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Long-term blood pressure changes in patients treated with anti-CGRP monoclonal antibodies: A retrospective real-world study

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Abstract

Background

Anti-CGRP monoclonal antibodies (mAbs) used for migraine prevention have raised concerns regarding elevated blood pressure. Existing real-world data come mostly from short observation windows or from cohorts treated with a single antibody. We examined how blood pressure evolves over prolonged treatment across all four available anti-CGRP mAbs.

Methods

We performed a retrospective real-world study of adults with chronic migraine treated with one of the four anti-CGRP mAbs (erenumab, fremanezumab, galcanezumab, or eptinezumab). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded at baseline and during routine follow-up visits. Longitudinal changes in SBP and DBP were analyzed using linear mixed-effects models.

Results

A total of 133 patients were included, with a median follow-up of 27 months (range 3–72). In the study group as a whole, there was no statistically significant change in SBP (− 0.047 mmHg/month; 95% CI − 0.108 to 0.013; p = 0.135) or DBP (0.006 mmHg/month; 95% CI − 0.040 to 0.051; p = 0.806). Eight patients (7.0%) developed new-onset hypertension during follow-up. Older age was associated with higher SBP, while pre-existing hypertension was associated with higher SBP and DBP. Individual anti-CGRP mAb revealed no statistically significant change in either SBP or DBP over time.

Conclusions

Anti-CGRP mAb treatment was not associated with a significant change in blood pressure, although new-onset hypertension occurred in a minority of patients underscoring the value of routine BP monitoring during treatment. These findings provide long-term reassurance regarding the blood pressure safety profile of anti-CGRP mAbs.

INTRODUCTION

Calcitonin gene-related peptide (CGRP) is a neuropeptide with well-established roles in nociceptive signaling and vascular regulation. Its pathway has become a major pharmacological target over the past decade, and monoclonal antibodies (mAbs) directed against either the CGRP ligand (fremanezumab, galcanezumab, and eptinezumab) or its receptor (erenumab) have been available since 2018, with demonstrated efficacy and good tolerability in both clinical trials and real-world settings (1–6). Despite this

favorable safety profile, the long-term physiological consequences of sustained CGRP blockade remain incompletely understood, particularly regarding its potential vascular and cardiovascular effects.

Although endogenous CGRP appears to have a limited role in maintaining resting vascular tone and blood pressure under physiological conditions, its vasodilatory effects are well documented and may become more important during cardiovascular stress. Consequently, chronic inhibition of CGRP signaling has raised concerns regarding potential cardiovascular effects, including alterations in blood pressure regulation (7). Although controlled trials did not identify a major cardiovascular risk, post marketing data and observational studies have raised concerns regarding possible increases in blood pressure during anti-CGRP mAb treatment, thereby posing a risk to patients with cardiovascular comorbidity (8–11). The available evidence is, however, inconsistent. Some real-world studies have shown small but clinically relevant blood pressure increases (12, 13), whereas others have not demonstrated significant longitudinal changes (8, 14, 15).

Current knowledge is limited by study design heterogeneity, follow-up duration, blood pressure assessment and patient selection. Moreover, patients treated in routine clinical practice often differ from trial populations with respect to age, comorbidities, baseline cardiovascular risk and concomitant medication. Long-term real-world data are therefore needed to better characterize blood pressure trajectories during treatment with anti-CGRP mAbs. The aim of this study was to assess the longitudinal effects of systolic blood pressure (SBP) and diastolic blood pressure (DBP) in patients with chronic headache disorders treated with anti-CGRP mAbs. A part of the work was presented at the 18th European Headache Congress (EHC) (Rotterdam, The Netherlands, 4–7 December 2025) as an oral presentation (16).

MATERIAL AND METHODS

This retrospective study included patients diagnosed with chronic headache disorders where chronic migraine disorder accounted for a majority of the population. All patients included in this study received treatment at SkåNeuro, a specialized headache clinic located in Lund, Sweden. Clinical data were retrospectively extracted exclusively from electronic medical records covering the period between January 2019 and February 2026.

Study patients

Included participants were adults (≥ 18 years) diagnosed according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) (17). Patients with migraine with and without aura were included, as well as other headache disorders such as cluster headache and other trigeminal autonomic cephalalgias (TACs). All patients were treated with at least one of four anti-CGRP mAbs: eptinezumab, erenumab, fremanezumab, or galcanezumab. Eptinezumab was administered intravenously, whereas the remaining therapies were administered by subcutaneous injection. All patients had previously failed at least two preventive treatments prior to initiation of CGRP mAb therapy, in accordance with Swedish headache treatment guidelines.

Patients were excluded if no blood pressure measurement was recorded at the baseline and first scheduled follow-up visit after treatment initiation. Patients with pre-existing hypertension who were receiving ongoing antihypertensive therapy were not excluded.

Blood pressure measurements

SBP and DBP measurements were obtained as part of standard clinical care at every visit for patients receiving anti-CGRP mAbs. All measurements followed the current guidelines/recommendations of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) (18): a validated automated device fitted with a correctly sized cuff was used, and readings were taken once the patient had rested in a seated position for five minutes with both feet flat on the floor. The attending nurse or physician performed the measurements. Hypertension was classified according to the ESC-ESH thresholds, namely an office SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg.

Information on previously established arterial hypertension along with any antihypertensive medication was retrieved from the medical records. The baseline measurements corresponded to the first evaluation visit typically occurring one to three weeks before initiation of the treatment. According to a standard protocol in our clinic, patient visits were scheduled at intervals of 3, 6, 12, 18, and 24 months, and thereafter yearly following initiation of subcutaneously administered anti-CGRP mAbs. For eptinezumab patients, visits were scheduled every third month. Therapeutic outcomes and potential side effects of the prescribed medication were systematically assessed at each visit. Demographic data, including age and sex, were also recorded, along with clinical data regarding treatment switches, pre-existing hypertension and previous or ongoing treatment with antihypertensive medication.

Ethical considerations

All patients included in the study provided informed consent prior to data collection and participation. Ethical approval for the study was obtained from the Swedish ethics review authority with diary number 2026-01392-02 before study initiation. The study was conducted according to the declaration of Helsinki.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation (SD) or median with interquartile range (IQR), as appropriate, and categorical variables as counts and percentages. Given the retrospective design, no sample-size calculation was performed.

Due to the absence in attendance for the scheduled follow-up visits, blood pressure measurements were not consistently available throughout the study period, resulting in missing data. A linear mixed-effects model was therefore selected as the primary statistical method for analysis of longitudinal changes in SBP and DBP. Time since treatment initiation, age, sex, concurrent antihypertensive medication use, pre-existing hypertension were included as fixed effects. Antihypertensive use was modelled as a time-varying covariate, coded as present whenever an antihypertensive agent was recorded at a given visit, in order to

account for the blood-pressure-lowering effect of these medications on individual measurements. Since some patients switched between anti-CGRP mAbs during follow-up, each course of treatment was handled as a separate treatment period nested within patients, with time reset to zero at the start of each new agent. A patient-level random intercept was included, together with a treatment-period-level random intercept and random slope for time nested within it. A sensitivity analysis was performed without adjustment for antihypertensive use, to assess whether its inclusion materially affected the estimated time effect.

Additionally, a treatment-specific analysis was performed, with a separate model fitted for each mAb (erenumab, fremanezumab, galcanezumab, and eptinezumab). Fixed effects were the same as in the pooled analysis. A treatment-period-level random intercept and random slope for time were used.

Fixed-effect estimates are reported as regression coefficients (mmHg per month for time; mmHg for categorical or scalar covariates) with 95% confidence intervals and corresponding p values. Model assumptions were assessed by inspection of residual distributions. Age and baseline SBP/DBP were compared using one-way ANOVA; sex, pre-existing hypertension and antihypertensive medication at baseline using the chi-square test. All hypothesis testing was two-tailed, and a p value < 0.05 was considered statistically significant. Analyses were performed in R version 4.6.0 using the lme4 and lmerTest packages. R scripts for analysis were generated with the assistance of Claude Sonnet 5.5 (Anthropic). All AI-generated code was reviewed, tested, and revised by the authors, who confirmed the accuracy and reproducibility of the results.

RESULTS

A total of 133 patients were included in the analysis (Fig. 1). The cohort was predominantly female (116/133, 87.2%), with a mean age of 50.6 ± 12.0 years. Most patients had a diagnosis of CM (126/133, 94.7%), while the remaining seven patients had other headache disorders, including hemicrania continua, cluster headache, and new daily persistent headache. Fifty-five patients received intravenous treatment with Eptinezumab, while the remaining patients were treated with subcutaneous CGRP mAbs: Erenumab (n = 22), fremanezumab (n = 27), or galcanezumab (n = 29). Pre-existing hypertension was documented in 18 patients (13.5%), and 10 patients (7.5%) were already receiving antihypertensive medication for hypertension at baseline. Mean baseline SBP and DBP were 123.8 ± 15.2 mmHg and 80.9 ± 9.8 mmHg, respectively. The median follow-up was 27.0 months (IQR 12–45; range 3–72), corresponding to a mean of 30.1 ± 20.5 months. Overall, 107 patients (80.5%) had at least 12 months of follow-up, 75 (56.4%) at least 24 months, and 53 (39.8%) at least 36 months. No statistically significant differences were observed between the four treatment groups with respect to age, sex, baseline blood pressure, pre-existing hypertension, or prior antihypertensive use ($p > 0.05$). Patient characteristics are shown in detail in Table 1.

During the observation period, 19 of the 133 patients (14.3%) switched anti-CGRP mAb at least once; 17 patients received two different agents and 2 patients received three. The most frequent transition was from erenumab to fremanezumab (n = 7), followed by fremanezumab to eptinezumab (n = 5). The

remaining switches were distributed across several combinations, including galcanezumab to erenumab (n = 3), galcanezumab to fremanezumab (n = 2).

Table 1
Baseline demographic and clinical characteristics

Characteristic	Total (N = 133)	Erenumab (n = 22)	Fremanezumab (n = 27)	Galcanezumab (n = 29)	Eptinezumab (n = 55)	p
Age ± SD, years	50.6 ± 12.0	54.9 ± 8.1	49.7 ± 9.8	49.1 ± 12.9	50.2 ± 13.5	0.322
Female sex, n (%)	116 (87.2)	17 (77.3)	25 (92.6)	28 (96.6)	46 (83.6)	0.136
Chronic migraine, n (%)	126 (94.7)	21 (95.4)	27 (100)	27 (93.1)	51 (92.7)	0.547
Pre-existing hypertension, n (%)	18 (13.5)	4 (18.1)	5 (18.5)	1 (3.4)	8 (14.5)	0.315
Antihypertensive medication at baseline, n (%)	10 (7.5)	3 (13.6)	2 (7.4)	1 (3.4)	4 (7.2)	0.598
Baseline SBP ± SD, mmHg	123.8 ± 15.2	123.4 ± 15.9	120.4 ± 16.1	120.5 ± 9.1	127.4 ± 16.6	0.123
Baseline DBP ± SD, mmHg	80.9 ± 9.8	80.4 ± 10.6	79.4 ± 10.1	79.0 ± 7.1	82.8 ± 10.3	0.269

SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation. Values are mean ± SD or n (%). Characteristics are shown for the first agent each patient received. No baseline statistical differences were found between the treatment groups (p values presented in rightmost column).

To evaluate whether blood pressure changed over the course of anti-CGRP treatment, we fitted linear mixed-effects models. When all anti-CGRP mAbs were pooled, time on treatment was not associated with a significant change in either SBP (− 0.047 mmHg per month; 95% CI − 0.108 to 0.013; p = 0.135) or DBP (0.006 mmHg per month; 95% CI − 0.040 to 0.051; p = 0.806) (Table 2). These estimates correspond to a projected change of less than 1 mmHg over a full year of treatment. In a sensitivity analysis without adjustments for antihypertensive use, SBP coefficient showed a small, non-significant decrease (− 0.060 mmHg/month, p = 0.065), DBP results were essentially unchanged (− 0.004 mmHg/month, p = 0.879). The direction and magnitude of these estimates were consistent with the primary analysis, supporting the finding that anti-CGRP treatment was not associated with an increase in blood pressure over time.

In contrast, several of the adjustment covariates were significantly associated with blood pressure, as expected. Older age was associated with higher SBP (0.177 mmHg per year; p = 0.006), and a pre-existing diagnosis of hypertension was associated with substantially higher SBP and DBP (16.8 and 7.9 mmHg higher, respectively; both p < 0.001). One patient with pre-existing, pharmacologically treated hypertension

experienced an increase in blood pressure while on erenumab (maximum 163/97 mmHg) and was switched to galcanezumab the elevation being regarded as a possible effect of the treatment.

Concurrent antihypertensive use was associated with lower SBP and DBP (− 3.8 and − 2.7 mmHg, respectively; p = 0.006 and p = 0.010), consistent with the expected pharmacological effect of these medications. Taken together, these findings suggest that anti-CGRP mAb treatment was not independently associated with any significant increase in blood pressure over time.

In total, 8 patients (7.0%) developed new-onset hypertension during a median follow-up of 44 months (44.6 ± 18.9 months, range 18–72). The mean age was 55.8 ± 4.9 years (range 47–61). Of these patients, 6 were started on antihypertensive medication, most commonly candesartan, followed by amlodipine and enalapril. After blood pressure was adequately controlled, all affected patients were able to continue anti-CGRP treatment.

Table 2
Linear mixed-effects models for systolic and diastolic blood pressure (All anti-CGRP mAbs, n = 133, 816 observations)

Predictor	SBP monthly change (mmHg)	95% CI	p	DBP monthly change (mmHg)	95% CI	p
Time (per month)	−0.047	−0.108, 0.013	0.135	0.006	−0.040, 0.051	0.806
Age (per year)	0.177	0.052, 0.302	**0.006**	0.081	−0.016, 0.178	0.103
Sex (male vs. female)	1.508	−2.954, 5.970	0.509	−2.075	−5.510, 1.360	0.239
Pre-existing hypertension	16.768	12.230, 21.306	**< 0.001**	7.859	4.366, 11.352	**< 0.001**
Antihypertensive use[a]	−3.841	−6.564, − 1.118	**0.006**	−2.686	−4.721, − 0.652	**0.010**

Bold p values are significant at p < 0.05. [a]Time-varying covariate indicating concurrent antihypertensive medication at a given visit. CI, confidence interval.

When each anti-CGRP mAb was analyzed separately, none showed a statistically significant change in either SBP or DBP over time (Table 3). For SBP, the estimated monthly changes ranged from − 0.151 mmHg/month with eptinezumab to + 0.029 mmHg/month with galcanezumab. DBP was similarly stable across all anti-CGRP mAbs, with monthly changes ranging from − 0.080 mmHg/month to + 0.046 mmHg/month. None of the associations were significant after Bonferroni correction. Altogether, the drug-specific analyses were consistent with the pooled model and indicated that there is no evidence of systematic longitudinal increase in blood pressure for any individual anti-CGRP mAb.

Table 3
Drug-specific effect of time on blood pressure

Anti-CGRP	Treatment periods, n	Observations, (n)	Monthly change (mmHg)	95% CI	p	p_adj
Systolic blood pressure						
Erenumab	26	118	0.025	−0.090, 0.139	0.682	1.000
Fremanezumab	36	198	−0.119	−0.246, 0.009	0.085	0.681
Galcanezumab	31	168	0.029	−0.064, 0.122	0.541	1.000
Eptinezumab	61	332	−0.151	−0.345, 0.043	0.139	1.000
Diastolic blood pressure						
Erenumab	26	118	0.046	−0.042, 0.134	0.320	1.000
Fremanezumab	36	198	0.015	−0.074, 0.104	0.745	1.000
Galcanezumab	31	168	0.031	−0.040, 0.102	0.405	1.000
Eptinezumab	61	332	−0.080	−0.203, 0.044	0.215	1.000

A treatment period refers to the interval a patient spent on a single anti-CGRP mAb; patients who switched mAb contributed one period per mAb. p_adj: Bonferroni-adjusted for 4 different anti-CGRP mAbs and SBP/DBP comparisons. CI, confidence interval; mo, month.

DISCUSSION

In this retrospective real-world study, we found no evidence of a systematic increase in SBP or DBP during longitudinal treatment with anti-CGRP mAbs. When all four available mAbs were analyzed together, the estimated change in blood pressure over time was small and not statistically significant, corresponding to less than 1 mmHg over one year of treatment. Similarly, no significant longitudinal increase in either SBP or DBP was observed when erenumab, fremanezumab, galcanezumab, and eptinezumab were analyzed separately. In contrast, pre-existing hypertension was associated with higher blood pressure during follow-up, emphasizing the importance of the patient's underlying cardiovascular risk profile.

These findings add to an evolving and partly conflicting literature concerning the cardiovascular consequences of CGRP pathway inhibition. CGRP is a potent vasodilatory neuropeptide and contributes to cardiovascular homeostasis, particularly under conditions of increased vascular stress (19). Consequently,

concerns have been raised that sustained inhibition of CGRP signaling could attenuate compensatory vasodilation and contribute to increased blood pressure (7). This concern gained further attention following post-marketing reports of new-onset or worsening hypertension, particularly in patients treated with the CGRP-receptor antibody erenumab (20).

A prospective real-world study by de Vries Lentsch et al. reported modest increases in SBP and DBP during treatment with erenumab or fremanezumab, with maximum estimated mean increases of approximately 5 mmHg systolic and 3–4 mmHg diastolic during 12 months of follow-up (12). The increase appeared more consistent in patients receiving erenumab, and a small proportion of previously normotensive patients required initiation of antihypertensive treatment. These observations together with other real-world data (21) raised the possibility that blockade of the CGRP receptor might have clinically relevant vascular effects in susceptible individuals.

However, subsequent observational studies have not consistently reproduced these findings. Kaltseis et al. examined 259 patients treated with anti-CGRP mAbs in a real-world headache cohort and found no treatment-associated increase in blood pressure; SBP and DBP instead showed small decreases during follow-up (14). Importantly, pre-existing hypertension was the strongest predictor of hypertensive blood pressure measurements during treatment, which is consistent with our findings. More recent prospective data using 24-hour ambulatory blood pressure monitoring have likewise not demonstrated a significant early hypertensive effect of anti-CGRP mAb treatment (22). Furthermore, recent registry-based data following patients treated with erenumab for at least 12 months reported stable SBP and DBP, with similar findings in a subgroup followed for up to 24 months (23).

Our study extends these observations in several aspects. First, the longitudinal analysis incorporated repeated measurements obtained during routine clinical care rather than relying on isolated baseline and endpoint comparisons. Second, all four currently available anti-CGRP mAbs were represented, including eptinezumab, for which longitudinal real-world blood pressure data remain comparatively limited. Third, patients with pre-existing hypertension were not excluded, allowing assessment in a population more representative of routine headache care practice. This is particularly relevant because patients encountered in clinical practice may have a greater cardiovascular burden than participants typically enrolled in randomized clinical trials.

We found no clear evidence of differences between receptor and ligand blockade with respect to longitudinal blood pressure changes. Erenumab, which targets the canonical CGRP receptor, was not associated with an increase in either SBP or DBP over time. Similarly, no significant changes were observed with the ligand-targeting antibodies fremanezumab, galcanezumab, or eptinezumab. These findings do not support a clinically meaningful progressive blood pressure effect specific to receptor blockade in our cohort. However, the drug-specific analyses included smaller numbers of patients and consequently had limited power to detect small differences between individual agents. Direct comparisons between monoclonal antibodies should therefore be interpreted cautiously.

In our cohort, 8 of 115 patients without pre-existing hypertension (7.0%) developed new-onset hypertension during a median follow-up of 44 months. These patients were older than the overall cohort (mean age 55.8 ± 4.9 vs 50.6 ± 12.0 years) and had a longer follow-up (median 44 vs 27 months). This appears broadly consistent with incidence rates reported in middle-aged Nordic/general populations, typically around 15–30 cases per 1,000 person-years depending on baseline blood pressure (24). Previous studies have also demonstrated that the use of CGRP antagonists does not affect blood pressure in elderly patients (25). Thus, the observed cases do not suggest a clear risk attributable to anti-CGRP treatment.

Another important observation was the association between pre-existing hypertension and blood pressure during follow-up. Patients with pre-existing hypertension had substantially higher SBP and DBP independent of treatment duration. This observation is consistent with previous research (14, 26) and is clinically relevant, as it indicates that baseline cardiovascular status may be a stronger determinant of subsequent blood pressure than the duration of anti-CGRP exposure. Nevertheless, absence of a mean increase at the population level does not exclude clinically relevant blood pressure elevations in individual susceptible patients. Routine blood pressure assessment therefore remains warranted, particularly in patients with established hypertension or other cardiovascular risk factors.

Several limitations of the current study should be considered. The retrospective and single-center design limits causal inference, and the absence of a control group prevents separation of treatment-related effects from background changes in blood pressure over time. A substantial proportion of potentially eligible patients were excluded because baseline or follow-up blood pressure measurements were unavailable, introducing the possibility of selection bias. When anti-CGRP mAbs were initially introduced, routine blood pressure monitoring was not in place, as phase 3 trials had not demonstrated a relevant increase in blood pressure (8–10). However, following broader clinical use of anti-CGRP therapies and emerging concerns regarding possible blood pressure elevations, we introduced new clinical routines, including regular blood pressure measurements and more systematic assessment of potential adverse effects. Blood pressure measurements were obtained during routine clinical care and, although performed according to a standardized clinical procedure, were based on office measurements rather than systematic ambulatory or home blood pressure monitoring. Furthermore, the number of patients differed between monoclonal antibodies, limiting statistical power for drug-specific comparisons. The cohort consisted predominantly of patients with chronic migraine, and the results may therefore not be fully generalizable to populations with episodic migraine or other headache disorders. Finally, changes in antihypertensive treatment during follow-up may influence longitudinal blood pressure measurements and should be considered when interpreting the observed trajectories.

Despite these limitations, our findings provide reassuring long-term real-world evidence regarding blood pressure during anti-CGRP mAb treatment. Across repeated measurements and four different antibodies, we found no evidence of a progressive increase in SBP or DBP over time. These results support the overall blood pressure safety of anti-CGRP mAbs at the population level while also highlighting pre-existing hypertension as an important determinant of blood pressure during treatment. Continued blood pressure monitoring appears particularly appropriate in patients with established hypertension or increased cardiovascular risk.

CONCLUSIONS

In this study treatment with anti-CGRP mAbs was not associated with a significant change in SBP or DBP. New-onset hypertension occurred in a minority of patients, and all were able to continue treatment once blood pressure was controlled. Pre-existing hypertension and older age were the main determinants of blood pressure during follow-up. These findings support the long-term blood pressure safety of anti-CGRP mAbs at the population level. Routine blood pressure monitoring remains advisable, particularly in patients with established hypertension or increased cardiovascular risk.

Abbreviations

CGRP
Calcitonin gene-related peptide
DBP
diastolic blood pressure
ESC
European Society of Cardiology
ESH
European Society of Hypertension
mAb
monoclonal antibody
SBP
systolic blood pressure

Declarations

Ethics approval and consent to participate

All patients included in the study provided informed consent prior to data collection and participation. Ethical approval for the study was obtained from the Swedish Ethics Review Authority, Etikprövningsmyndigheten, (etikprovningsmyndigheten.se) with diary number 2026-01392-02 before study initiation. The study was conducted according to the declaration of Helsinki.

Consent for publication

Not applicable

Competing Interests

GS has received consulting and speaking fees from Allergan, AbbVie, Lundbeck, Novartis, Pfizer, and Teva. He participated as principal investigator and national coordinator in clinical trials sponsored by AbbVie, Lundbeck, Pfizer, and Teva. ET, PN, PP, SU have no conflict of interest to declare.

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Author Contribution

SU: Data curation, Formal analysis, Investigation, Project administration, Visualization, Writing – review & editing, Writing – original draft. ET: Data curation, Investigation, Writing – review & editing, Writing – original draft. . PN: Data curation, Writing – review & editing, Writing – original draft. PP: Methodology, Supervision, Writing – review & editing. GS: Resources, Conceptualization, Methodology, Writing review & editing, Supervision.

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Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

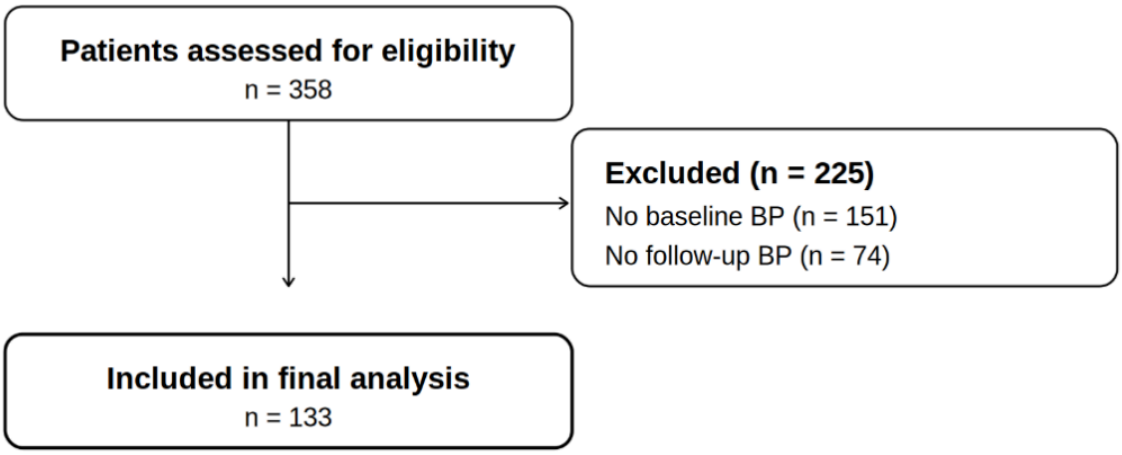


Figure 1

Patient flow diagram. Of 358 patients assessed for eligibility, 225 were excluded because of missing blood pressure data (151 lacking baseline reading and 74 lacking a follow-up measurement), leaving 133 patients in the final analysis. BP, blood pressure.