Lipid lowering in patients with treatment-resistant hypertension: an analysis from the Treating to New Targets (TNT) trial

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Aim

Patients with resistant hypertension are at high risk for adverse cardiovascular events. Efforts have been focused on lowering the surrogate endpoint of blood pressure (BP) with scant focus on reduction of hard cardiovascular endpoints. However, whether or not intensive lipid lowering is beneficial for reducing the risk of cardiovascular events in this high-risk cohort is not known.

Methods and results

We evaluated 10,001 patients with coronary artery disease and a low-density lipoprotein cholesterol level <130 mg/dL randomized to atorvastatin 80 vs. 10 mg, enrolled in the Treating to New Targets trial. Treatment-resistant hypertension (TRH) was defined as BP ≥ 140 mmHg despite being on three antihypertensive agents or <140 mmHg on four or more agents. Subjects were followed up for a median duration of 4.9 years. The primary outcome was major cardiovascular events (composite of non-fatal myocardial infarction (MI), fatal coronary heart disease (CHD), resuscitated cardiac arrest, and stroke). Among the 10,001 patients in the trial, 1,112 (11.1%) patients had TRH. Atorvastatin 80 mg, in patients with TRH, was associated with a significant reduction in the risk of the primary outcome (HR = 0.70; 95% CI 0.52–0.93; P = 0.01), driven largely by a significant reduction in CHD deaths (HR = 0.55; 95% CI 0.32–0.97; P = 0.04). In addition, atorvastatin 80 mg was associated with a reduction in major coronary events (HR = 0.67; 95% CI 0.49–0.93; P = 0.02), and any cardiovascular or coronary event and with a trend (P = 0.05) towards reduction in all-cause mortality (HR = 0.68; 95% CI 0.46–1.01) when compared with atorvastatin 10 mg. The results were similar when analysed for the two separate components of the TRH cohort.

Conclusion

In subjects with TRH, intensive lipid lowering with atorvastatin 80 mg is associated with a significant reduction in cardiovascular events.

Keywords

Lipid lowering • Intensive • Outcome • Resistant hypertension • Standard

Introduction

Hypertension is the leading risk factor for cardiovascular morbidity and mortality and is the third most common cause of disability-adjusted life years.1 Data from clinical trials show that antihypertensive therapy is associated with 35–40% reduction in stroke, 20–25% reduction in the risk of myocardial infarction (MI), and more than 50% reduction in the risk of heart failure.2,3 It is thus an important ‘modifiable’ risk factor. There has been remarkable progress in the last decade with the control of hypertension (to systolic/diastolic blood pressure (BP) targets of <140/90 mmHg), which has increased from 29% in 1999–2000 to 50% in 2007–2008.4 Despite the above, 3–30% of patients have treatment-resistant hypertension (TRH).5–7 The American Heart Association (AHA) defines TRH as ‘BP that remains above goal in spite of concurrent use of 3 antihypertensive agents of different classes. Patients whose

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BP is controlled with 4 or more medications are also considered to have resistant hypertension. Patients with TRH have a worse prognosis with significant increase in the risk of cardiovascular events. In an analysis of 53,530 patients from the REACH registry, TRH was associated with a 23% increase in the risk of the composite outcome of cardiovascular death, MI, or stroke, a 26% increase in the risk of non-fatal stroke, and a 36% increase in the risk of heart failure hospitalization, attesting to the grave prognosis of these patients. Nevertheless, TRH and its adverse cardiovascular outcomes are frequently an ill-recognized entity in clinical practice. New therapies using catheter-based radiofrequency ablation of the renal sympathetic nerves and electrical stimulation of carotid sinus baroreceptors are being tested, specifically aimed at reducing the BP in this high-risk subset. While the focus has been on reducing the surrogate marker of BP, none of these trials have been powered to show a significant reduction in the risk of cardiovascular morbidity and mortality. Given the extremely high risk of cardiovascular events, the effect of intensive lipid lowering on cardiovascular outcomes in these high-risk subsets is not known. In clinical practice, patients with TRH are not being currently singled out for intensive lipid-lowering therapy, perhaps due to lack of data attesting to their benefit. Our objective was to evaluate the role of intensive lipid lowering on the risk of cardiovascular outcomes in patients with TRH.

**Methods**

**Patient population**

The design and the main results of the Treating to New Targets (TNT) Study have been described in detail previously. Briefly, this was a double-blind, parallel group study in patients 35–75 years of age who had clinically evident coronary artery disease (CAD), defined by one or more of the following: previous MI, previous or current angina with objective evidence of atherosclerotic CAD, or a history of coronary revascularization, with a low-density lipoprotein (LDL) cholesterol <130 mg/dL, who were randomized to atorvastatin 80 vs. 10 mg. For the purpose of this analysis, patients with TRH at baseline, defined as those with BP ≥140 mmHg on ≥3 medications vs. <140 mmHg on ≥4 medications, were selected. This was a non-prespecified subgroup analysis from the TNT trial.

**Treatment groups**

The study protocol, including treatment groups, has been described previously. Briefly, any previously prescribed lipid-lowering drugs were discontinued at least 4 weeks prior to entering an 8-week run-in period on 10 mg atorvastatin. At the end of this period, patients with a mean LDL cholesterol level <130 mg/dL were randomly assigned to double-blind therapy with either 10 or 80 mg of atorvastatin per day.

**Follow-up**

Patients were followed up at Week 12 and at Months 6, 9, and 12 during the first year and then every 6 months thereafter. At each visit, vital signs (including BP), clinical endpoints, adverse events (AEs), and concurrent medication information were collected. In addition, on alternating visits (i.e. annually), physical examinations and electrocardiograms were performed and laboratory specimens collected. Blood pressure measurements were performed according to local practice. Prior to the double-blind phase of the TNT trial, BP measurements were done at screening, 8 weeks, 4 weeks, and 2 weeks prior to randomization and the lowest BP measurement was used to determine the TRH status. Uptitration of antihypertensive medication was per local practice, targeting a systolic pressure of 130–140 mmHg based on national and international guidelines for a CAD cohort.

**Statistical analyses**

Patients with TRH were divided into two groups based on the randomized treatment group—atorvastatin 10 mg vs. atorvastatin 80 mg. All analyses were performed on an intention-to-treat basis. All randomized patients with TRH who were dispensed at least one dose of the study drug were included in the analyses. Baseline characteristics between the two groups were compared using the t-test for continuous variables and chi-square statistics for categorical variables. All the variables were normally distributed except for triglycerides, for which the median and the interquartile range are reported, along with non-parametric testing. For comparison of lipids over time, analysis of covariance (ANCOVA) was used with the treatment and baseline in the model. The primary and secondary outcomes were analysed from the time of the first dose of study drug to the first event, according to the Kaplan–Meier method. Percentages of patients with treatment emergent AEs, discontinuations due to AEs, and incidence of myalgia, as well as ALT and AST abnormalities, were summarized and treatment groups were compared using Fisher’s exact test. A P-value of <0.05 (two-sided) was considered statistically significant. All analyses were performed using the SAS software version 9.0 (SAS Institute, Cary, NC, USA).

**Sensitivity analysis**

Sensitivity analysis was performed to assess the consistency of treatment effect (atorvastatin 10 vs. 80 mg) in patients with and without TRH, by testing treatment-by-resistant/non-resistant interaction in the Cox model. Further analysis was performed based on the component definition of TRH (≥140 mmHg on ≥3 medications vs. <140 mmHg on ≥4 medications). The difference between the treatment effects between the two cohorts was assessed by a test for interaction. Pinteraction < 0.10 was considered statistically significant.

**Results**

Among the 10,001 patients in the trial, 1112 (11.1%) patients had TRH using the definition described in the methodology. Of the patients with TRH, 724 (65%) patients did not achieve systolic BP goals despite being on three antihypertensive agents, while the remaining 388 (35%) patients required four or more antihypertensive agents to achieve a BP goal of <140 mmHg. The baseline characteristics of the TRH vs. no TRH groups are described in Supplementary material online, Table S1. Patients with TRH were older, with lower percentages of men and whites, and with higher proportions of...
patients with diabetes, prior MI, prior coronary artery bypass graft surgery, prior angioplasty, and chronic kidney disease when compared with patients without TRH (Supplementary material online, Table S1).

**Baseline characteristics**

Among the 1112 patients with TRH, 559 (50.3%) patients were in the atorvastatin 10 mg arm, while 553 (49.7%) patients were in the atorvastatin 80 mg arm. The baseline characteristics of the two groups are described in Supplementary material online, Table S2. The two groups were well balanced for the baseline demographics, cardiovascular history, baseline systolic and diastolic pressures, baseline lipid values, and baseline medications (Supplementary material online, Table S2).

**Blood pressure during follow-up**

At baseline, the mean BP in the TRH group was 140.8 ± 19.2 mmHg. This was higher in the group who did not achieve systolic BP goals despite being on three antihypertensive agents, where the mean systolic pressure was 151.4 ± 12.4 mmHg. Given a CAD cohort, the most common antihypertensive agent used in the TRH group was a beta blocker (80.65%), followed by calcium channel blockers (CCBs) (65.10%), angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blockers (ARBs) (52.80 and 11.93%, respectively), and diuretics (26.76%). As expected, there was no significant reduction in BP from the baseline between the atorvastatin 10 vs. 80 mg groups. At the end of the trial, the most common antihypertensive agents used in the TRH group were beta blockers, ACEi or ARBs, CCBs, long-acting nitrates, and diuretics (Supplementary material online, Table S2). Of note, the majority of the fixed dose combination medications included a combination with a diuretic. More than 60% of patients were on at least four antihypertensive agents, with >30% and 15% of patients on at least five and six antihypertensive agents, respectively (Supplementary material online, Table S2).

**Lipid levels during follow-up**

As expected, and similar to the results of the main trial, there was significant reduction in LDL cholesterol (Figure 1A), non-HDL cholesterol (Figure 1B), total cholesterol (Figure 1C), and triglycerides (Figure 1D) in the group on atorvastatin 80 mg when compared with the group on atorvastatin 10 mg. At the last follow-up time period, the LDL cholesterol was 20.8 mg/dL lower in the atorvastatin 80 mg group when compared with the atorvastatin 10 mg group (mean 78.6 vs. 99.4 mg/dL; \( P \), 0.001) (Figure 1A). The curves separated within 3 months and remained relatively steady through to the end of follow-up.

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**Figure 1** (A) Mean LDL cholesterol values through the study. (B) Mean non-HDL cholesterol values through the study. (C) Mean total cholesterol values through the study. (D) Mean triglyceride values through the study.
Primary outcome
Atorvastatin 80 mg was associated with a 30% reduction in the risk of the primary outcome when compared with atorvastatin 10 mg (14.5 vs. 19.9%; $P = 0.01$) (Figures 2 and 3A). This was mainly driven by a 45% reduction in CHD deaths with the atorvastatin 80 mg therapy (Figures 2 and 3B). The other components of the primary outcome were, however, no different between the two groups (Figure 2). Atorvastatin 80 mg did not have any significant effect on reducing the risk of stroke (event rates 4.0 vs. 4.7%; $P = 0.53$) (Figures 2 and 3C).

Secondary outcomes
Atorvastatin 80 mg was associated with a 33% reduction in the risk of a major coronary event, 17% reduction in any cardiovascular event, and 23% reduction in any coronary event (Figures 2 and 4A–C) when compared with the atorvastatin 10 mg therapy. In addition, there was a trend ($P = 0.05$) towards a 32% reduction in the risk of all-cause mortality (Figures 2 and 4D) with the atorvastatin 80 mg therapy. There were no differences between the two groups for other secondary outcomes (Figure 2).

Sensitivity analysis
Sensitivity analysis performed to assess atorvastatin 80 vs. 10 mg in patients with and without TRH showed a similar effect. In general, the event rates for most outcomes were several folds higher in the TRH cohort when compared with the no-TRH cohort (Table 1). In addition, the test for interaction was significant for death ($P_{\text{interaction}} = 0.03$) such that the reduction in the risk of death for atorvastatin 80 mg subjects was borderline significant in the TRH cohort (HR = 0.68, 95% CI 0.46, 1.01, $P = 0.0533$) but not in the no-TRH cohort (HR = 1.10; 95% CI 0.91, 1.32, $P = 0.3147$) (Table 1). Moreover, the absolute reduction in events was several folds higher with atorvastatin 80 mg (vs. 10 mg) in the TRH cohort when compared with the no-TRH cohort—absolute risk reduction for primary outcome 5.4 vs. 1.8%; for CHD death 2.7 vs. 0.3%; for major coronary events 4.7 vs. 1.3%; any cardiovascular events 6.4 vs. 5.2%; and any coronary events 7.8 vs. 4.5%. Consequently, the number needed to treat (NNT) for a reduction of events was much lower in the TRH cohort when compared with the no-TRH cohort—for primary outcome 18 vs. 55; for CHD death 37 vs. 333; for major coronary events 21 vs. 77; for any cardiovascular event 16 vs. 19; and for any coronary events 13 vs. 22. In addition, analysis based on the component definition of TRH ($\geq 140$ mmHg on $\geq 3$ medications vs. $< 140$ mmHg on $\geq 4$ medications) showed a similar benefit of atorvastatin 80 vs. 10 mg except for stroke, where treatment by the type of TRH was significant ($P = 0.0596$) (Supplementary material online, Table S3).

Adverse effects
There was no difference between atorvastatin 80 vs. 10 mg for treatment-emergent AEs, or drug discontinuation due to AEs or myalgia (Supplementary material online, Table S4). In addition, the proportion of patients with elevation in hepatic enzymes was low
in both groups, although the incidence was higher in the atorvastatin 80 mg group; no patients had a CPK elevation $\times 10 \times$ ULN in both groups (Supplementary material online, Table S4).

**Discussion**

In enrolled patients with TRH, intensive lipid-lowering therapy with atorvastatin 80 mg was associated with a significant reduction in the risk of the primary outcome, driven largely by a reduction in CHD deaths. In addition, intensive lipid-lowering therapy was associated with a significant reduction in the risk of major coronary event, any cardiovascular or coronary event with a trend towards a decrease in all-cause mortality when compared with the atorvastatin 10 mg therapy.

**Treatment-resistant hypertension and outcomes**

Treatment-resistant hypertension has gained prominence/significance in recent years and there is increasing recognition of and
Treatment-resistant hypertension and interventions

There has been recent resurgence of interest in various therapeutic options for patients with TRH, partially due to increased awareness of the enormous cardiovascular risk associated with this condition and partially because previously unknown or abandoned interventional procedures such as renal denervation and carotid sympathetic nerve stimulation have been found to have promising BP-lowering effects in this clinical condition. Moreover, previously less used treatment options such as aldosterone antagonists have been shown to be effective in reducing BP in a certain proportion of patients with TRH. Cather-based renal sympathetic nerve denervation has been proved to be effective with a reduction of ~30 mmHg systolic BP within 6 months of the procedure, with sustained BP reduction even at the 2-year follow-up in the SIMPLICITY 2 trial. While the BP reduction with the above strategies is encouraging, these studies have not been powered to detect differences in cardiovascular morbidity and mortality.

The role of statins in primary prevention of cardiovascular disease is well established. In a meta-analysis of 18 randomized trials, statins were associated with a significant reduction in morbidity and mortality when compared with controls. Two of the trials included were trials in the hypertensive cohort, while the other trials included had 15–67% of patients with hypertension. Our study showed significant reduction in cardiovascular morbidity and CHD death, and a trend towards a decrease in all-cause mortality with intensive lipid-lowering therapy with atorvastatin 80 mg in a cohort with CAD and TRH. The results were largely similar, based on the component definition of TRH used. The results of this study are all the more important as, in patients with TRH, all efforts on the part of physicians and patients are focused on reducing BP. While BP reduction is extremely important to reduce the long-term risk of cardiovascular and cerebrovascular events, this is extremely difficult to achieve although the newer therapies in the horizon are promising. Our results show that a non-BP reducing strategy, i.e. a strategy of intensive lipid lowering with atorvastatin 80 mg, results in a dramatic reduction in the risk of cardiovascular morbidity and mortality. In the overall TNT trial, there was no reduction in all-cause mortality with intensive lipid-lowering therapy (HR = 1.01, 95% CI 0.85–1.19; P = 0.92). However, in patients with TRH there was a reduction in CHD deaths and a similar trend (P = 0.05) towards reduction in all-cause mortality with intensive lipid lowering when compared with standard lipid-lowering therapy. The all-cause mortality rate in the atorvastatin 10 mg arm in the main trial was 5.6% but this was almost double in patients with TRH (11.1%) attesting to the high risk of this subgroup. Moreover, the absolute risk reduction was greater (for atorvastatin 80 vs. 10 mg) for the TRH cohort when compared with the no-TRH cohort. Consequently, the NNT to prevent one event was lower for the TRH cohort when compared with the no-TRH cohort. Aggressive therapies such as intensive lipid-lowering therapies are thus more beneficial in higher risk subgroups. The fact that intensive lipid lowering did not reduce the risk of stroke should not be surprising as the risk of stroke is more closely tied to BP rather than lipid reduction. Stroke is disabling and has a large impact on the quality of life, and efforts to reduce BP to lower this risk of stroke should be aggressively pursued.

Study limitations

This is a post hoc, non-prespecified analysis of a CAD population not specifically enrolled for the management of BP, and hence the results cannot be extrapolated to other populations. In our definition of TRH we did not have data to rule out a secondary cause of TRH (including medication non-compliance) and hence the definition conforms to the definition of apparent TRH used by Egan et al. The usage of diuretics was low, but is likely reflective of the CAD cohort with a greater usage of beta blockers, ACE inhibitors, ARBs, and CCBs. We also did not adjust our analyses for the dosage of antihypertensive agents received (because of lack of data) or for the compliance with the assigned treatment. Moreover, there was no predefined protocol for BP measurements and is likely more reflective of real-world practice. Nevertheless, this study provides important insights into the management of these high-risk subsets.
**Table 1: Primary and secondary outcomes for the treatment-resistant hypertension and no-treatment-resistant hypertension cohort based on the treatment strategy**

<table>
<thead>
<tr>
<th>Event</th>
<th>TRH AT10 mg (n = 559) (%)</th>
<th>TRH AT80 mg (n = 553) (%)</th>
<th>No TRH AT10 mg (n = 4447) (%)</th>
<th>No TRH AT80 mg (n = 4442) (%)</th>
<th>Pinteraction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major cardiovascular event</td>
<td>111 (19.9)</td>
<td>80 (14.5)</td>
<td>437 (9.8)</td>
<td>354 (8.0)</td>
<td>0.3853</td>
</tr>
<tr>
<td>CHD death</td>
<td>34 (6.1)</td>
<td>19 (3.4)</td>
<td>93 (2.1)</td>
<td>82 (1.8)</td>
<td>0.1501</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>61 (10.9)</td>
<td>46 (8.3)</td>
<td>247 (5.6)</td>
<td>197 (4.4)</td>
<td>0.7105</td>
</tr>
<tr>
<td>Resuscitated cardiac arrest</td>
<td>6 (1.1)</td>
<td>3 (0.5)</td>
<td>20 (0.4)</td>
<td>22 (0.5)</td>
<td>0.2972</td>
</tr>
<tr>
<td>Stroke</td>
<td>26 (4.7)</td>
<td>22 (4.0)</td>
<td>129 (2.9)</td>
<td>95 (2.1)</td>
<td>0.6894</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major coronary event</td>
<td>89 (15.9)</td>
<td>62 (11.2)</td>
<td>329 (7.4)</td>
<td>273 (6.1)</td>
<td>0.2768</td>
</tr>
<tr>
<td>Cerebrovascular event</td>
<td>38 (6.8)</td>
<td>34 (6.1)</td>
<td>214 (4.8)</td>
<td>162 (3.6)</td>
<td>0.5259</td>
</tr>
<tr>
<td>CHF</td>
<td>34 (6.1)</td>
<td>26 (4.7)</td>
<td>130 (2.9)</td>
<td>96 (2.2)</td>
<td>0.9579</td>
</tr>
<tr>
<td>PVD</td>
<td>43 (7.7)</td>
<td>44 (8.0)</td>
<td>239 (5.4)</td>
<td>231 (5.2)</td>
<td>0.8066</td>
</tr>
<tr>
<td>Death</td>
<td>62 (11.1)</td>
<td>43 (7.8)</td>
<td>220 (4.9)</td>
<td>241 (5.4)</td>
<td>0.0309</td>
</tr>
<tr>
<td>Any cardiovascular event</td>
<td>281 (50.3)</td>
<td>243 (43.9)</td>
<td>1396 (31.4)</td>
<td>1162 (26.2)</td>
<td>0.7372</td>
</tr>
<tr>
<td>Any coronary event</td>
<td>236 (42.2)</td>
<td>190 (34.4)</td>
<td>1090 (24.5)</td>
<td>888 (20.0)</td>
<td>0.7864</td>
</tr>
</tbody>
</table>

AT, atorvastatin; CI, confidence interval; HR, hazard ratio; Pinteraction: treatment × cohort (TRH/no TRH) interaction; TRH, treatment-resistant hypertension.

**Conclusions**

In summary, in patients with TRH, a strategy of intensive lipid lowering with atorvastatin 80 mg is associated with significant reduction in the risk of cardiovascular morbidity and CHD death, and a trend towards reduction in all-cause mortality when compared with atorvastatin 10 mg. Given the exceedingly high cardiovascular morbidity and mortality in patients with TRH, this strategy should be considered in all such high-risk patients and be studied in future trials.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

**Authors’ contributions**

S.B. and R.F. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. S.B. and F.H.M. contributed towards the study concept and design. TNT investigators contributed to acquisition of data. R.F. and S.B. contributed to the analysis and interpretation of data. S.B. contributed to the drafting of the manuscript and its revision. S.B., R.F., R.L., P.D., J.B.K., F.H.M., and D.D. contributed to the critical revision of the manuscript for important intellectual content. R.F. contributed towards the statistical analysis. S.B. and F.H.M. contributed towards the study supervision.

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**Conflict of interest:** S.B.: Ad hoc Consultant: Daiichi Sankyo, Boehringer Ingelheim, Pfizer, Gilead, Abbott; R.F.: Pfizer employee; R.L.: Pfizer employee; P.D.: Consultant speaker for Pfizer; J.B.K.: Research Grants: Novartis (significant); AngelMed (significant); Medtronic (modest). Speakers’ Bureau: Merck (modest); Sanofi-Aventis (modest). Consultant: Merck (significant); F.H.M.: Ad hoc consultant: Abbott, Novartis, Pfizer, Bayer, Forest, Takeda, Daiichi. Research grants: Novartis, Boehringer. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. None of the academic authors received any compensation for the work on this manuscript.

**References**