4 (7)	5 (5)	1.71 (0.42–7.05)	0.46
Ever had hypertension	27 (50)	38 (35)	2.45 (1.04–5.75)	0.04
Cholesterol level at start of followup, mean ± SD mmol/liter	5.4 ± 1.4	5.2 ± 1.5	1.10 (0.87–1.38)	0.44
Ever user of prednisone	39 (72)	72 (67)	1.41 (0.62–3.21)	0.42
Ever user of immunosuppressive drugs	21 (39)	38 (36)	1.21 (0.58–2.50)	0.62

\* Except where indicated otherwise, values are the number (%) of patients. 95% CI = 95% confidence interval; aCL = anticardiolipin antibody; PL units = IgG or IgM phospholipid units.

単変量でも多変量でもHCQは血栓症の頻度を下げる

**Table 3.** Risk factors identified by multivariate analysis as showing a significant association with thrombovascular events during the 2-year followup in patients with systemic lupus erythematosus\*

Variable	Odds ratio (95% CI)	P
Ever use of antimalarial drugs	0.32 (0.14–0.74)	<0.01
Older age	1.04 (1.01–1.07)	0.02

\* 95% CI = 95% confidence interval.

信頼性は高そうなスタディではあるが、血栓リスクにaPL Abが入らないことや抗血小板、抗凝固薬使用は考慮されていない点などは難点か。

8. Hsu C-Y, Lin Y-S, Su Y-J, Lin H-F, Lin M-S, Syu Y-J, et al. Effect of long-term hydroxychloroquine on vascular events in patients with systemic lupus erythematosus: a database prospective cohort study.

台湾のNational Health Insurance Research Databaseを用いた解析。  
 新規発症SLE患者で最初の1年間にHCQ処方者が8割以上処方された患者（6011人）と全く処方されなかった患者（2386人）においてpropensity-matchした1946人ずつの血栓症の頻度を平均7.4年間前向きに追った。

TABLE 1 Characteristics of the study patients before and after propensity score matching

Variable	Before matching			After matching		
	HCQ (n=6011)	Control (n=2386)	P-value	HCQ (n=1946)	Control (n=1946)	P-value
Characteristic						
Age at SLE diagnosis, mean (s.d.), years	35.7 (16.0)	35.6 (17.0)	0.755	35.3 (17.0)	35.6 (17.0)	0.613
Age group, mean (s.d.), n (%)			<0.001			0.804
<18 years	715 (11.9)	417 (17.5)		339 (17.4)	325 (16.7)	
18-49 years	4172 (69.4)	1483 (62.2)		1215 (62.4)	1228 (63.1)	
≥50 years	1124 (18.7)	486 (20.4)		392 (20.1)	393 (20.2)	
Female gender, n (%)	5317 (88.5)	2091 (87.6)	0.294	1702 (87.5)	1702 (87.5)	1.000
Comorbidity, n (%)						
Hypertension	645 (10.7)	357 (15.0)	<0.001	260 (13.4)	275 (14.1)	0.520
Diabetes mellitus	185 (3.1)	93 (3.9)	0.058	77 (4.0)	74 (3.8)	0.870
Dyslipidaemia	265 (4.4)	158 (6.6)	<0.001	116 (6.0)	120 (6.2)	0.838
Gout	240 (4.0)	75 (3.1)	0.065	66 (3.4)	69 (3.5)	0.860
Chronic kidney disease	858 (14.3)	687 (28.8)	<0.001	515 (26.5)	501 (25.7)	0.607
Coronary artery disease	179 (3.0)	69 (2.9)	0.834	59 (3.0)	61 (3.1)	0.925
Malignancy	69 (1.1)	33 (1.4)	0.375	23 (1.2)	25 (1.3)	0.885
Medication, n (%)						
Arthrosclerosis medication						
Aspirin	1095 (18.2)	215 (9.0)	<0.001	200 (10.3)	205 (10.5)	0.826
Statin	252 (4.2)	238 (10.0)	<0.001	170 (8.7)	170 (8.7)	1.000
Warfarin	120 (2.0)	35 (1.5)	0.104	36 (1.8)	32 (1.6)	0.708
NSAID	3860 (64.2)	1252 (52.5)	<0.001	1081 (55.5)	1079 (55.4)	0.974
Immunosuppressant						
Systemic glucocorticoids	5563 (92.5)	1747 (73.2)	<0.001	1604 (82.4)	1616 (83.0)	0.577
AZA	2062 (34.3)	558 (23.4)	<0.001	524 (26.9)	525 (27.0)	1.000
CYC	564 (9.4)	270 (11.3)	<0.001	233 (12.0)	231 (11.9)	0.960
MTX	323 (5.4)	62 (2.6)	<0.001	66 (3.4)	61 (3.1)	0.721
Overlapping immune diseases, n (%)						
SS	1237 (20.6)	131 (5.5)	<0.001	141 (7.2)	131 (6.7)	0.495
RA	630 (10.5)	129 (5.4)	<0.001	127 (6.5)	122 (6.3)	0.792
Number of admissions due to SLE, mean (s.d.)	0.6 (1.2)	0.8 (1.8)	<0.001	0.7 (1.5)	0.7 (1.5)	0.866
Follow-up, mean (s.d.), years	6.6 (3.5)	7.6 (3.6)	<0.001	7.4 (3.5)	7.3 (3.6)	0.249

HCQ(+)で血栓症139人（7.1%）、HCQ(-)で149人（7.7%）。  
 有意差なし。

HCQのSLEにおける血栓症の予防効果をみた最大の  
 コホート研究。  
 詳細な交絡因子を調整したのち、HCQによる血栓症  
 予防効果なしと結論。

難点は健康保険データベースの解析であり、登録  
 された合併症などが正確かどうか。

## 結 論

以上からHCQの血栓症予防効果に関しては弱いエビデンスが多数あるが、少なくとも明らかな有効性エビデンスはないといえる。  
もしかすると高容量HCQでしか有効性はないのかもしれない。