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Treatment Patterns and Control of Hypertension in Systemic Lupus Erythematosus (SLE)

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Treatment Patterns and Control of Hypertension in Systemic Lupus Erythematosus (SLE)

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Short running head (maximum of 4 words):
SLE blood pressure control

Objective: Hypertension (HTN) is common in SLE, representing a key risk factor for cardiovascular and renal disease. We described HTN treatment patterns in SLE, evaluated uncontrolled HTN according to Canadian and American guidelines, and identified factors associated with uncontrolled HTN.

Methods: We performed a cross-sectional study, identifying all McGill Lupus Clinic registry patients with an annual visit between January 2017 and May 2019 who were taking HTN medications. We excluded those taking medications only for another indication (e.g. Raynaud's). We determined the frequency of uncontrolled HTN according to Canadian and ACC/AHA guidelines. Multivariate logistic regression (adjusted for age, sex, and race/ethnicity) evaluated if uncontrolled HTN was more common with high body mass index (BMI), longer SLE duration, high disease activity, renal damage, multiple concomitant antihypertensives, prednisone and NSAIDs.

Results: Of 442 SLE patients, 108 were taking medications to treat HTN, and 38 took multiple medications concurrently. Angiotensin-receptor blockers were most common, followed by calcium-channel blockers, diuretics, angiotensin-converting enzyme inhibitors, and beta-blockers. Among the 108 patients, 39.8% (n=43) had blood pressure >140/90 mmHg, while 66.7% (n=72) had blood pressure >130/80 mmHg. In multivariate analyses, uncontrolled HTN (>130/80 mmHg) was more likely in Caucasians (OR 2.72, 95% CI 1.12-6.78) and patients with higher BMI (OR 1.08, 95% CI 1.00-1.19). Patients with renal damage had better HTN control (OR 0.39, 95% CI 0.16-0.97). We could not draw definitive conclusions regarding other variables.

Conclusion: Caucasians and patients with higher BMI had more uncontrolled HTN. The negative association with renal damage is reassuring, as controlled BP is key for renal protection.

Strengths and limitations of this study

-Hypertension is a common comorbidity of SLE, therefore understanding and addressing risk factors to suboptimal control is crucial to avoid future cardiovascular and renal consequences.
- Our study was performed on a large cohort of SLE patients who receive annual standardized evaluations of clinical characteristics.
- Results were computed using multivariate logistic regression analyses adjusted for age, sex, and race/ethnicity.
- The cross-sectional nature of our study does not permit assumption of causal inferences.

Introduction

In systemic lupus erythematosus (SLE), hypertension (HTN) is common (1,2) and represents a major, correctable risk factor for cardiovascular disease and renal damage, two frequent adverse outcomes in SLE (3,4). Certain SLE patient subgroups have traditionally had worse disease outcome, including older patients, males, non-Caucasians, those with active disease, high body mass index (BMI), and renal damage (5-8). To our knowledge, data on risk factors leading to uncontrolled HTN in SLE patients remain scarce. We conducted an assessment of the McGill University Health Center Lupus Clinic registry to describe HTN treatment patterns, evaluate the prevalence of uncontrolled HTN according to Hypertension Canada and the more stringent American College of Cardiology/American Heart Association (ACC/AHA) guidelines for HTN, and assess uncontrolled HTN in the traditionally vulnerable groups of males, non-Caucasians, older SLE patients, as well as patients with high BMI, active SLE, or renal damage. The effects of prednisone and NSAID use on uncontrolled HTN were also evaluated.

Materials and Methods

We conducted a cross-sectional assessment of data extracted from the McGill University Health Center Lupus Clinic registry. Patients enrolled in the cohort received an SLE diagnosis in accordance to the American College of Rheumatology (ACR) criteria confirmed by a lupus specialist (9). Informed written consent was obtained from each patient prior to cohort enrolment. Prospectively collected data include demographics (age, sex, race/ethnicity) and clinical characteristics (SLE disease activity and damage, medications, BMI, and other variables)

updated during standardized annual assessments where blood pressure (BP) is measured once, seated, with an automated cuff.

We identified all patients between January 2017 and May 2019 taking medications for HTN at the time of their last annual visit. We did not include anti-hypertensive agents taken for other reasons, such as Raynaud's syndrome and proteinuria. The frequency of use for each class of HTN medication (i.e. angiotensin-converting enzyme inhibitors [ACEI], angiotensin II receptor blocker [ARB], calcium channel blocker [CCB], beta-blocker, diuretics) was computed.

We examined the prevalence of uncontrolled HTN within the cohort according to 2017 HTN guidelines from both Hypertension Canada and the American College of Cardiology/American Heart Association (ACC/AHA). The 2017 Canadian guidelines recommend a target systolic arterial BP of <140 mmHg and diastolic arterial BP of <90 mmHg for cardiovascular disease prevention (10). Conversely, the more stringent ACC/AHA guidelines target a systolic arterial pressure <130 mmHg, and a diastolic arterial pressure <80 mmHg (11).

We analyzed characteristics and demographics of patients with uncontrolled HTN, defined using the more stringent ACC/AHA guidelines of a BP surpassing 130/80 mmHg despite the use of antihypertensive medications, as SLE patients are at risk of cardiovascular disease. We developed multivariate logistic regression analyses including sex, Caucasian race/ethnicity, age, BMI, SLE disease duration, renal damage, number of current HTN medications, as well as prednisone and NSAID use. Variables also included the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), a global SLE disease activity index used clinically and in research which measures 24 clinical variables across all systems (12).

We received institutional review board approval through the McGill University Health Centre (SLE Annual Registry, IRB number 96-060 REC).

Results

During the study period of January 2017 to May 2019, 442 SLE patients from the McGill University Health Center Lupus Clinic registry were assessed. The mean age at assessment was 48 years old, with a mean age at SLE diagnosis of 31 years. Females comprised 87.8% of the cohort. Regarding race/ethnicity, 60.4% were Caucasian, 14.5% Black, 13.1% Asian, and the remainder (12.0%) of other race/ethnicity. The mean BMI was 26.6.

Of the 442 patients, 108 (24.4%) were currently taking medications to treat HTN, with 38 patients taking multiple antihypertensives concurrently. Angiotensin receptor blockers were most commonly prescribed (N=44), followed by CCB (N=40), diuretics (N=33), ACEI (N=25), and beta-blockers (N=16).

Among the 108 patients taking antihypertensive medications, 39.8% (N=43) had a BP greater than 140/90 mmHg, representing suboptimal control as per Canadian guidelines. More than two-thirds (66.7%, N=72) of patients on anti-hypertensive medications had BP greater than 130/80 mmHg, representing suboptimal control as per ACC/AHA guidelines (Table 1).

Renal damage, defined as a SLICC renal score $\geq$ 1, was present in 21% (N=15) of Caucasian patients taking HTN medications, and in 46% (N=17) of patients of another race taking HTN medications.

Multivariate analyses of the 108 patients included sex, race/ethnicity, age at last visit, BMI, SLE duration, disease activity (SLEDAI-2K), renal damage, number of anti-hypertensive

medications, as well as prednisone and NSAID use. Caucasian SLE patients were more likely to have uncontrolled HTN according to the ACC/AHA definition (odds ratio, OR 2.72, 95% CI 1.12-6.78). We noted that higher BMI also was associated with uncontrolled HTN (OR 1.08, 95% CI 1.00-1.19). Conversely, patients with renal damage had better BP control (OR 0.39, 95% CI 0.16-0.97). The effects of the other variables assessed were not clear as the 95% CIs were wide and included the null value (Table 2).

Discussion

Hypertension is an important contributor to cardiovascular disease, renal damage and death in SLE patients (3,4). Prior studies have identified risk factors for HTN onset in SLE (13), but there are less data assessing risk factors for uncontrolled HTN. In our cohort, 24.4% of SLE patients were taking medications for HTN. Prior studies have estimated that 33% to 48% of SLE patients take an antihypertensive medication or have a BP measure surpassing 140/90 mmHg (2,14-15). Importantly, we found a high prevalence of uncontrolled hypertension, with 43 (39.8%) of the 108 patients taking antihypertensive medications having uncontrolled BP according to the Canadian guidelines, and 72 patients (66.7%) according to ACC/AHA guidelines. This finding reinforces the need to examine risk factors contributing to uncontrolled BP in SLE, in order to better manage our patients.

Among the 108 patients from the cohort currently taking anti-hypertensive medications, the most commonly used medication class were ARBs, followed by CCB, diuretics, ACEI, and beta-blockers. There are no specific guidelines for the first-line antihypertensive medication to use in SLE, however ARB and ACEI have been recommended due to their additional beneficial effect in renal and cardiovascular disease (16,17). The next most commonly used antihypertensive agent

in our cohort, CCB, is useful in patients with Raynaud's syndrome and/or pulmonary artery hypertension, important clinical manifestations of SLE (16). Diuretics and beta-blockers have not been widely studied in hypertensive SLE patients. While they can be efficacious, they may cause photosensitivity, a common comorbidity in SLE, with early reports suggesting they may trigger cutaneous lupus (18). Beta-blockers may also worsen Raynaud's phenomenon, which is prevalent in SLE. Of note, many of our patients received combination HTN therapies.

In our cohort, Caucasians were more likely to have uncontrolled HTN. This finding differs from previous studies in SLE, which found that race/ethnicity groups traditionally at high risk of suboptimal BP control, such as black patients, were indeed more likely to have resistant HTN (5). However, Caucasian race has not always been associated with good HTN control in the general American population (19). The observed associations between Caucasian race/ethnicity and uncontrolled HTN in our SLE sample may suggest that non-Caucasians were aggressively treated, perhaps because of the knowledge that this demographic is susceptible to poor outcomes. In addition, renal damage in our cohort was negatively associated with uncontrolled HTN (OR 0.39 95% CI 0.16-0.97), which is reassuring as controlling BP is key to preventing further renal damage. Although our analysis has adjusted for renal disease, this result may contribute to why Caucasian patients, with less renal damage than non-Caucasians, had poorer blood pressure control. We noted that patients with higher BMI were more likely to have poor BP control (OR 1.08, 95% CI 1.00-1.19). Risk factors for uncontrolled HTN were analyzed according to ACC/AHA guidelines, as they recommend a lower blood pressure target, which could be beneficial to SLE patients given the increased risk of cardiovascular disease. Of note, current published HTN guidelines do not

specifically provide a target for SLE patients, therefore studies aiming to define a target are needed.

We could not draw definitive conclusions on the other variables assessed as the 95% CIs were imprecise and included the null value. Further work using a longitudinal repeated measure design is needed to explore the effects of those variables, in addition to HTN treatment, disease activity, disease damage (e.g., renal failure associated with SLE), and concomitant medications (e.g. steroids, NSAIDs) on HTN in SLE.

Potential limitations to our study should be noted. Our study was cross-sectional, and the blood pressure of cohort patients was taken as a single measurement at annual visits. Also, we studied patients from a tertiary care centre within a specialized clinic, and within the setting of universal health care. The results do suggest that good BP control is possible in high-risk SLE patients including non-Caucasians and those with renal damage, though this may be more difficult in other settings (such as non-universal health care, where problems with health care access and patient adherence may create difficulties).

In summary, our cross-sectional analysis showed that 24.4% of SLE patients were currently taking medications to treat HTN, and that over one-third required two or more medications concurrently. Angiotensin receptor blockers, ACEI, and CCB were common antihypertensive choices, and diuretics were often used despite concerns in the literature regarding photosensitivity and lupus rash. Among the 108 patients taking antihypertensive medications, 39.8% had suboptimal control as per Canadian guidelines and 66.7% had suboptimal control as per ACC/AHA guidelines. In our cohort, Caucasian SLE patients were more likely to have uncontrolled HTN, and we found a negative association between renal damage and our outcome.

The results suggest that good BP control is possible in high-risk SLE patients including non-Caucasians and those with renal damage, though this may be more difficult in other settings (such as non-universal health care and suboptimal care access).

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Tables

Table 1. Characteristics of the 108 SLE patients treated for HTN, controlled vs. uncontrolled HTN (>130/80 mmHg).

Variables	All patients N=108	Controlled, N= 36	Uncontrolled, N=72	Differences (95% CI)[a]
Male sex, N (%)	18 (16.7)	6 (16.7)	12 (16.7)	**<0.01 (-0.17, 0.14)**
Caucasian race/ethnicity, N (%)	71 (65.7)	19 (52.8)	52 (72.2)	**0.19 (0.00, 0.38)**
Age at last visit > 65 years, N (%)	45 (41.7)	12 (33.3)	33 (45.8)	**0.12 (-0.07, 0.30)**
Mean body mass index, BMI (SD)	26.6 (5.2)	25.6 (5.1)	27.1 (5.2)	**2.04 (-0.42, 4.17)**
Mean SLE duration, years (SD)	23.5 (14.2)	23.1 (15.2)	23.7 (13.8)	**0.94 (-5.01, 6.96)**
SLEDAI-2K ≥4, N (%)	48 (44.4)	18 (50.0)	30 (41.7)	**0.08 (-0.11, 0.27)**
Renal damage ≥1, N (%)	32 (29.6)	16 (44.4)	16 (22.2)	**0.22 (0.04, 0.40)**
Prednisone use, N (%)	16 (14.8)	5 (13.9)	11 (15.3)	**0.01 (-0.15, 0.14)**
NSAIDs use, N (%)	5 (4.6)	1 (2.8)	4 (5.6)	**0.03 (-0.09, 0.11)**
Using >1 BP medication, N (%)	38 (35.2)	10 (27.8)	28 (38.9)	**0.11 (-0.08, 0.28)**
Mean Systolic BP, (SD)	134.2 (18.2)	116.0 (9.4)	143.2 (14.3)	**26.0 (21.0, 31.0)**
Mean Diastolic BP, (SD)	**79.9 (10.8)**	**70.7 (6.3)**	**84.6 (9.5)**	**13.0 (10.0, 16.0)**

[a] The difference in proportions between groups (Controlled (n = 36) and Uncontrolled (n = 72) as well as their 95% confidence intervals. This analysis was performed using the Newcombe-Wilson score method. For continuous variables. For continuous variables (body mass index, SLE duration, systolic BP and diastolic BP), we used the Wilcoxon test to determine the confidence intervals for the difference.

Table 2. Logistic regression of SLE patients treated for HTN: Odds Ratios (OR) for uncontrolled HTN (>130/80 mmHg).

VARIABLES	UNADJUSTED OR (95% CI)	ADJUSTED OR (95% CI)[A]
MALE SEX	1.00 (0.35-3.11)	1.27 (0.42-4.24)
CAUCASIAN RACE/ETHNICITY	**2.33 (1.01-5.40)**	**2.72 (1.12-6.78)**
AGE AT LAST VISIT > 65 YEARS	1.69 (0.74-3.99)	1.68 (0.71-4.08)
BODY MASS INDEX	1.06 (0.98-1.15)	**1.08 (1.00-1.19)**
SLE DURATION (YEARS)	1.00 (0.97-1.03)	0.99 (0.96-1.02)
SLEDAI-2K ≥ 4	0.71 (0.32-1.60)	0.77 (0.33-1.76)
RENAL DAMAGE ≥ 1	**0.36 (0.15-0.84)**	**0.39 (0.16-0.97)**
USING MORE >1 BP MEDICATION	1.65 (0.71-4.08)	1.54 (0.63-3.96)
PREDNISONE	1.12 (0.37-3.81)	1.17 (0.38-4.14)
NSAIDS	2.06 (0.29-41.10)	1.99 (0.26-41.0)

[a] Adjusted for: age at last visit, sex and race/ethnicity.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5, 6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5, 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5, 6
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8,9
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Full title of manuscript:

Treatment Patterns and Control of Hypertension in Systemic Lupus Erythematosus (SLE): A Cross-Sectional Study

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The authors declare no conflict of interest.

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JLL contributed to the design, interpretation of the data and writing of the manuscript. CAP, LPG, EV FK contributed to the collection of cohort data, design, interpretation of the data and writing of the manuscript. LL contributed to the design, analysis, and interpretation of the data. SB contributed to the collection of cohort data, conception, design, interpretation of the data and writing of the manuscript. All authors read and approved the final version of the manuscript.

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Short running head (maximum of 4 words):
SLE blood pressure control

Objective: Hypertension (HTN) is common in Systemic Lupus Erythematosus (SLE), representing a key risk factor for cardiovascular and renal disease. We described HTN treatment patterns in SLE, evaluated uncontrolled HTN according to Canadian and American guidelines, and identified factors associated with uncontrolled HTN.

Methods: We performed a cross-sectional study, identifying all McGill Lupus Clinic registry patients with an annual visit between January 2017 and May 2019 who were taking HTN medications. We excluded those taking medications only for another indication (e.g. Raynaud's). We determined the frequency of uncontrolled HTN according to Canadian and American College of Cardiology (ACC)/American Heart Association (AHA) guidelines. Multivariate logistic regression (adjusted for age, sex, and race/ethnicity) evaluated if uncontrolled HTN was more common with high body mass index (BMI), longer SLE duration, high disease activity, renal damage, multiple concomitant antihypertensives, prednisone and Nonsteroidal anti-inflammatory drugs (NSAIDs).

Results: Of 442 SLE patients, 108 were taking medications to treat HTN, and 38 took multiple medications concurrently. Angiotensin-receptor blockers were most common, followed by calcium-channel blockers, diuretics, angiotensin-converting enzyme inhibitors, and beta-blockers. Among the 108 patients, 39.8% (n=43) had blood pressure >140/90 mmHg, while 66.7% (n=72) had blood pressure >130/80 mmHg. In multivariate analyses, uncontrolled HTN (>130/80 mmHg) was more likely in Caucasians (OR 2.72, 95% CI 1.12-6.78) and patients with higher BMI (OR 1.08, 95% CI 1.00-1.19). Patients with renal damage had better HTN control (OR 0.39, 95% CI 0.16-0.97). We could not draw definitive conclusions regarding other variables.

Conclusion: Caucasians and patients with higher BMI had more uncontrolled HTN. The negative association with renal damage is reassuring, as controlled BP is key for renal protection.

Strengths and limitations of this study

- -Hypertension is a common comorbidity of SLE, therefore understanding and addressing risk factors to suboptimal control is crucial to avoid future cardiovascular and renal consequences.
- Our study was performed on a large cohort of SLE patients who receive annual standardized evaluations of clinical characteristics.
- Results were computed using multivariate logistic regression analyses adjusted for age, sex, and race/ethnicity.
- The cross-sectional nature of our study may only allow for identification of associations.
  - Our study was performed in a specialized clinic within a tertiary hospital.

Introduction

In systemic lupus erythematosus (SLE), hypertension (HTN) is common (1,2) and represents a major, correctable risk factor for cardiovascular disease and renal damage, two frequent adverse outcomes in SLE (3,4). Certain SLE patient subgroups have traditionally had worse disease outcome, including older patients, males, non-Caucasians, those with active disease, high body mass index (BMI), and renal damage (5-8). To our knowledge, data on risk factors leading to uncontrolled HTN in SLE patients remain scarce. We conducted an assessment of the McGill University Health Center Lupus Clinic registry to describe HTN treatment patterns, evaluate the prevalence of uncontrolled HTN according to Hypertension Canada and the more stringent American College of Cardiology/American Heart Association (ACC/AHA) guidelines for HTN, and assess uncontrolled HTN in the traditionally vulnerable groups of males, non-Caucasians, older SLE patients, as well as patients with high BMI, active SLE, or renal damage. The effects of prednisone and NSAID use on uncontrolled HTN were also evaluated.

Materials and Methods

We conducted a cross-sectional assessment of data extracted from the McGill University Health Center Lupus Clinic registry. Patients enrolled in the cohort received an SLE diagnosis in accordance to the American College of Rheumatology (ACR) criteria confirmed by a lupus specialist (9). Informed written consent was obtained from each patient prior to cohort enrolment. Prospectively collected data include demographics (age, sex, race/ethnicity) and clinical characteristics (SLE disease activity and damage, medications, BMI, and other variables)

updated during standardized annual assessments where blood pressure (BP) is measured once, seated, with an automated cuff.

We identified all patients between January 2017 and May 2019 taking medications for HTN at the time of their last annual visit. We did not include anti-hypertensive agents taken for other reasons, such as Raynaud's syndrome and proteinuria. The frequency of use for each class of HTN medication (i.e. angiotensin-converting enzyme inhibitors [ACEI], angiotensin II receptor blocker [ARB], calcium channel blocker [CCB], beta-blocker, diuretics) was computed.

We examined the prevalence of uncontrolled HTN within the cohort according to 2017 HTN guidelines from both Hypertension Canada and the American College of Cardiology/American Heart Association (ACC/AHA). The 2017 Canadian guidelines recommend a target systolic arterial BP of <140 mmHg and diastolic arterial BP of <90 mmHg for cardiovascular disease prevention (10). Conversely, the more stringent ACC/AHA guidelines target a systolic arterial pressure <130 mmHg, and a diastolic arterial pressure <80 mmHg (11).

We analyzed characteristics and demographics of patients with uncontrolled HTN, defined using the more stringent ACC/AHA guidelines of a BP surpassing 130/80 mmHg despite the use of antihypertensive medications, as SLE patients are at risk of cardiovascular disease. We developed multivariate logistic regression analyses including sex, Caucasian race/ethnicity, age, BMI, SLE disease duration, renal damage, number of current HTN medications, as well as prednisone and NSAID use. Variables also included the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), a global SLE disease activity index used clinically and in research which measures 24 clinical variables across all systems (12). The analysis was carried out using

the Generalized linear model (GLM) function of the *R* software. The overall regression diagnosis has been validated by the ROC curve and the Hosmer-Lemeshow test.

We received institutional review board approval through the McGill University Health Centre (SLE Annual Registry, IRB number 96-060 REC).

Results

During the study period of January 2017 to May 2019, 442 SLE patients from the McGill University Health Center Lupus Clinic registry were assessed. The mean age at assessment was 48 years old, with a mean age at SLE diagnosis of 31 years. Females comprised 87.8% of the cohort. Regarding race/ethnicity, 60.4% were Caucasian, 14.5% Black, 13.1% Asian, and the remainder (12.0%) of other race/ethnicity. The mean BMI was 26.6.

Of the 442 patients, 108 (24.4%) were currently taking medications to treat HTN, with 38 patients taking multiple antihypertensives concurrently. Angiotensin receptor blockers were most commonly prescribed (N=44), followed by CCB (N=40), diuretics (N=33), ACEI (N=25), and beta-blockers (N=16).

Among the 108 patients taking antihypertensive medications, 39.8% (N=43) had a BP greater than 140/90 mmHg, representing suboptimal control as per Canadian guidelines. More than two-thirds (66.7%, N=72) of patients on anti-hypertensive medications had BP greater than 130/80 mmHg, representing suboptimal control as per ACC/AHA guidelines (Table 1).

Renal damage, defined as a SLICC renal score $\geq$ 1, was present in 21% (N=15) of Caucasian patients taking HTN medications, and in 46% (N=17) of patients of another race taking HTN medications.

Multivariate analyses of the 108 patients included sex, race/ethnicity, age at last visit, BMI, SLE duration, disease activity (SLEDAI-2K), renal damage, number of anti-hypertensive medications, as well as prednisone and NSAID use. Caucasian SLE patients were more likely to have uncontrolled HTN according to the ACC/AHA definition (odds ratio, OR 2.72, 95% CI 1.12-6.78). We noted that higher BMI also was associated with uncontrolled HTN (OR 1.08, 95% CI 1.00-1.19). Conversely, patients with renal damage had better BP control (OR 0.39, 95% CI 0.16-0.97). The effects of the other variables assessed were not clear as the 95% CIs were wide and included the null value (Table 2).

Discussion

Hypertension is an important contributor to cardiovascular disease, renal damage and death in SLE patients (3,4). Prior studies have identified risk factors for HTN onset in SLE (13), but there are less data assessing risk factors for uncontrolled HTN. In our cohort, 24.4% of SLE patients were taking medications for HTN. Prior studies have estimated that 33% to 48% of SLE patients take an antihypertensive medication or have a BP measure surpassing 140/90 mmHg (2,14-15). Importantly, we found a high prevalence of uncontrolled hypertension, with 43 (39.8%) of the 108 patients taking antihypertensive medications having uncontrolled BP according to the Canadian guidelines, and 72 patients (66.7%) according to ACC/AHA guidelines. This finding reinforces the need to examine risk factors contributing to uncontrolled BP in SLE, in order to better manage our patients.

Among the 108 patients from the cohort currently taking anti-hypertensive medications, the most commonly used medication class were ARBs, followed by CCB, diuretics, ACEI, and beta-blockers. There are no specific guidelines for the first-line antihypertensive medication to use in

SLE, however ARB and ACEI have been recommended due to their additional beneficial effect in renal and cardiovascular disease (16,17). The next most commonly used antihypertensive agent in our cohort, CCB, is useful in patients with Raynaud's syndrome and/or pulmonary artery hypertension, important clinical manifestations of SLE (16). Diuretics and beta-blockers have not been widely studied in hypertensive SLE patients. While they can be efficacious, they may cause photosensitivity, a common comorbidity in SLE, with early reports suggesting they may trigger cutaneous lupus (18). Beta-blockers may also worsen Raynaud's phenomenon, which is prevalent in SLE. Of note, many of our patients received combination HTN therapies.

In our cohort, Caucasians were more likely to have uncontrolled HTN. This finding differs from previous studies in SLE, which found that race/ethnicity groups traditionally at high risk of suboptimal BP control, such as African Americans, were indeed more likely to have resistant HTN (5). However, Caucasian race has not always been associated with good HTN control in the general American population (19). The observed associations between Caucasian race/ethnicity and uncontrolled HTN in our SLE sample may suggest that non-Caucasians were aggressively treated, perhaps because of the knowledge that this demographic is susceptible to poor outcomes. In addition, renal damage in our cohort was negatively associated with uncontrolled HTN (OR 0.39 95% CI 0.16-0.97), which is reassuring as controlling BP is key to preventing further renal damage. Although our analysis has adjusted for renal disease, this result may contribute to why Caucasian patients, with less renal damage than non-Caucasians, had poorer blood pressure control. We noted that patients with higher BMI were more likely to have poor BP control (OR 1.08, 95% CI 1.00-1.19). Risk factors for uncontrolled HTN were analyzed according to ACC/AHA guidelines, as they recommend a lower blood pressure target, which could be beneficial to SLE

patients given the increased risk of cardiovascular disease. Of note, current published HTN guidelines do not specifically provide a target for SLE patients, therefore studies aiming to define a target are needed. We could not draw definitive conclusions on the other variables assessed as the 95% CIs were imprecise and included the null value.

Potential limitations to our study should be noted. Our study was cross-sectional, and the blood pressure of cohort patients was taken as a single measurement at annual visits. Further work using a longitudinal repeated measure design is needed to explore the effects of those variables, in addition to HTN treatment, disease activity, disease damage (e.g., renal failure associated with SLE), and concomitant medications (e.g. steroids, NSAIDs) on HTN in SLE. Also, we studied patients from a tertiary care centre within a specialized clinic, and within the setting of universal health care. The results do suggest that good BP control is possible in high-risk SLE patients including non-Caucasians and those with renal damage, though this may be more difficult in other settings such as non-universal health care, where problems with health care access and patient adherence may create difficulties.

In summary, our cross-sectional analysis showed that 24.4% of SLE patients were currently taking medications to treat HTN, and that over one-third required two or more medications concurrently. Angiotensin receptor blockers, ACEI, and CCB were common antihypertensive choices, and diuretics were often used despite concerns in the literature regarding photosensitivity and lupus rash. Among the 108 patients taking antihypertensive medications, 39.8% had suboptimal control as per Canadian guidelines and 66.7% had suboptimal control as per ACC/AHA guidelines. In our cohort, Caucasian SLE patients were more likely to have uncontrolled HTN, and we found a negative association between renal damage and our outcome.

The results suggest that good BP control is possible in high-risk SLE patients including non-Caucasians and those with renal damage, though this may be more difficult in other settings (such as non-universal health care and suboptimal care access).

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Tables

Table 1. Characteristics of the 108 SLE patients treated for HTN, controlled vs. uncontrolled HTN (>130/80 mmHg).

Variables	All patients N=108	Controlled, N= 36	Uncontrolled, N=72	Differences (95% CI)[a]
Male sex, N (%)	18 (16.7)	6 (16.7)	12 (16.7)	**<0.01 (-0.17, 0.14)**
Caucasian race/ethnicity, N (%)	71 (65.7)	19 (52.8)	52 (72.2)	**0.19 (0.00, 0.38)**
Age at last visit > 65 years, N (%)	45 (41.7)	12 (33.3)	33 (45.8)	**0.12 (-0.07, 0.30)**
Mean body mass index, BMI (SD)	26.6 (5.2)	25.6 (5.1)	27.1 (5.2)	**2.04 (-0.42, 4.17)**
Mean SLE duration, years (SD)	23.5 (14.2)	23.1 (15.2)	23.7 (13.8)	**0.94 (-5.01, 6.96)**
SLEDAI-2K ≥4, N (%)	48 (44.4)	18 (50.0)	30 (41.7)	**0.08 (-0.11, 0.27)**
Renal damage ≥1, N (%)	32 (29.6)	16 (44.4)	16 (22.2)	**0.22 (0.04, 0.40)**
Prednisone use, N (%)	16 (14.8)	5 (13.9)	11 (15.3)	**0.01 (-0.15, 0.14)**
NSAIDs use, N (%)	5 (4.6)	1 (2.8)	4 (5.6)	**0.03 (-0.09, 0.11)**
Using >1 BP medication, N (%)	38 (35.2)	10 (27.8)	28 (38.9)	**0.11 (-0.08, 0.28)**
Mean Systolic BP, (SD)	134.2 (18.2)	116.0 (9.4)	143.2 (14.3)	**26.0 (21.0, 31.0)**
Mean Diastolic BP, (SD)	**79.9 (10.8)**	**70.7 (6.3)**	**84.6 (9.5)**	**13.0 (10.0, 16.0)**

[a] The difference in proportions between groups (Controlled (n = 36) and Uncontrolled (n = 72) as well as their 95% confidence intervals. This analysis was performed using the Newcombe-Wilson score method. For continuous variables. For continuous variables (body mass index, SLE duration, systolic BP and diastolic BP), we used the Wilcoxon test to determine the confidence intervals for the difference.

Table 2. Logistic regression of SLE patients treated for HTN: Odds Ratios (OR) for uncontrolled HTN (>130/80 mmHg).

VARIABLES	UNADJUSTED OR (95% CI)	ADJUSTED OR (95% CI)[a]
MALE SEX	1.00 (0.35-3.11)	1.27 (0.42-4.24)
CAUCASIAN RACE/ETHNICITY	**2.33 (1.01-5.40)**	**2.72 (1.12-6.78)**
AGE AT LAST VISIT > 65 YEARS	1.69 (0.74-3.99)	1.68 (0.71-4.08)
BODY MASS INDEX	1.06 (0.98-1.15)	**1.08 (1.00-1.19)**
SLE DURATION (YEARS)	1.00 (0.97-1.03)	0.99 (0.96-1.02)
SLEDAI-2K ≥ 4	0.71 (0.32-1.60)	0.77 (0.33-1.76)
RENAL DAMAGE ≥ 1	**0.36 (0.15-0.84)**	**0.39 (0.16-0.97)**
USING MORE >1 BP MEDICATION	1.65 (0.71-4.08)	1.54 (0.63-3.96)
PREDNISONE	1.12 (0.37-3.81)	1.17 (0.38-4.14)
NSAIDS	2.06 (0.29-41.10)	1.99 (0.26-41.0)

[a] Adjusted for: age at last visit, sex and race/ethnicity.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5, 6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5, 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5, 6
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	n/a
		(*d*) If applicable, explain how loss to follow-up was addressed	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8,9
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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