

Impact of the new American College of Cardiology/ American Heart Association definition of hypertension on atherosclerotic vascular events in systemic lupus erythematosus

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ABSTRACT

Background The 2017 American College of Cardiology/American Heart Association guidelines defined hypertension at $\geq 130/80$ mm Hg. Studies on patients with connective tissue diseases were not considered. Our aim was to assess the impact of this definition on atherosclerotic vascular events (AVEs) in systemic lupus erythematosus.

Patients methods Individuals from the Toronto Lupus Clinic with at least 2 years of follow-up and no prior AVE were divided in three groups according to their mean blood pressure (BP) over that period ($\geq 140/90$ mm Hg, 130–139/80–89 mm Hg and $< 130/80$ mm Hg). They were followed until the first occurrence of an AVE (fatal or non-fatal coronary artery disease, cerebrovascular event and peripheral vascular disease) or last visit. Groups were compared as per the baseline atherosclerotic risk factors. A multivariable time-dependent analysis was performed to adjust for the presence of other risk factors.

Results Of 1532 patients satisfying the inclusion criteria, 155 (10.1%) had a BP $\geq 140/90$ mm Hg, 316 (20.6%) 130–139/80–89 mm Hg and 1061 (69.3%) were normotensives. After a mean follow-up of 10.8 years, 124 AVEs were documented. The incidence rates were 18.9, 11.5 and 4.5 per 1000 patient-years for the three groups, respectively ($p=0.0007$ between the 130–139/80–89 mm Hg group and the normotensives). A mean BP of 130–139/80–89 mm Hg over the first 2 years was independently associated with the occurrence of AVEs (HR 1.73, 95% CI 1.13 to 2.65, $p=0.011$).

Conclusion Patients with lupus with a sustained mean BP of 130–139/80–89 mm Hg over 2 years had a significantly higher incidence of AVEs compared with normotensive individuals. This BP level should be the target for antihypertensive therapy to minimise their cardiovascular risk.

INTRODUCTION

The recently published guidelines for the management of arterial hypertension in adults by the American College of Cardiology/American Heart Association (ACC/AHA) recommended a significantly lower threshold of systolic and diastolic blood pressure (SBP, DBP) for diagnosis.¹ The levels of 130–139 mm Hg for SBP and 80–89 mm Hg for DBP are now considered as stage 1 hypertension, in contrast to the previous recommendations in which hypertension was defined as BP $\geq 140/90$ mm Hg.²

Key messages

What is already known about this subject?

► The new guidelines for arterial hypertension from the American College of Cardiology/ American Heart Association define hypertension at a level of 130/80 mm Hg. However, studies in patients with systemic autoimmune diseases were not considered and recommendations were not made for such patients.

What does this study add?

► This observational longitudinal study of 1532 patients with systemic lupus erythematosus, followed by 10.8 years on average, showed that an adjusted mean blood pressure (BP) level of 130–139/80–89 mm Hg over the first 2 years of observation is associated with a 2.5-fold increase in the risk of atherosclerotic cardiovascular events (AVEs) compared with normotensive ($< 130/80$ mm Hg) patients with lupus. This level of BP conferred a 73% increased risk for AVEs after adjustment for all traditional and disease-related atherosclerotic risk factors.

How might this impact on clinical practice or future developments?

► These findings support that the target level of BP should be $< 130/80$ mm Hg for all patients with lupus.

According to the same guidelines, pharmacologic treatment should be offered in all individuals with stage 1 hypertension and a 10-year cardiovascular (CV) risk $\geq 10\%$ (as calculated by the Atherosclerotic Cardiovascular Disease (ASCVD) risk estimator), regardless of age.¹ Despite the fact that an entire section was devoted on special patient groups and certain comorbidities, no recommendations were made for patients with connective tissue diseases such as systemic lupus erythematosus (SLE).

Hypertension is detected in up to 74% of patients with lupus and is one of the strongest predictors for accelerated atherosclerosis and atherosclerotic vascular events (AVEs).^{3,4} Patients with lupus have a fivefold increased lifetime risk for AVEs, while the relative risk is even higher in premenopausal

women.^{5,6} Therefore, proper management of hypertension is of paramount importance in SLE. However, on the basis of the recent guidelines, the patient with typical lupus (young female with no traditional atherosclerotic risk factors) would be considered as a low-risk individual⁷ and not offered treatment for a BP of 130–139/80–89 mm Hg. Moreover, CV risk calculation is problematic in SLE, primarily because the available risk scores do not take into account the disease itself and most are designed for patients older than 40 years. Although there are no studies that used the ASCVD risk estimator⁷ in patients with lupus, other risk scores, such as the modified 10-year Framingham Risk Score indicate that the classic risk scores significantly underestimate CV risk.⁸

As such, the management of hypertension in lupus may be delayed, particularly at the levels of 130–139/80–89 mm Hg. The aim of the present study was to assess whether the new definition of hypertension is predictive for AVEs in patients with lupus and, specifically investigate if the BP threshold of 130–139/80–89 mm Hg carries an excessive CV risk in SLE.

Patients and methods

The University of Toronto Lupus Clinic (UTLC) has currently enrolled 2008 patients since its establishment in 1970. All patients fulfilled the revised American College of Rheumatology criteria for SLE classification⁹ or had three criteria and a supportive biopsy. Patients are followed regularly at 2–6 months intervals according to a standardised research protocol, which is regularly updated. This protocol captures demographic, clinical, immunological and therapeutic variables as well as most comorbidities. Concerning hypertension, the protocol captures the actual BP (SBP/DBP) during the clinic visit (mean of two measurements in the sitting position with an aneroid sphygmomanometer after a 5 min rest) as well as the current pharmacological treatment, including all major classes of the antihypertensive drugs (diuretics, ACE inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, calcium channel blockers, centrally acting agents and others). All individuals have provided written informed consent for studies being conducted at the UTLC.

For the purpose of the present study, included patients should have had at least 2 years of follow-up after enrolment in the UTLC and at least one additional clinic visit after that 2-year period. Patients with less than 2 years of follow-up or with an AVE at any time prior to the 2 years time point (baseline) were excluded. Given that the levels of BP may fluctuate significantly over time in SLE and that BP measurements at one point in time are unreliable for the prediction of long-term outcomes,¹⁰ the adjusted mean BP was calculated for all eligible patients. This considered all BP measurements (regardless of treatment) that a patient had had in the first 2 years of follow-up and the time spent with each BP (time from visit to visit), assuming that this would remain practically unaltered between clinic visits. The mathematical equation used was

$$\frac{\sum_{i=2}^n \left(\frac{x_i + x_{i-1}}{2} - 1 \right) t_i}{\sum_{i=2}^n t_i}$$

where x_i is the level of the variable (SBP or DBP) at visit i , and t_i is the time interval between visit i and $i-1$. By incorporating the time interval between measurements in its calculation, the adjusted mean BP considers the length of time that SBP and DBP are presumed to have remained at a particular level.

Patients were then categorised in three different groups according to their adjusted mean BP, as follows:

1. Group 1: patients with an adjusted mean BP <130/80 mm Hg (normotensives).
2. Group 2: patients with an adjusted mean BP 130–139/80–89 mm Hg (stage 1 hypertension).
3. Group 3: patients with an adjusted mean BP \geq 140/90 mm Hg (stage 2 hypertension).

In cases where the SBP and DBP would classify a given patient in a different group, the individual was categorised in the group with the higher BP (eg, a patient with a BP of 125/85 mm Hg was classified in group 2). Hypertension was defined regardless of use of antihypertensive therapy. The baseline was defined as the 2-year time point since enrolment to the UTLC. All individuals were followed until the occurrence of an AVE or the last visit. AVEs were defined as new-onset angina, myocardial infarction (MI), revascularisation procedures (percutaneous transluminal coronary angioplasty or coronary artery by-pass graft), congestive heart failure (CHF) of ischaemic origin, peripheral vascular disease (PVD) requiring angioplasty, transient ischaemic attack (TIA), stroke and CV deaths (fatal MI or stroke).

The three groups of patients were compared at baseline as per the variables that have been reported to increase the risk for AVEs according to a recent systematic review.⁴ These included demographic (age, sex, race/ethnicity), clinical (disease duration, disease activity, accrued damage, current renal function), immunological (antiphospholipid antibodies) and therapeutic variables (antimalarials and glucocorticosteroids). The prevalence of traditional atherosclerotic risk factors (diabetes, dyslipidaemia, smoking) was compared as well as the frequency of the antihypertensive, hypolipidaemic and antiplatelet/anticoagulant drugs used. Incidence rates of AVEs were calculated as first occurrence of an event by 1000 patient-years for each group, while the effect of baseline BP groups was modelled using time-dependent Cox regression.

Statistical analysis

The adjusted mean BP was used as a categorical variable to classify patients into the three groups (normotensives, stage 1 hypertension, stage 2 hypertension). Patients' demographics, clinical and immunological variables and treatments, as well as the traditional atherosclerotic risk factors are presented as mean \pm SD or counts (percentages) and were compared using analysis of variance for continuous variables and χ^2 tests for categorical variables. Univariate and multivariable Cox proportional hazards regressions were performed using the demographic variables as time fixed and the other features as time-dependent predictors (being updated at each visit). All potential confounders along with the main variable of interest (groups based on the adjusted mean BP) were included in the analysis. Proportionality assumption tests for Cox models were done using Schoenfeld residuals whereas the linearity of continuous variables in Cox models was tested using Martingale residuals.¹⁰ Statistical analysis was performed with SAS V.9.4; $p < 0.05$ was considered significant.

RESULTS

Of 2008 patients, 1532 (88.1% females) satisfied the inclusion criteria. Of the excluded patients, 455 had a follow-up shorter than 2 years (median 1 year) and 21 had an AVE prior to the baseline. The mean age of the included patients at baseline was 36.2 ± 14.3 years and mean disease duration 6.1 ± 6.3 years. One hundred and fifty-five patients (10.1%) had an adjusted mean BP \geq 140/90 mm Hg and 316 (20.6%) a mean BP of 130–139/80–89 mm Hg over the first 2 years; the rest 1061 (69.3%) were normotensives. The calculation of the adjusted mean BP was based on

Table 1 Traditional and lupus-related atherosclerotic risk factors at baseline

Variable	≥140/90 mm Hg (n=155)	130-139/80-89 mm Hg (n=316)	<130/80 mm Hg (n=1061)	P value
Age (year)	46.8±14.6	39.7±13.2	33.6±13.7	<0.001
Females (n, %)	126 (81.3)	266 (84.2)	957 (90.2)	<0.001
Caucasians (n, %)	119 (76.8)	226 (71.5)	647 (61)	<0.001
Blacks (n, %)	23 (14.8)	40 (12.7)	154 (14.5)	
Others (n, %)	13 (8.4)	50 (15.8)	260 (24.5)	
Adjusted mean BP (mm Hg)	149/91	135/86	112/71	<0.001
Diabetes (n, %)	17 (11.0)	18 (5.7)	23 (2.2)	<0.001
Dyslipidaemia* (n, %)	94 (60.6)	121 (38.3)	195 (18.4)	<0.001
Total cholesterol (mmol/L)	5.9±1.8	5.1±1.3	4.5±1.1	<0.001
Smoking (current, n, %)	36 (23.2)	57 (18.0)	159 (15.0)	0.004
Disease duration (y)	5.5±5.8	6.9±7.0	6.0±6.0	0.026
SLEDAI-2K	5.2±5.0	5.2±5.6	4.3±4.4	<0.001
SDI	1.0±1.3	0.7±1.2	0.5±0.9	<0.001
eGFR (mL/min/1.73 m ²)	69.9±31.6	86.0±32.4	102.0±29.4	<0.001
aPL† (n, %)	53 (34.2)	75 (23.7)	216 (20.4)	0.003
Antimalarials (n, %)	49 (31.6)	176 (55.7)	721 (68.0)	<0.001
Glucocorticosteroids (GCS) (n, %)	125 (80.6)	230 (72.8)	690 (65.0)	<0.001
Cumulative GCS dose (g)†‡	16.9±17.9	18.9±22.6	15.5±18.7	<0.001
Antihypertensives (n, %)	59 (38.1)	95 (30.1)	168 (15.8)	<0.001
Statins (n, %)	0 (0)	1 (0.3)	0 (0)	0.146
Antiplatelets/anticoagulants (n, %)	8 (5.2)	19 (6)	94 (8.9)	0.106

P values: trend from ANOVA for continuous variables, X² test for categorical variables.

*Abnormal total cholesterol or low-density lipoprotein for two consecutive visits.

†Lupus anticoagulant and/or anticardiolipin antibodies (IgM, IgG).

‡From enrolment up to the baseline.

ANOVA, analysis of variance; aPL, antiphospholipid antibodies; BP, blood pressure; eGFR, estimated glomerular filtration rate; SDI, Systemic Damage Index; SLEDAI, SLE Disease Activity Index 2000.

6.3 BP measurements (average) over 2 years. The traditional and lupus-related atherosclerotic risk factors as well as the treatment variables at baseline are shown in [table 1](#).

After a mean follow-up of 10.8 years (16 601 patient-years), 124 AVEs were documented, including 20 CV deaths. The non-fatal AVEs were new-onset angina (n=40), acute MI (n=23),

revascularisation procedures (n=12), CHF of ischaemic origin (n=9), cerebrovascular events (n=18) and PVD (n=2). The overall prevalence of AVEs was 32 (20.6%), 41 (13%) and 51 (4.8%) in the ≥140/90 mm Hg, the 130–139/80–89 mm Hg and the <130/80 mm Hg groups, respectively. The incidence rates were 18.9, 11.5 and 4.5 per 1000 patient-years, respectively. The Kaplan-Meier curve for the occurrence of AVEs over time (censored at 15 years) in the three groups is shown in [figure 1](#). The differences were statistically significant among all groups (p=0.0007 between normotensives and stage 1 hypertension, p=0.008 between stage 1 and stage 2 hypertension and p<0.0001 between normotensives and stage 2 hypertension). Similar trends were observed in the subcategories of the AVEs, such as hard AVEs (excluding angina and TIAs), coronary artery disease (CAD) events, cerebrovascular events and CV deaths alone, [figure 2](#).

In a time-dependent multivariable analysis for the identification of predictors for AVEs, an adjusted BP of 130–139/80–89 mm Hg over the first 2 years since enrolment in the UTLC was independently associated with the occurrence of AVEs (HR 1.73, 95% CI 1.13 to 2.69, p=0.011). Other associated factors were smoking, use of glucocorticosteroids, use of antiplatelet/anticoagulant agents and disease activity (as expressed by the SLE Disease Activity Index 2000), details in [table 2](#).

A sensitivity analysis excluding 30 patients with end-stage renal disease (7 in the normotensive group, 13 in the 130–139/80–89 mm Hg group and 10 in the ≥140/90 mm Hg group) yielded similar results (online supplementary tables 1 and 2).

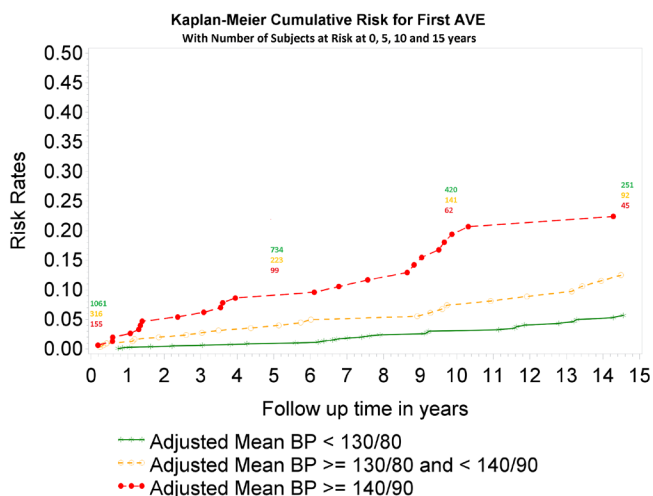


Figure 1 Kaplan-Meier curve for the occurrence of AVEs over time (censored at 15 years) in the three patient groups (red line: ≥140/90 mm Hg, yellow line: 130–139/80–89 mm Hg, green line <130/80 mm Hg). The differences were statistically significant among all groups. The baseline (T0) is 2 years after enrolment in the clinic. AVEs, atherosclerotic vascular events; BP, blood pressure.

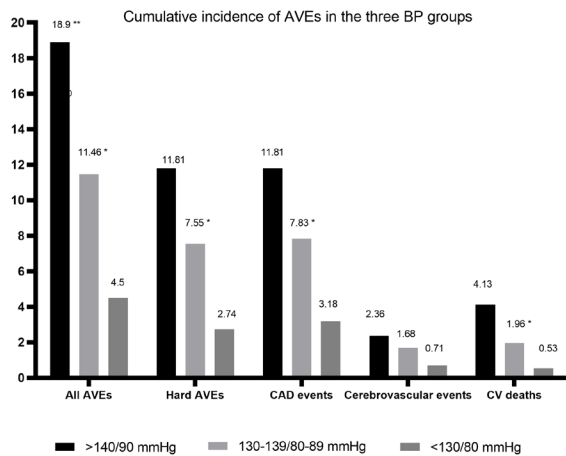


Figure 2 Cumulative incidence of AVEs in the three bP groups. Similar trends were observed with REGARDs to the hard AVEs (excluding angina and transient ischaemic attacks), CAD events and CV deaths. The differences in the incidence rates of cerebrovascular events were not statistically significant. * $P < 0.001$, ** $P = 0.008$. AVEs, atherosclerotic vascular events; BP, blood pressure; CAD, coronary artery disease; CV, cardiovascular.

DISCUSSION

In the present study, we showed that patients with SLE with an adjusted mean BP of 130–139/80–89 mm Hg (regardless of anti-hypertensive therapy) over the first 2 years of observation had a significantly higher risk for the development of AVEs compared with normotensive patients (adjusted mean BP <130/80 mm Hg). These patients had a higher prevalence of other traditional and lupus-related risk factors for atherosclerosis as well. However, a time-dependent multivariable analysis with multiple corrections for all these factors revealed that this level of BP independently increased the risk for AVEs by 73% over the entire follow-up period (10.8 years on average).

A time-adjusted measure of BP over the first 2 years of observation was selected instead of the traditional ACC/AHA definition of the average BP of ≥ 2 readings in two separate

occasions.¹ This was based on previous studies that showed that BP fluctuates considerably in patients with lupus, primarily because of variations in disease activity (and, consequently, increased use of glucocorticosteroids and/or non-steroidal anti-inflammatory drugs) and renal involvement.³ This means that a given patient may have high BP readings intermittently and for a short period of time; the BP will normalise after successful control of disease activity. It is unknown if these individuals carry a higher CV risk compared with other patients. Nonetheless, Nikpour *et al* showed that time-adjusted BP, reflecting the cumulative exposure to hypertension over time, was more reliable than single BP readings for the prediction of AVEs in patients with lupus.¹¹

The new ACC/AHA definition inevitably increases the prevalence of hypertension and, consequently, the number of patients that should be considered for management. In a recent study of 38 276 American adults from the National Health and Nutrition Examination Survey, Dorans *et al* reported an age-standardised prevalence of 45.4% and an increase of more than 20% in the total number of individuals with hypertension in the USA.¹² In our cohort, the prevalence of hypertension (based on the adjusted mean BP over the first 2 years) was 10.1% according to the previous definition of $\geq 140/90$ mm Hg and increased dramatically to 30.7% with the new threshold. In older studies in patients with lupus that used the previous definition of hypertension, the prevalence reached 74%³; this should be expected to rise with the new definition.

Several studies in SLE showed that hypertension is independently associated with increased rates of AVEs with a HR ranging from 1.05 to 3.5.^{6 13–18} Furthermore, hypertension has been related to every surrogate end-point for atherosclerosis, including impaired endothelial function,^{19 20} arterial stiffness,^{21–23} increased carotid intima-media thickness and plaque formation,^{24–26} coronary artery calcification²⁷ and angiographically proven CAD.²⁸ It was also an independent risk factor for myocardial perfusion defects.²⁹ In all these studies, the threshold for the definition of hypertension was $\geq 140/90$ mm Hg. It seems possible that the application of a lower threshold, such as the 130–139/80–89 mm Hg, may further increase the impact of hypertension on the CV risk of such patients.

Table 2 Univariable and multivariable time dependent COX regression analysis for predictors of AVEs

Variable	Univariable analysis			Multivariable analysis		
	HR	95% CI	P value	HR	95% CI	P value
Stage 1 hypertension versus normotensives	1.77	1.17 to 2.68	0.007	1.73	1.13 to 2.65	0.0112
Stage 2 hypertension versus normotensives	1.96	1.23 to 3.12	0.0047	1.65	1.01 to 2.69	0.0456
Age	1.06	0.94 to 1.19	0.3311	2.01	0.96 to 4.22	0.064
Age squared	1.004	0.99 to 1.01	0.4396	0.99	0.99 to 1.00	0.0675
Female	0.51	0.31 to 0.82	0.0059	0.70	0.42 to 1.74	0.1787
Caucasian	1.16	0.75 to 1.80	0.5036	1.18	0.74 to 1.88	0.4771
Diabetes	1.60	0.93 to 2.86	0.0891	1.31	0.73 to 2.35	0.3686
Dyslipidaemia*	2.55	0.58 to 11.24	0.2169	1.71	0.33 to 8.83	0.5202
Smoking	1.61	1.03 to 2.50	0.0352	1.86	1.17 to 2.96	0.0084
SLEDAI-2K	1.11	1.07 to 1.15	<0.0001	1.10	1.06 to 1.15	<0.0001
eGFR	0.99	0.99 to 1.00	0.0593	1.00	0.99 to 1.00	0.2388
Antiphospholipid antibodies†	1.70	1.15 to 2.53	0.00081	1.38	0.92 to 2.07	0.1236
Glucocorticoids	2.02	1.40 to 2.92	0.0002	1.76	1.19 to 2.60	0.0043
Anticoagulants/antiplatelets	3.05	2.09 to 4.46	<0.0001	3.34	2.25 to 4.94	<0.0001

Bold indicates variables associated with increased risk for atherosclerotic vascular events in the multivariable analysis.

*Abnormal total cholesterol or low-density lipoprotein for two consecutive visits.

†Lupus anticoagulant and/or anticardiolipin antibodies (IgM, IgG).

AVE, atherosclerotic vascular event; eGFR, estimated glomerular filtration rate; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

The findings of the present study support that the target BP should be less than 130/80 mm Hg in all patients with lupus in order to minimise their CV risk. This seems to be independent of age or the absence of other traditional risk factors that could erroneously lead to a low predicted 10-year CV risk. As mentioned above, most CV risk calculators are not designed to estimate the CV risk in patients younger than 40 years. Hence, the CV risk cannot be reliably predicted for the majority of patients with lupus. The average age of the patients with an adjusted mean BP of 130–139/80–89 mm Hg in our study was 40 years, which is exactly the threshold used in the ASCVD risk estimator.⁷ Therefore, it seems reasonable that clinicians should not rely on CV risk calculators in SLE and commence treatment as soon as possible in cases of sustained BP elevation above the threshold of 130/80 mm Hg.

The optimal level of BP to maximise CV risk reduction is not known. In the Systolic Blood Pressure Intervention Trial, it was shown that intensive treatment of high-risk, non-diabetic patients aiming at a SBP <120 mm Hg conferred a 25% reduction in the rate of AVEs compared with individuals with an SBP target of less than 140 mm Hg.³⁰ The average SBP of the intensive treatment patients was 121.4 mm Hg compared with the 136.2 mm Hg of the standard treatment individuals. Would lower BP levels further reduce the incidence rates of AVEs? In a population-wide study from Sweden in 187 106 patients with type 2 diabetes and no prior AVE, it was shown that there was a linear reduction of the non-fatal AVEs for gradually decreasing BP levels.³¹ The minimum CV risk (for non-fatal AVEs) was observed at the levels of 110–119 mm Hg (for SBP), while there was a significant increase at the levels of 120–129 mm Hg and a further significant increase at 130–139 mm Hg. The difference in the HR for AVEs between the lowest SBP threshold that was assessed in that study (110–119 mm Hg) to the 130–139 mm Hg level was 12% for all AVEs. However, these levels (110–119 mm Hg) were also associated with a 20% higher risk for heart failure and 28% higher risk for all-cause mortality compared with the 130–139 mm Hg levels.³¹ Based on these data, targeting lower levels of BP might be unsafe in certain patients with lupus (eg, with prior heart disease or heart failure).

The purpose of the current study was not the assessment of the effect of treatment on CV outcomes in patients with lupus. Nevertheless, it was recently shown that the effective management of the traditional atherosclerotic risk factors (including hypertension) led to a decrease of 60% in the incidence of AVEs from the 1980s to the 2010s.³² As such, it should be expected that the effective treatment of hypertension to levels lower than 130/80 mm Hg will further reduce the incidence of AVEs in SLE.

The present report is an observational longitudinal study and not a randomised controlled trial. Therefore, its findings should be interpreted with caution, particularly since the patients with a BP of 130–139/80–89 mm Hg also had a higher prevalence of other atherosclerotic risk factors. Moreover, certain risk factors (obesity and family history of premature CAD) were not included in the analysis due to the large proportion of missing data in our cohort. Nevertheless, CV risk reduction is multidimensional and should not be restricted to the tight control of hypertension alone but include all modifiable risk factors, such as dyslipidaemia, diabetes.

CONCLUSION

In conclusion, patients with lupus with an adjusted mean BP of 130–139/80–89 mm Hg over the first 2 years from enrolment to the clinic had significantly higher incidence rates of AVEs

over more than 10 years of follow-up on average compared with normotensive individuals. In a multivariable time-dependent analysis, this level of BP conferred a 73% higher risk for AVEs after adjusting for other traditional and lupus-related risk factors. The management of hypertension in patients with lupus should commence early and aim at levels below 130/80 mm Hg.

Contributors All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. MU had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Patient consent for publication Not required.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. All authors were involved in the study conception and design, acquisition of data, analysis and interpretation of data.

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Supplementary Table 1. TRADITIONAL AND LUPUS-RELATED ATHEROSCLEROTIC RISK FACTORS AT BASELINE (EXCLUDING PATIENTS WITH ESRD)				
Variable	≥140/90mmHg (n=145)	130-139/80-89mmHg (n=303)	<130/80mmHg (n=1054)	p
Age (y)	47.3 ± 14.8	39.9 ± 13.3	33.4 ± 12.1	<0.001
Females (n, %)	117 (80.7%)	254 (83.8%)	95 (90.1%)	<0.001
Caucasians (n, %)	115 (79.3%)	220 (72.6%)	647 (61.4%)	<0.001
Blacks (n, %)	20 (13.8%)	37 (12.2%)	150 (14.2%)	
Others (n, %)	10 (6.9%)	46 (15.2%)	257 (24.4%)	
Adjusted mean BP (mmHg)	149/90	129/82	112/71	<0.001
Diabetes (n, %)	17 (11.7%)	17 (5.6%)	23 (2.2%)	<0.001
Dyslipidemia* (n, %)	88 (60.7%)	117 (38.6%)	194 (18.4%)	<0.001
Total cholesterol (mmol/l)	6.0 ± 1.8	5.1 ± 1.3	4.5 ± 1.1	<0.001
Smoking (current, n, %)	34 (23.4%)	56 (18.5%)	159 (15.1%)	0.003
Disease duration (y)	5.4 ± 5.9	6.6 ± 6.7	6.0 ± 6.1	0.125
SLEDAI-2K	5.2 ± 4.9	5.2 ± 5.6	4.2 ± 4.4	<0.001
SDI	0.8 ± 1.1	0.6 ± 1.0	0.5 ± 0.9	<0.001
eGFR (ml/min/1.73m²)	74.6 ± 27.2	88.9 ± 29.7	102.6 ± 28.5	<0.001
aPL** (n, %)	53 (36.6%)	82 (27.1%)	243 (23.1%)	0.001
Antimalarials (n, %)	47 (32.4%)	170 (56.1%)	717 (68.0%)	<0.001
Glucocorticosteroids (GCS) (n, %)	119 (82.1%)	219 (72.3%)	684 (64.9%)	<0.001
Cumulative GCS dose (g)***	15.3 ± 18.6	17.1 ± 19.1	15.3 ± 18.6	0.414
Antihypertensives (n, %)	51 (35.2%)	86 (28.4%)	164 (15.6%)	<0.001
Antiplatelets/Anticoagulants (n, %)	7 (4.8%)	18 (5.9%)	91 (8.6%)	0.117
P values: trend from ANOVA for continuous variables, Chi-square test for categorical variables				
*Abnormal total cholesterol or low-density lipoprotein for two consecutive visits				
** Lupus anticoagulant and/or anticardiolipin antibodies (IgM, IgG)				
***From enrolment up to the baseline				
SLEDAI-2K: SLE Disease Activity Index 2000, SDI: Systemic Lupus International Collaborating Clinics Damage Index, eGFR:				

estimated glomerular filtration rate, aPL: antiphospholipid antibodies

Supplementary Table 2. UNI- AND MULTIVARIABLE TIME DEPENDENT COX REGRESSION ANALYSIS FOR PREDICTORS OF AVEs (excluding patients with ESRD)						
Variable	Univariable analysis			Multivariable analysis		
	HR	95% CI	p	HR	95% CI	p
Stage 1 hypertension vs. normotensives	1.69	1.11-2.57	0.015	1.64	1.06-2.52	0.0246
Stage 2 hypertension vs. normotensives	1.99	1.25-3.18	0.0038	1.66	1.02-2.71	0.0417
Age	1.06	0.94-1.20	0.3107	2.06	0.95-4.46	0.0656
Age-squared	1.00	1.00-1.00	0.4132	0.99	0.99-1.00	0.0707
Female	0.50	0.31-0.81	0.005	0.70	0.42-1.17	0.1700
Caucasian	1.24	0.78-1.95	0.3592	1.26	0.78-2.04	0.3451
Diabetes	1.64	0.93-2.88	0.0862	1.32	0.73-2.36	0.3576
Dyslipidemia*	2.55	0.58-11.27	0.216	1.71	0.33-8.89	0.5209
Smoking	1.64	1.05-2.56	0.0283	1.86	1.17-2.96	0.0088
SLEDAI-2K	1.11	1.07-1.15	<.0001	1.10	1.06-1.15	<.0001
eGFR	0.99	0.99-1.00	0.0593	1.00	0.99-1.00	0.4157
Antiphospholipid antibodies**	1.74	1.17-2.59	0.0061	1.41	0.93-2.12	0.1036
Glucocorticoids	2.06	1.42-2.99	0.0002	1.79	1.21-2.65	0.0036
Anticoagulants/Antiplatelets	2.88	1.96-4.23	<.0001	3.14	2.11-4.68	<.0001

*Abnormal total cholesterol or low-density lipoprotein for two consecutive visits
 ** Lupus anticoagulant and/or anticardiolipin antibodies (IgM, IgG)
 SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000, eGFR: estimated glomerular filtration rate

Blood pressure control should be a key target for people with Lupus



Target blood pressure should be under 130/80 mmHg for all patients with Lupus.

INTRODUCTION

Systemic lupus erythematosus (often called Lupus or SLE) is an autoimmune disease. It typically starts in women between the ages of 15 and 45. Lupus symptoms can vary from patient to patient. People with Lupus are often very tired, have joint pain, and their skin may be sensitive to sunlight. Lupus is caused by hyperactive immune cells and the production of autoantibodies. An antibody is a protein that the immune system makes to attack foreign substances in the body, such as viruses or bacteria. In autoimmune diseases, the body makes antibodies that attack its own tissues. These are called autoantibodies. People with Lupus can also have heart and vascular problems earlier in life than people without the disease, and high blood pressure is common.

In 2017, the American College of Cardiology and American Heart Association published new guidelines to help decide whether people have high blood pressure (hypertension). They brought the measurement (threshold) down to 130/80 mmHg – which is a lot lower than the old limit of 140/90 mmHg. This means there are now more people who will be diagnosed with high blood pressure, and who need to be treated because they may have a significant risk of developing a heart attack or stroke in the next 10 years. This risk is calculated by adding together other risk factors such as age, sex, race/ethnicity, diabetes (high blood sugar), high cholesterol and smoking. However, the equation used was designed for people over the age of 40, and does not consider whether people have Lupus.

WHAT DID THE AUTHORS HOPE TO FIND?

The authors wanted to find out the risk of heart attacks and strokes in people with Lupus classed as having high blood pressure according to the limit in the new guidelines.

WHO WAS STUDIED?

The study looked at 1532 people with Lupus who had been treated at a clinic in Canada. Everyone was over the age of 18, and had had Lupus for an average of 6 years.

HOW WAS THE STUDY CONDUCTED?

This was an observational study. There was no treatment being studied. Everyone was seen every 2–6 months, and their blood pressure was measured at each visit. The authors calculated each person's average blood pressure over 2 years, and divided them into three groups: 155 people had blood pressure consistently above the old threshold of 140/90 mmHg, 316 people were between the old and new thresholds (130–139/80–89 mmHg), and 1061 people had normal blood pressure that came in under the new threshold (less than 130/80 mmHg). Everyone was followed until they had a first episode of heart attack or stroke, or until the last time they came to the clinic. The authors did a statistical analysis to adjust for other risk factors that might have contributed.

WHAT WERE THE MAIN FINDINGS OF THE REVIEW?

After 10 years, there had been 124 heart attacks or strokes, 20 of which were fatal. People in the middle group were more than twice as likely to have a heart attack or stroke compared to people with normal blood pressure. When the authors looked at this more closely with a statistical model, they found that people with a blood pressure of 130–139/80–89 mmHg over the first 2 years had a 73% increased risk of a heart attack or stroke independently from other risk factors.

ARE THESE FINDINGS NEW?

Yes, this is the first time that a large study for hypertension in Lupus has been published.

WHAT ARE THE LIMITATIONS OF THE STUDY?

The major limitation of this observational study was that people with high blood pressures also tended to have more other risk factors when compared to people with normal blood pressure. It is difficult to adjust for these extra risk factors without doing a randomised controlled trial, but that would be difficult.

WHAT DO THE AUTHORS PLAN ON DOING WITH THIS INFORMATION?

The authors are working to help patients reduce their blood pressure regardless of their overall cardiovascular risk (e.g. age, sex, high cholesterol, high blood sugar). They believe this will help prevent heart attack and stroke in people with Lupus. They are also doing more studies to look at whether blood pressure drugs can help.

WHAT DOES THIS MEAN FOR ME?

If you have Lupus, you might have a higher risk of heart and vascular diseases. Having high blood pressure will increase these risks even more. If you have high blood pressure, no matter what age you are, you should get treatment to try and get below the new guideline threshold of 130/80 mmHg.

If you have any concerns about your disease or its treatment, you should speak to your doctor.

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