Full title:
Remnant Cholesterol and Intensive Blood Pressure Control in Older Patients with Hypertension: A Post hoc Analysis of the STEP Randomized Trial

Running header title:
Remnant Cholesterol and Intensive Blood Pressure Control in Older Patients

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Previous presentation:

Part of the results has been presented orally at the 32nd Scientific Meeting of the European Society of Hypertension (ESH) on June 24th.
Abstract

Aims: Emerging evidence shows a close relationship between remnant cholesterol (RC) and hypertension. However, it is unknown whether RC is associated with the effects of intensive systolic blood pressure (SBP) lowering on cardiovascular outcomes.

Methods: We performed a post-hoc analysis of the Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) trial. Participants were randomly allocated to intensive (110 to <130 mmHg) or standard (130 to <150 mmHg) treatment groups. The effects of intensive SBP lowering on the primary composite outcome (stroke, acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation or cardiovascular death), the components thereof and all-cause mortality were analyzed by tertile of baseline RC (lowest, middle, highest).

Results: We followed 8,206 patients for 3.33 years (median). The adjusted hazard ratios (95% confidence interval) for the primary outcome were 1.06 (0.73–1.56), 0.58 (0.38–0.87) and 0.67 (0.46–0.96) in the lowest, middle and highest RC tertiles, respectively (P for interaction=0.11). However, significant heterogeneity in the treatment effects was observed when comparing the upper two tertiles with the lowest tertile (P for interaction=0.033). For all-cause mortality, the adjusted hazard ratios (95% confidence interval) were 2.48 (1.30–4.73), 1.37 (0.71–2.65) and 0.42 (0.22–0.80) in the lowest, middle and highest RC tertiles, respectively (P for interaction<0.0001).

Conclusion: Baseline RC concentrations were associated with the effects of intensive SBP lowering on the primary composite cardiovascular outcome and all-cause mortality.
in hypertensive patients. These results are hypothesis-generating and merit further study.

Registration: STEP ClinicalTrials.gov number, NCT03015311

Key words: Hypertension; Intensive SBP lowering; Cardiovascular outcomes; Remnant cholesterol
Lay summary

In our post hoc analysis of the STEP trial, baseline remnant cholesterol (RC) concentrations were associated with the effects of intensive SBP lowering on the primary composite cardiovascular outcome and all-cause mortality in hypertensive patients.

- Patients with higher RC experienced greater cardiovascular benefits from intensive SBP lowering, while lower RC was associated with attenuated benefits or even negative effects of intensive SBP lowering. These results are hypothesis-generating and merit further study.

- If confirmed, RC measurements could permit identification of a subset of patients with high RC and hypertension who may receive greater benefit from intensive SBP lowering to less than 130 mmHg.
Introduction

Despite lipid control therapy recommended by current guidelines, a high residual risk of cardiovascular disease exists.\(^1\) Remnant cholesterol (RC) contributes to this residual risk.\(^2\) RC refers to the cholesterol content in triglyceride-rich lipoproteins. Under fasting conditions, RC comprises very low-density lipoprotein cholesterol and intermediate-density lipoprotein cholesterol; under non-fasting conditions, RC comprises chylomicron remnants with the aforementioned two lipoproteins.\(^3\) RC is highly atherogenic; therefore, elevated RC is associated with a high risk of arterial stiffness, coronary heart disease, aortic valve stenosis, ischaemic stroke and all-cause mortality.\(^4\)–\(^12\)

With various shared risk factors, dyslipidaemia, such as abnormal RC and hypertension often coexist and have a close relationship. Both cross-sectional and prospective studies have shown that RC is associated with high central systolic blood pressure (SBP)\(^13\) and the development of hypertension.\(^14\)–\(^16\) In turn, hypertensive patients have high RC concentrations.\(^17\) Patients with both hypertension and high RC have a higher risk of cardiovascular disease than those with hypertension or high RC alone, which suggests hypertension and high RC may have a combined effect on cardiovascular risk.\(^18\) Recently, the Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) trial demonstrated that, compared with standard SBP lowering, intensive SBP lowering achieved significant cardiovascular benefits in Chinese patients aged 60–80 years.\(^19\)

Given the close relationship between RC and hypertension, RC may influence the
effects of intensive SBP lowering on cardiovascular outcomes in hypertensive patients. Accordingly, we performed a secondary analysis of the STEP trial to determine for the first time whether baseline RC is associated with the effects of intensive SBP lowering in hypertensive patients aged 60–80 years. Furthermore, we aimed to identify individuals who may derive the greatest benefits from intensive SBP control.

Methods

Study design and population

This study was a post hoc analysis of the multicentre, prospective randomized STEP trial. The study design, protocol, procedure and results were published previously. Participants aged 60–80 years with SBP of 140–190 mmHg or antihypertensive medication use were included. Those with ischaemic or haemorrhagic stroke history were excluded. In total, 8,511 participants were included and received either intensive SBP treatment (110 to <130 mmHg) or standard SBP treatment (130 to <150 mmHg) to evaluate the effects on cardiovascular outcomes. After excluding participants with missing data for baseline RC value or key covariates, 8,206 participants were included. All STEP participants provided written informed consent, and the study was approved by the institutional review board of each participating institution.

Intervention

All participants received either intensive or standard SBP treatment. Physicians
collected information on the use of antihypertensive drugs and other concomitant medication at each follow-up visit. Adjustments in antihypertensive medication were allowed to achieve SBP targets in either intensive or standard treatment arms throughout the study.

**BP measurement**

BP was measured monthly during the first 3 months and every 3 months thereafter. During each visit, trained staff used a validated monitor (Omnion Healthcare, Kyoto, Japan) to measure office BP three times in a seated position, and the mean values were recorded.

**Data collection**

Fasting blood samples were collected at randomization and appropriately transported to the central laboratory at Beijing CIC Clinical Laboratory. Serum concentrations of triglyceride, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), glucose and creatinine were measured using an automatic biochemical analyzer (AU5800; Beckman Coulter, Brea, CA, USA). RC was calculated as fasting TC minus HDL-C minus LDL-C. The mean RC during follow-up was calculated for each subject as the mean achieved RC. Estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease equation for Chinese patients. Weight and height were measured by trained staff to calculate body mass index (BMI). The Framingham 10-year cardiovascular death risk was assessed using the Framingham risk score. Standardized questionnaires were used to obtain data on...
demographics, lifestyle, medical history and medication use.

Outcomes

The primary composite cardiovascular outcome comprised stroke (ischaemic or haemorrhagic), acute coronary syndrome (acute myocardial infarction and hospitalization for unstable angina), acute decompensated heart failure, coronary revascularization, atrial fibrillation and death from cardiovascular causes. The secondary outcomes were the individual components of the primary outcome and death from any cause. Safety outcomes were also assessed and comprised adverse events (hypotension and dizziness) and serious adverse events (syncope and fracture). The safety outcomes were defined in the previous analysis. The event adjudication committee of the STEP trial was responsible for final assessment of all outcomes.

Statistical analysis

The present analyses were non-prespecified in the trial protocol. Baseline characteristics were compared across tertiles of baseline RC using Pearson’s chi-squared test for categorical variables. Continuous variables were compared using the one-way ANOVA test for normally-distributed data and the Kruskal–Wallis rank sum test for non-normally-distributed data. We calculated the mean achieved SBP during follow-up by averaging the SBP measurements from month 3 to the last available reading.

We assessed the primary and secondary outcomes for intensive vs. standard SBP treatment arms by baseline RC tertile. This was performed using the Fine–Gray sub-
distribution hazard model to account for the competing risk of all-cause death or non-cardiovascular death, except for all-cause mortality, which was evaluated by a Cox proportional hazards regression model. Analyses were multivariable-adjusted for potential confounders in accordance with previous studies and comprised baseline patient characteristics (age, sex, BMI, eGFR, fasting serum glucose, SBP, diastolic BP, LDL-C, HDL-C, cardiovascular disease history [yes/no], diabetes history [yes/no], hyperlipidaemia history [yes/no], statin use history [yes/no] and current smoking status [yes/no]). Proportional hazards assumptions were not violated. To determine the interaction between SBP treatment arm and RC tertile, we included the product term (SBP treatment arm × RC tertile) in the aforementioned models.

We also performed logistic regression analyses between the treatment arms to evaluate the safety outcomes across RC tertiles, both unadjusted and adjusted for the aforementioned covariates. We included interaction terms between SBP treatment arm and RC tertile to assess heterogeneity of treatment effects regarding adverse events.

Several sensitivity analyses were performed. First, given the influence of baseline statin use on RC concentrations, we repeated the aforementioned analyses in a subset of the cohort that comprised participants without statin use at baseline. Second, sensitivity analyses were performed by additional adjustment of the mean achieved RC during follow-up. Furthermore, to investigate possible reverse causation bias for all-cause mortality, we also excluded individuals who died from

1  distribution hazard model to account for the competing risk of all-cause death or
2  non-cardiovascular death, except for all-cause mortality, which was evaluated by a
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6  diastolic BP, LDL-C, HDL-C, cardiovascular disease history [yes/no], diabetes
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23 achieved RC during follow-up. Furthermore, to investigate possible reverse
24 causation bias for all-cause mortality, we also excluded individuals who died from
any cause within 2 years after randomization, as a sensitivity analysis.

All analyses were performed using R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided $P<0.05$ and 95\% confidence intervals (CI) were used for all statistical comparisons.

Results

Study cohort and population characteristics

The selection of participants is shown in Figure S1. The present study included 8,206 participants (mean age: 66.3 ± 4.8 years; male sex: 46.5\%; mean baseline SBP: 146.1 ± 16.7 mmHg; mean baseline diastolic BP: 82.5 ± 10.6 mmHg; mean BMI: 25.6 ± 3.2 kg/m$^2$). The baseline demographic, clinical and laboratory characteristics across tertiles of the baseline RC are summarized in Table 1 and Table S1. We showed the median RC concentrations at baseline and during follow-up by tertile in Figure S2. The median (interquartile range) of RC concentrations at baseline were 0.5 (0.4–0.6), 0.8 (0.7–0.9) and 1.3 (1.1–1.6) mmol/L in the lowest, middle and highest RC tertiles, respectively. Generally, individuals in the highest tertile were slightly younger and more often female and had higher BP, poorer glycaemic and lipid control, higher 10-year Framingham risk score and lower proportion of a history of statin use compared with those in the lower tertiles.

BP

Intensive and standard SBP-lowering strategies quickly resulted in BP differences between the treatment arms across RC tertiles. BP values during follow-up in the
RC tertiles are shown in Figure S3. At the end of the trial, in the intensive SBP-lowering treatment arm, mean SBP (95% CI) was 124.6 mmHg (123.5–125.6), 126.8 mmHg (125.8–127.9) and 125.9 mmHg (124.7–127.1) in the lowest, middle and highest RC tertiles, respectively. In the standard SBP-lowering treatment arm, mean SBP (95% CI) was 135.5 mmHg (134.4–136.7), 135.0 mmHg (133.9–136.2) and 134.7 mmHg (133.5–136.0) in the lowest, middle and highest RC tertiles, respectively.

The mean achieved SBP levels (mmHg) were controlled within the target range during follow-up (intensive vs. standard: 127.0 [95% CI 126.7–127.3] vs. 135.8 [135.5–136.1] in the lowest tertile; 127.6 [127.2–127.9] vs. 136.1 [135.8–136.4] in the middle tertile and 127.6 [127.3–127.9] vs. 136.4 [136.1–136.8] in the highest tertile).

**RC and intensive SBP control**

The number of events for each of the outcomes by baseline RC tertile and study assignment are shown in Figure 1. During a median follow-up of 3.33 years, there were 109, 104 and 117 primary composite outcome events in the lowest, middle and highest RC tertiles, respectively. The adjusted hazard ratios (HRs) (95% CI) for intensive vs. standard SBP lowering were 1.06 (0.73–1.56), 0.58 (0.38–0.87) and 0.67 (0.46–0.96) in the lowest, middle and highest RC tertiles, respectively (P for interaction=0.11). Next, we compared the HRs for the effect of intensive SBP lowering on the primary outcome between the lowest and the upper two tertiles (Figure 2). A significant difference for treatment effect on the primary outcome
between the lowest RC tertile and the upper two tertiles was observed. The adjusted
HR (95% CI) for the primary outcome was 1.06 (0.73–1.56) in the lowest RC tertile
and 0.63 (0.48–0.83) in the upper two RC tertiles (P for interaction=0.033). For all-
cause mortality (Figure 1), there was a significant interaction (P for
interaction<0.0001) in which participants in the highest RC tertile derived strong
benefit from intensive SBP lowering (adjusted HR, 0.42 [95% CI, 0.22–0.80]), with
no appreciable benefit or even with a negative effect in those in the middle (adjusted
HR, 1.37 [95% CI, 0.71–2.65]) and lowest RC tertiles (adjusted HR, 2.48 [95% CI,
1.30–4.73]). In the analyses of other secondary outcomes, risk reduction was
nominally significant for acute coronary syndrome in the highest RC tertile;
however, none of the P-values for the interactions for these outcomes (i.e., stroke,
acute coronary syndrome, acute decompensated heart failure, coronary
revascularization, atrial fibrillation and death from cardiovascular causes) by RC
tertile were statistically significant.

Regarding adverse events, including hypotension and dizziness, the effects of
intensive vs. standard SBP lowering did not differ by RC tertile (all P for
interactions>0.05; Figure S4). The results of the univariable analysis for serious
adverse events, such as syncope and fracture, are shown in Table S2. No
multivariable analyses were performed because of the small number of serious
adverse events.

Results were not materially changed in the sensitivity analyses performed by
excluding participants with baseline statin use (Table S3 and S4) and by additional
adjustment of the mean achieved RC during follow-up (Table S5 and S6). To limit reverse causation bias for all-cause mortality, we excluded 60 participants who died from any cause within 2 years (the causes of death are listed in Table S7), and a significant interaction between baseline RC tertile and SBP treatment arm for all-cause mortality was consistently observed ($P$ for interaction=0.0012; Table S8).

**Discussion**

In this post hoc analysis of the STEP trial, we found that baseline RC was associated with the effects of intensive SBP lowering in patients with hypertension. Specifically, in the upper two RC tertiles, participants in the intensive SBP treatment group had a lower incidence of the primary composite outcome than those in the standard treatment group; whilst this cardiovascular benefit was attenuated in those in the lowest RC tertile. There was a reduction in all-cause mortality in the intensive treatment group compared with the standard treatment group in the highest RC tertile; however, no significant or even an increased all-cause mortality was observed in the intensive vs. standard treatment groups in the middle and lowest tertiles. Our novel findings suggest that the benefits of intensive SBP lowering may differ by baseline RC, whereby hypertensive patients with higher RC may garner the greatest benefits from intensive SBP lowering.

Emerging evidence has emphasized the important role of RC in residual cardiovascular risk. Observational and Mendelian randomization studies have found that elevated RC concentrations increase the risk of coronary heart disease, aortic
valve stenosis, ischaemic stroke and all-cause mortality.\textsuperscript{4–11} Compared with LDL-C, RC appears to have a higher predictive value for cardiovascular risk.\textsuperscript{23} Even under statin-treated conditions, high RC remains associated with high rates of coronary artery disease.\textsuperscript{24} Mechanistically, RC is more likely to penetrate and accumulate in the arterial wall and cause atherosclerosis and cardiovascular disease.\textsuperscript{2} Recently, the relationship between RC and hypertension has received increased attention. A previous study found that high RC was associated with arterial stiffness as measured by brachial-ankle pulse wave velocity.\textsuperscript{25} In a Chinese community-based cohort, high RC was associated with high central SBP independent of the other lipid levels.\textsuperscript{13} After a 10-year follow-up in a Japanese general population, more new-onset hypertension occurred in subjects with higher baseline RC.\textsuperscript{14} Consistently, a cross-sectional analysis of 2,199,366 individuals found a close relationship between RC and hypertension prevalence and incidence and suggested that high RC precedes hypertension development in a cross-lagged analysis.\textsuperscript{15} Among patients with diabetes, high RC also increases the risk of hypertension.\textsuperscript{16} In turn, hypertensive patients often have high RC levels.\textsuperscript{17} Individuals with concurrent hypertension and high RC experience more cardiovascular risks compared with those with hypertension or high RC alone,\textsuperscript{18} suggesting that high RC and hypertension may interact and worsen cardiovascular disease. These results from epidemiological studies may be explained by plausible biological mechanisms. RC can enter and be retained in the subendothelial space and is easily taken up by macrophages to promote atherosclerotic plaque formation, impair endothelial function and induce...
inflammation. Persistent inflammation further impairs nitric oxide-mediated endothelium-dependent relaxation and exacerbates vascular oxidant stress; thereby, aggravating vascular injury. These factors worsen vasomotor function and subsequently promote hypertension. Furthermore, high RC is associated with insulin resistance and aldosterone secretion (mainly the role of very low-density lipoprotein cholesterol [VLDL-C]), which are also hallmarks in the pathogenesis of hypertension.

Intensive SBP lowering has been recognized as an effective intervention to reduce cardiovascular diseases in hypertensive patients following the success of the SPRINT trial, which is also supported by the STEP trial results. However, individualized intensive SBP treatment remains a challenge. To our knowledge, ours is the first study to examine whether baseline RC concentrations modify the effects of intensive SBP lowering, and we found that patients with higher RC experienced greater benefits from intensive SBP lowering. Intensive SBP management may mediate the aforementioned overlapping pathogenic mechanisms, resulting in reduced vascular damage, attenuated inflammation, improved insulin resistance and decreased sodium and water retention. As a result, intensive SBP lowering could reasonably reduce the incidence of the primary cardiovascular outcome and all-cause mortality in hypertensive patients with higher RC. On the other hand, the baseline RC tertile in the present study stratified participants into three groups representing different Framingham risk scores, whereby those with higher baseline RC showed higher Framingham risk scores. Previous studies demonstrated that
patients at higher risk are more likely to receive benefits and experience fewer adverse effects with intensive SBP lowering.\textsuperscript{33–35} Accordingly, we found that participants with higher RC, who may experience a higher cardiovascular risk, benefitted most from intensive SBP lowering. Notably, although RC is increasingly considered to be associated with higher cardiovascular risk, RC has not been used for comprehensively estimating and predicting cardiovascular risk.

Unexpectedly, we found a higher all-cause mortality in the intensive SBP treatment group compared with the standard treatment group in the lowest RC tertile. The reasons for this increased all-cause mortality in patients with lower RC remain elusive. Previous studies have found a U-shaped association between low cholesterol and high mortality, which is often attributed to reverse causation.\textsuperscript{36,37} That is, low RC may reflect debilitation, illness, malnutrition and malignancy rather than the cause of death. Considering this possibility, we excluded individuals who died from any cause within 2 years to limit reverse causation bias. However, the analysis yielded similar results. It appears that our finding challenges the “lower is better” concept for “bad cholesterol”. The optimal range of RC levels is still under investigation, and we are unable to rule out the possibility that lower RC is associated with potential health risks. Furthermore, intensive SBP lowering may influence coronary and cerebral perfusion pressure; thereby, influencing vascular function and exerting negative effects. Accordingly, it appears reasonable that when using intensive SBP treatment in patients with lower RC, the potential negative effects of lower RC and intensive SBP treatment may interact to amplify health
 risks. Therefore, the increased all-cause mortality was observed in patients with lower RC in our study. However, this finding should be interpreted with great caution and merits further study. Despite adjusting for multiple confounders and considering the influence of reverse causation, we cannot fully exclude unmeasured residual confounding, and the possibility of reverse causality cannot be entirely excluded. Notably, the subtle differences in participants’ baseline characteristics between the intensive and standard treatment groups in each RC tertile should not be ignored because unmeasured residual confounding factors may exist. Furthermore, given the small number of events, relatively low statistical power and exploratory nature of this post hoc analysis, our results should be considered hypothesis-generating. Overall, further investigation is urgently needed to determine the causal relationship and explain the underlying molecular mechanism.

Our findings, if confirmed by other studies, may have important clinical implications. Our findings provide a better understanding of the benefit-risk profile of intensive SBP lowering and emphasize the importance of individualized treatment strategies. The present study suggests that intensive SBP lowering may be particularly important for hypertensive patients with higher RC, and that these patients could benefit more from intensive SBP treatment. Although novel RC therapies have emerged, such as PCSK9 inhibitors, n-3 fatty acids and gene-silencing technologies, RC management remains a challenge. For example, although RC, triglyceride, VLDL cholesterol and apolipoprotein C-III levels were reduced in the PROMINENT (Pemafibrate to Reduce Cardiovascular Outcomes by
Reducing Triglycerides in Patients with Diabetes) trial that included almost hypertensive patients (9605/10495 [91.5%]), participants receiving pemafibrate did not gain cardiovascular benefits compared with those receiving placebo. However, for hypertensive patients with higher RC, intensive SBP intervention may be a favourable strategy to help patients gain cardiovascular benefits. Notably, for patients with lower RC, it is prudent to comprehensively assess and weigh the benefit-risk profile before initiating intensive SBP treatment. Additionally, more study is needed to explore the links between RC and hypertension and draw conclusions about causality.

The present study has limitations. First, the RC concentration was determined by indirect calculation rather than by direct measurement, which may be considered a limitation of the present study. However, although directly-measured RC is reported to be superior to identify overlooked individuals at high risk, calculated RC is closely related to measured RC and more affordable and easily acquired for wide use in clinical studies. Second, this was a non-prespecified post hoc analysis of the STEP randomized trial data; residual confounding is always a possibility. Owing to the relatively short follow-up period and small number of events, the statistical power is limited, and no adjustments were made for multiple comparisons. Therefore, our study should be viewed as hypothesis-generating, warranting further investigation. Furthermore, our study is limited by including only Han Chinese persons aged 60–80 years without a previous history of stroke. As such, generalization of the results to other ethnicities or age groups should be made with
In conclusion, in this post hoc analysis, baseline RC concentrations were associated with the effects of intensive SBP lowering on the primary composite cardiovascular outcome and all-cause mortality in hypertensive patients. These results are hypothesis-generating and may susceptible to potential confounding factors. Additional studies are needed to corroborate these findings. If confirmed, RC measurements could permit identification of a subset of patients with high RC and hypertension who may receive greater benefit from intensive SBP lowering to less than 130 mmHg.
Acknowledgments: We sincerely thank the efforts and contributions of all members and participants in the STEP study group. We thank Dr. Jun Wen (Fuwai hospital) and Dr. Zhou Fang (Anzhen hospital) for their valuable suggestions.

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Conflict of interest: None declared.

Authors’ contributions: JC and RY designed the study. JC and RY participated in acquisition and interpretation of the data. RY performed the statistical analysis and drafted the manuscript. JC supervised the study and revised the manuscript for important intellectual content. JZ, XY, and GY revised the manuscript for important intellectual content. All co-authors contributed to interpretation of the results and editing of the manuscript. All co-authors agreed to publish the paper. JC is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data availability: The dataset used and analyzed during the current study are available from the corresponding author on reasonable request.
References


40. Varbo A, Nordestgaard BG. Directly measured vs. calculated remnant cholesterol identifies additional overlooked individuals in the general population at higher risk of myocardial infarction. Eur Heart J. 2021;42:4833–43.

Figure legends:

Figure 1. Forest plot depicting the effect of intensive SBP lowering by tertile of baseline remnant cholesterol
For the primary and secondary outcomes except for death from any cause, the hazard ratios (HRs), 95% confidence intervals (CIs), P values and P for interaction (for interaction term, tertile of baseline remnant cholesterol × study assignment) were calculated using the Fine-Gray sub-distribution hazard model for the competing risk of all-cause death or non-cardiovascular death. For death from any cause, the Cox regression model was used. The adjusted HRs were calculated by adjusting baseline characteristics including age, sex, body mass index, estimated glomerular filtration rate, fasting serum glucose, systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, cardiovascular disease history (yes/no), diabetes history (yes/no), hyperlipidaemia history (yes/no), statin use history (yes/no), and current smoking status (yes/no).

The primary outcome was a composite of stroke, acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes.

SBP, systolic blood pressure; T1, the lowest RC tertile; T2, the middle RC tertile; T3, the highest RC tertile.

Figure 2. Forest plot depicting the effect of intensive SBP lowering on the primary outcome when categorized into the upper two tertiles (T2–T3 were grouped as one) vs. lowest tertile (T1 group)
The hazard ratios (HRs), 95% confidence intervals (CIs), P values and P for interaction (for interaction term, subgroups of baseline remnant cholesterol × study assignment) are shown in the forest plot. To evaluate the primary outcome, the Fine-Gray sub-distribution hazard model was used for the competing risk of noncardiovascular death. The adjusted HRs were calculated by adjusting baseline characteristics including age, sex, body mass index, estimated glomerular filtration rate, fasting serum glucose, systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, cardiovascular disease history (yes/no), diabetes history (yes/no), hyperlipidaemia history (yes/no), statin use history (yes/no), and current smoking status (yes/no).

The primary outcome was a composite of stroke, acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes.

SBP, systolic blood pressure; T1, the lowest RC tertile; T2, the middle RC tertile; T3, the highest RC tertile.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall</th>
<th>Baseline remnant cholesterol</th>
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<tbody>
<tr>
<td></td>
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<td>Tertile 1 (&lt;0.67 mmol/L)</td>
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<td>Standard treatment</td>
</tr>
<tr>
<td>n</td>
<td>8206</td>
<td>1383</td>
</tr>
<tr>
<td>Age, years</td>
<td>66.3 (4.8)</td>
<td>66.6 (4.9)</td>
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<tr>
<td>Male sex, n (%</td>
<td>3813 (46.5)</td>
<td>740 (53.5)</td>
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<tr>
<td>BMI, kg/m²</td>
<td>25.6 (3.2)</td>
<td>25.3 (3.2)</td>
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<tr>
<td>Waist circumference, cm</td>
<td>88.7 (14.6)</td>
<td>88.1 (11.5)</td>
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<td>Baseline office BP, mmHg</td>
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<tr>
<td>Systolic</td>
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<td>Diastolic</td>
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<td>6.1 (1.6)</td>
<td>6.0 (1.4)</td>
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<tr>
<td>Median triglycerides [IQR]</td>
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<td>0.9 [0.7, 1.1]</td>
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<tr>
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<td>4.3 (0.9)</td>
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<td>High-density lipoprotein cholesterol</td>
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<td>1.3 (0.3)</td>
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<td>Low-density lipoprotein cholesterol</td>
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<td>Median remnant cholesterol [IQR]</td>
<td>0.8 [0.6, 1.1]</td>
<td>0.5 [0.4, 0.6]</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
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<tr>
<td>Cardiovascular disease</td>
<td>526 (6.4)</td>
<td>103 (7.4)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>1573 (19.2)</td>
<td>254 (18.4)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>3019 (36.8)</td>
<td>398 (28.8)</td>
</tr>
<tr>
<td>Median Framingham 10-year cardiovascular death risk in % [IQR] *</td>
<td>24.7 [15.8, 38.0]</td>
<td>22.3 [13.9, 34.3]</td>
</tr>
<tr>
<td>Statin use, n (%)</td>
<td>1568 (19.1)</td>
<td>269 (19.5)</td>
</tr>
<tr>
<td>------------------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>Aspirin use, n (%)</td>
<td>697 (8.5)</td>
<td>127 (9.2)</td>
</tr>
<tr>
<td>Current Smoking, n (%)</td>
<td>1325 (16.1)</td>
<td>236 (17.1)</td>
</tr>
<tr>
<td>Current Drinking, n (%)</td>
<td>2171 (26.5)</td>
<td>404 (29.2)</td>
</tr>
</tbody>
</table>

1. Data are shown as the number (%), mean (SD), or median [interquartile range] unless otherwise indicated. To convert the values for fasting serum glucose concentrations to mmol/L, multiply by 0.05551. To convert the values for cholesterol to mmol/L, multiply by 0.02586. To convert the values for triglycerides to mmol/L, multiply by 0.01129.
2. BMI, body mass index; BP, blood pressure; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; FSG, fasting serum glucose; IQR, interquartile range.
3. Significant differences between intensive and standard SBP treatment groups are indicated in \textbf{bold}.
4. In participants without a history of cardiovascular disease.
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Standard treatment N/Total (%)</th>
<th>Intensive treatment N/Total (%)</th>
<th>Adjusted HR (95% CI)</th>
<th>P for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>52/1383 (3.8)</td>
<td>57/1434 (4.0)</td>
<td>0.96 (0.73–1.26)</td>
<td>0.75</td>
</tr>
<tr>
<td>T2</td>
<td>68/1360 (4.9)</td>
<td>55/1272 (2.8)</td>
<td>0.59 (0.38–0.87)</td>
<td>0.0002</td>
</tr>
<tr>
<td>T3</td>
<td>80/1348 (6.0)</td>
<td>40/1379 (3.0)</td>
<td>0.67 (0.46–0.96)</td>
<td>0.031</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>23/1383 (1.7)</td>
<td>19/1434 (1.3)</td>
<td>0.78 (0.42–1.45)</td>
<td>0.44</td>
</tr>
<tr>
<td>T2</td>
<td>22/1390 (1.6)</td>
<td>10/1272 (0.8)</td>
<td>0.50 (0.24–1.07)</td>
<td>0.074</td>
</tr>
<tr>
<td>T3</td>
<td>24/1348 (1.8)</td>
<td>17/1379 (1.2)</td>
<td>0.97 (0.56–1.68)</td>
<td>0.21</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>22/1383 (1.6)</td>
<td>23/1434 (1.5)</td>
<td>1.00 (0.55–1.81)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>T2</td>
<td>27/1390 (1.9)</td>
<td>15/1272 (1.2)</td>
<td>0.62 (0.33–1.17)</td>
<td>0.14</td>
</tr>
<tr>
<td>T3</td>
<td>30/1348 (2.2)</td>
<td>17/1379 (1.2)</td>
<td>0.51 (0.26–0.92)</td>
<td>0.024</td>
</tr>
<tr>
<td>Acute decompensated heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>2/1383 (0.1)</td>
<td>1/1434 (0.1)</td>
<td>0.47 (0.10–2.31)</td>
<td>0.36</td>
</tr>
<tr>
<td>T2</td>
<td>3/1390 (0.2)</td>
<td>0/1272 (0.0)</td>
<td>0.01 (0.00–0.33)</td>
<td>0.0045</td>
</tr>
<tr>
<td>T3</td>
<td>2/1348 (0.1)</td>
<td>1/1379 (0.1)</td>
<td>0.03 (0.00–0.33)</td>
<td>0.0045</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>9/1383 (0.7)</td>
<td>8/1434 (0.5)</td>
<td>1.33 (0.45–4.38)</td>
<td>0.61</td>
</tr>
<tr>
<td>T2</td>
<td>14/1390 (1.0)</td>
<td>7/1272 (0.6)</td>
<td>0.54 (0.22–1.33)</td>
<td>0.16</td>
</tr>
<tr>
<td>T3</td>
<td>11/1348 (0.8)</td>
<td>7/1379 (0.5)</td>
<td>0.70 (0.24–2.13)</td>
<td>0.34</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>6/1383 (0.4)</td>
<td>10/1434 (0.7)</td>
<td>1.70 (0.62–4.69)</td>
<td>0.31</td>
</tr>
<tr>
<td>T2</td>
<td>11/1390 (0.8)</td>
<td>7/1272 (0.6)</td>
<td>0.50 (0.25–1.17)</td>
<td>0.40</td>
</tr>
<tr>
<td>T3</td>
<td>7/1348 (0.5)</td>
<td>6/1379 (0.4)</td>
<td>0.74 (0.24–2.20)</td>
<td>0.50</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>9/1383 (0.7)</td>
<td>9/1434 (0.6)</td>
<td>1.85 (0.59–4.33)</td>
<td>0.20</td>
</tr>
<tr>
<td>T2</td>
<td>6/1390 (0.4)</td>
<td>2/1272 (0.2)</td>
<td>0.44 (0.07–2.69)</td>
<td>0.30</td>
</tr>
<tr>
<td>T3</td>
<td>5/1348 (0.4)</td>
<td>6/1379 (0.5)</td>
<td>0.70 (0.23–1.42)</td>
<td>0.23</td>
</tr>
<tr>
<td>Death from any cause</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>13/1383 (0.9)</td>
<td>33/1434 (2.3)</td>
<td>2.48 (1.30–4.73)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>T2</td>
<td>17/1390 (1.2)</td>
<td>19/1272 (1.5)</td>
<td>1.37 (0.71–2.66)</td>
<td>0.35</td>
</tr>
<tr>
<td>T3</td>
<td>30/1348 (2.2)</td>
<td>14/1379 (1.0)</td>
<td>0.42 (0.22–0.89)</td>
<td>0.0079</td>
</tr>
</tbody>
</table>

**Figure 1**

334x214 mm (x DPI)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Standard treatment N/Total (%)</th>
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<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>52/1383 (3.8)</td>
<td>57/1434 (4.0)</td>
<td>1.06 (0.73–1.56)</td>
<td>0.033</td>
</tr>
<tr>
<td>T2+T3</td>
<td>136/2736 (5.0)</td>
<td>89/2651 (3.2)</td>
<td>0.63 (0.48–0.83)</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2**

225x62 mm (x DPI)
Remnant Cholesterol and Intensive Blood Pressure Control in Older Patients with Hypertension: A Post hoc Analysis of the STEP Randomized Trial

Background: Emerging evidence shows a close relationship between remnant cholesterol (RC) and hypertension. However, it is unknown whether RC is associated with the effects of intensive systolic blood pressure (SBP) lowering on cardiovascular outcomes.

Methods

- **STEP cohort**
  - N=8511
  - Included in this analysis N=6206

- **Intensive treatment**: 110 to <130 mmHg
  - SBP
  - RC Tertile 1: 2817
  - RC Tertile 2: 2682
  - RC Tertile 3: 2727

- **Standard treatment**: 130 to <150 mmHg

- **Primary composite outcome**
  - Stroke, acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation, and cardiovascular death

- **Secondary outcomes**
  - The individual components of the primary outcome and death from any cause

Results: Hazard ratios (intensive treatment vs. standard treatment)

- **RC Tertile 1**
  - RC Tertile 1
  - RC Tertile 2 + Tertile 3

  - P for interaction: 0.11

- **RC Tertile 1**
  - RC Tertile 2
  - RC Tertile 3

  - P for interaction: 0.033

Conclusion: Baseline RC concentrations were associated with the effects of intensive SBP lowering on the primary composite cardiovascular outcome and all-cause mortality in hypertensive patients. These results are hypothesis-generating and merit further study.

Graphical Abstract

180x125 mm (x DPI)