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| タイトル | Professor Special Lecture: 158th Regular Meeting of the Medical Society of Toho University Effects of Pitavastatin Beyond Cholesterol Reduction: Surprises and Lessons from a Prospective Randomized Open-Label Clinical Trial |
| 作成者（著者） | Moroi,Masao |
| 公開者 | The Medical Society of Toho University |
| 発行日 | 2022.03.01 |
| ISSN | 21891990 |
| 掲載情報 | Toho Journal of Medicine. 8(1). p.1-10. |
| 資料種別 | 学術雑誌論文 |
| 内容記述 | Opinion Piece |
| 著者版フラグ | publisher |
| JaLCDOI | info:doi/10.14994/tohojmed.2021-013 |
| メタデータのＵＲＬ | https://mylibrary.toho-u.ac.jp/webopac/TD30750140 |

Professor Special Lecture: 158th Regular Meeting of the Medical Society of Toho University

Opinion Piece

# Effects of Pitavastatin Beyond Cholesterol Reduction: Surprises and Lessons from a Prospective Randomized Open-Label Clinical Trial

Masao Moroi

Department of Cardiovascular Medicine, Toho University Ohashi Medical Center, Tokyo, Japan

**ABSTRACT**: Statins (hydroxymethylglutaryl-CoA reductase inhibitors) are used globally in patients with hypercholesterolemia to prevent atherosclerotic diseases. The effectiveness of statins in reducing the number of cardiovascular events depends on the degree to which low-density lipoprotein cholesterol (LDL-C) levels are reduced. In Japan, the three most commonly used moderate-intensity statins are pitavastatin (2 mg/day), atorvastatin (10 mg/day), and rosuvastatin (2.5 mg/day). Until recently, the frequency of cardiovascular events among patients taking these statins had not been explored. We reported the outcomes of patients with hypercholesterolemia treated with either pitavastatin or atorvastatin in the TOHO lipid intervention trial using pitavastatin (TOHO-LIP). In this article, the beneficial effects of pitavastatin beyond cholesterol reduction discovered in the TOHO-LIP trial are described and a historical backdrop is provided. The subjects were patients with hypercholesterolemia with one or more risk factors for atherosclerosis, randomized to receive either pitavastatin (2 mg/day; n = 332) or atorvastatin (10 mg/day; n = 332). The follow-up period was 240 weeks. The primary composite end point was cardiovascular death, sudden death of unknown origin, nonfatal myocardial infarction, nonfatal stroke, transient ischemic attack, or heart failure requiring hospitalization. Patients who received pitavastatin treatment experienced fewer cardiovascular events during the follow-up than those who received atorvastatin treatment, although both statins produced similar effects on LDL-C levels. Subgroup analyses revealed that the cardio-ankle vascular index was significantly lower among patients in the pitavastatin group than in the atorvastatin group. Moreover, the preheparin serum lipoprotein lipase mass level, which correlates negatively with coronary atherosclerosis progression, was higher in the pitavastatin group than in the atorvastatin group. Recently, pitavastatin has been shown to have anticancer effects by inhibiting cell growth. Pitavastatin may similarly inhibit atherosclerosis-related cell growth, thereby reducing rates of cardiovascular events in high-risk patients.

**Toho J Med 8 (1): 1–10, 2022**

**KEYWORDS: statins, HMG-CoA reductase inhibitors, cardiovascular diseases, prevention**

*Corresponding Author: Masao Moroi, 2–22–36 Ohashi, Meguro-ku, Tokyo, 153–8515, Japan, tel: 03–3468–1251
e-mail: moroi@med.toho-u.ac.jp
DOI: 10.14994/tohojmed.2021-013

Received Sept. 29, 2021
Toho Journal of Medicine 8 (1), Mar. 1, 2022
ISSN 2189–1990, CODEN: TJMOA2

## Background to the TOHO-LIP Trial

High levels of low-density lipoprotein cholesterol (LDL-C) have been shown to cause atherosclerotic disease. Statins are drugs designed to lower circulating LDL-C levels and therefore reduce atherosclerotic disease risk. In 2006, pravastatin (Mevalotin®), a low-to moderate-intensity statin, was shown to be effective for primary cardiovascular disease (CVD) in patients with hypercholesterolemia in Japan.[1] Atorvastatin (Lipitor®), a moderate-to high-intensity statin, was approved for medical use in the United States (US) in 1996 under Pfizer's patent and in Japan in 2002. Pitavastatin was introduced in Japan by Nissan Chemical Industries and was developed by Kowa Pharmaceuticals, Tokyo. Pitavastatin was approved for medical use in Japan in 2003 and in the US by the Food and Drug Administration in 2009 under the trade name Livalo®. Professor Koji Shirai of the Department of Internal Medicine, Toho University Sakura Medical Center, planned to conduct a head-to-head multicenter prospective randomized open-label study of atorvastatin and pitavastatin to compare their effects on cardiovascular event reduction at three affiliated Medical Centers of Toho University. The TOHO-LIP trial began in 2008, before pitavastatin was approved in the US, and we anticipated that the TOHO-LIP trial would provide important insights that could affect the treatment of patients with hypercholesterolemia worldwide. In April 2007, the JIKEI Heart study was published in the Lancet, reporting the effects of the antihypertensive drug valsartan (Diovan®) on cardiovascular event prevention. The publication was retracted in 2013 because of data falsification and inappropriate disclosure of conflicts of interest. Furthermore, a series of papers on the effects of Diovan from five universities (the Jikei University School of Medicine, Kyoto Prefectural University of Medicine, Shiga University of Medical Science, Chiba University, and Nagoya University) were retracted because of falsification. Since the Diovan scandal, all clinical research in Japan is tightly controlled by institutional review boards, which apply strict clinical trial regulations.

In contrast, the excellent cardiovascular event-suppressing effects of atorvastatin were reported at that time. Pitavastatin (2 mg/day) and atorvastatin (10 mg/day) have both been shown to lower LDL-C levels.[2,3] We therefore predicted that both pitavastatin (2 mg/day) and atorvastatin (10 mg/day) would also lower patients' risks of experiencing a cardiovascular event. The subjects were patients with hypercholesterolemia with one or more risks for atherosclerotic CVD attending Toho University's Omori, Ohashi, or Sakura Medical Centers. Either atorvastatin or pitavastatin treatment was assigned randomly to participants in an open-label fashion and the rates of cardiovascular events were observed in both treatment groups for 5 years. The study design is illustrated in Fig. 1.[4]

## Sample Size and Participant Recruitment

It was estimated that 678 participants would be required for statistical power to show the non-inferiority of pitavastatin to atorvastatin therapy at reducing rates of cardiovascular events. There were many discussions with Professor Yamamura of Josai International University regarding the patient number setting. The number of patients recruited was calculated with a non-inferiority margin of 8%. The recruitment period was extended from 1 to 2 years as the recruitment rate was low. The largest number of patients were recruited at Sakura Medical Center, under the control of Professor Shirai in the Department of Diabetes and Metabolism. Consequently, a large number of diabetic patients with hypercholesterolemia were recruited into the TOHO-LIP trial. Study participants and their laboratory data were registered with the cooperation of the Department of Diabetes and Metabolism, the Department of Cardiology, the Department of Neurology, and the Department of Pharmacy at three Toho University medical centers. In particular, I believe that the data input of lipid levels and glucose metabolism markers from the electronic medical records by pharmacists, and not physicians, improved the reliability of the trial data because pharmacists at the medical centers had no conflicts of interest involving Kowa Pharmaceuticals and Pfizer Japan Inc. This is important because inaccurate data entry and failure to disclose conflicts of interest detrimentally affect the integrity of a paper, as was the case for the papers involved in the Diovan scandal in Japan. The last enrolled patient was recruited in 2012, and the 5-year follow-up period extended to 2017.

## Confirmation of Cardiovascular Events for Data Fixation

The most distinctive feature of the TOHO-LIP trial was that every cardiovascular event that was reported

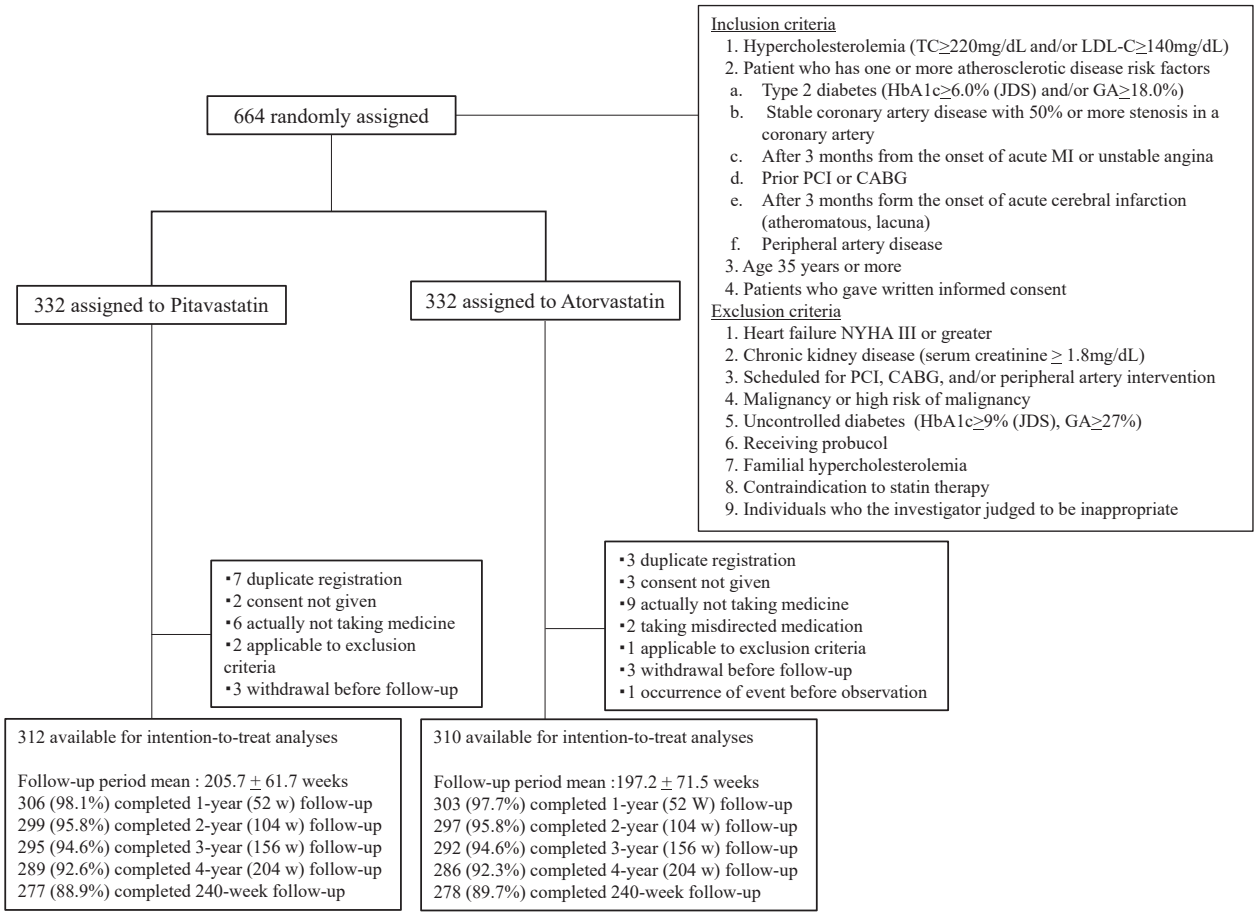


Fig. 1 Disposition of patients. TC, total cholesterol; LDL, low-density lipoprotein; HbA1c, hemoglobin A1c; JDS, Japan Diabetes Society; GA, glycoalbumin; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; and NYHA, New York Heart Association. Figure 1 was drawn from Moroi et al. [4]

during the 5-year follow-up period was confirmed in the electronic medical records of each participant. Professor Shirai and the members of the event-judging committee discussed and adjudicated all 88 cardiovascular event end points using relevant patient medical records. The committee was blinded to the treatment group that each participant belonged to; however, the participants themselves were not blinded as this was an open-label trial, which has its own inherent limitations. The Diovan scandal had been reported at that time, and we could prove that the events were judged correctly. It was important that each cardiovascular event was judged by more than one physician, based on a strict definition of the event.

## Data Analyses and Paper Writing

The patients recruited into the TOHO-LIP trial had hypercholesterolemia and had one or more risk factors for atherosclerotic CVD. Surprisingly, there was a significant difference in the Kaplan–Meier curves between the pitavastatin (2 mg/day) and atorvastatin (10 mg/day) therapies, although the cholesterol-lowering effects of both statins were similar over 5 years (Fig. 2). We asked Professor Yamamura of Josai International University to determine whether there was a statistically significant difference in the cholesterol levels associated with either pitavastatin or atorvastatin over 5 years. Members of the statistical committee used applicable models, such as mixed-effect models and generalized estimating equations, until they all could understand the unclear points in the data analyses over time under consideration of missing values. It was a new series of learning, and I remember having been impressed. The discussion with Professor Yamamura was valuable to us in statistical analyses. Dr. Daiji Nagayama also contributed to the statistical analyses, drawing figures, and tabularization. He

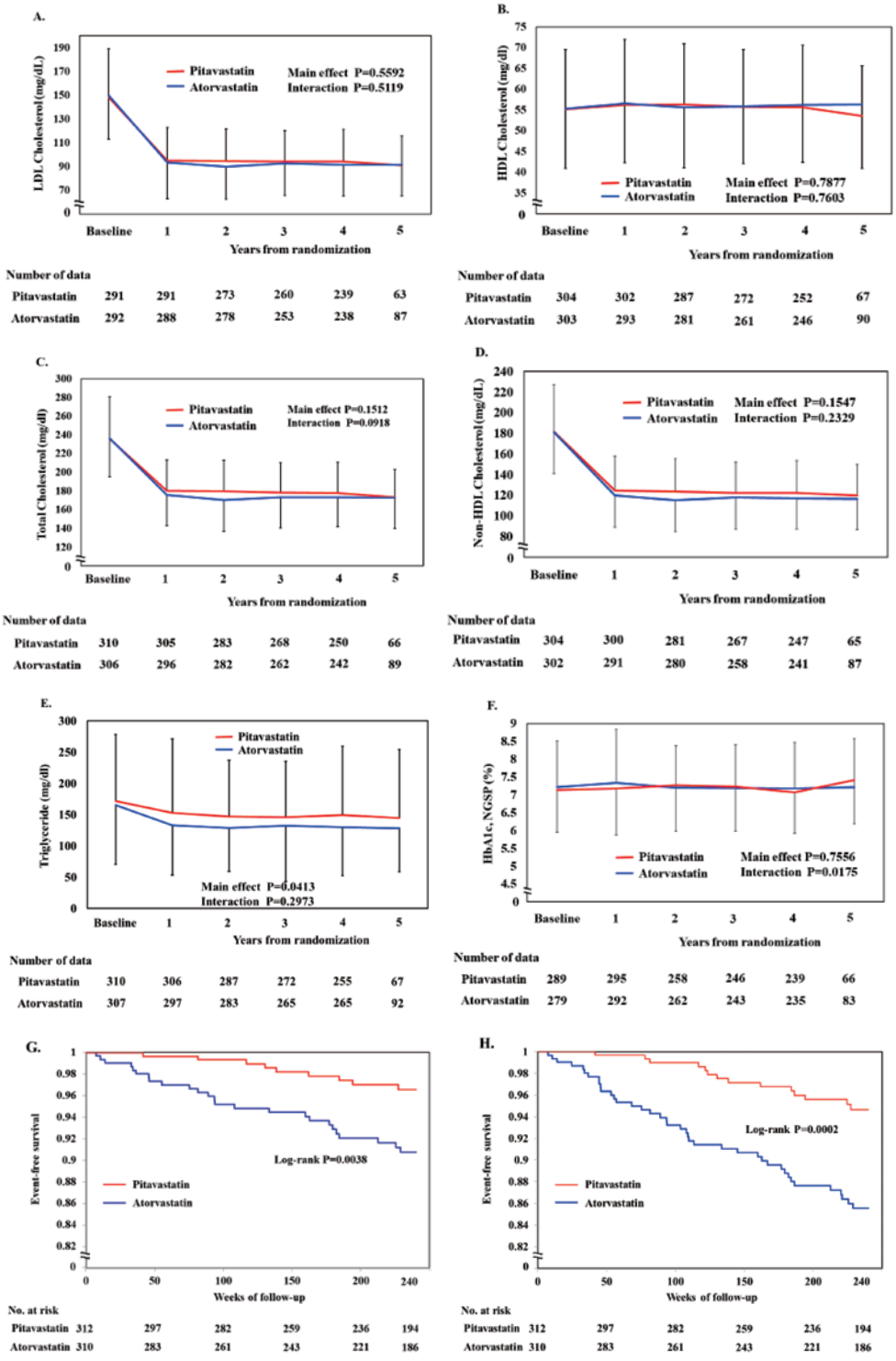


Fig. 2 Changes in lipid parameters and hemoglobin A1c levels over time and Kaplan–Meier curves for the primary and secondary composite end points (primary end point plus coronary revascularization). A–F: Changes through the trial period in low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, total cholesterol, non-HDL cholesterol, triglycerides, and hemoglobin A1c levels. Values are derived from measurements made at three medical centers at Toho University. G and H: Kaplan–Meier curves for the primary end point (a composite of cardiovascular death, sudden, nonfatal myocardial infarction, nonfatal stroke, or heart failure requiring hospitalization) and for a secondary composite end point (a composite of primary end point or coronary revascularization). HR, hazard ratio; CI, confidence interval. Figure 2 was drawn from Moroi et al. [4]

had already resigned from Toho University and has been working as a primary care physician at his own clinic. It never seemed that making research, including statistical analysis, was easy for him in addition to his daily work. What was his energy source for research? Having made research with Dr. Nagayama made me aware of the significance of academic interest and passion for knowledge.

The Diovan scandal started when an employee of the drug company that sold Diovan became involved in the statistical analysis of the clinical trial. This employee was later described as a researcher belonging to the university, with no disclosure that his employer was the company selling the drug under investigation. This lack of disclosure breaches the rules of journal publications internationally. The problem was not that the identity of the university was listed, but that the conflict of interest was not disclosed. At the beginning of the research, there were few specialists of statistical analyses belonging to the medical school or department of medicine at the university, and it was not easy for the statisticians to participate in clinical research. Professor Yamamura is a statistician and had been at the Faculty of Pharmaceutical Sciences, Toho University, at the start of the TOHO-LIP trial. Professor Koji Shirai, a principal investigator of the TOHO-LIP trial, asked Professor Yamamura to participate in TOHO-LIP research as a collaborative researcher. This was a wise decision for Professor Shirai.

The results of the TOHO-LIP trial were unexpected. Patients with hypercholesterolemia treated with pitavastatin (2 mg/day) experienced fewer cardiovascular events than those treated with atorvastatin (10 mg/day). The primary composite end point was cardiac death, nonfatal myocardial infarction, nonfatal stroke, transient ischemic attack, or heart failure requiring hospitalization. The secondary composite end point was a primary composite end point as well as percutaneous coronary intervention for chronic coronary artery disease (Fig. 2). The results for the primary and secondary end points were consistent across several pre-specified subgroups (Fig. 3).

## Journal Policies Should Be Considered during the Submission of the Manuscript

The manuscript was submitted to one of the American high-impact factor cardiovascular journals. Unexpectedly, it was rejected 5 days after submission without peer review because the content was not appropriate for the journal. We then submitted the manuscript to another American high-impact factor journal and it was subjected to peer review. One reviewer was favorably disposed toward acceptance, but the other rejected it because the manuscript was not appropriate for the journal. As pitavastatin, which is made in Japan, was found to be superior to atorvastatin in the prevention of cardiovascular events, we suspected that the reason for unacceptance might have been because the journals were American journals. We then submitted the manuscript to journals related to arteriosclerosis. However, the paper was rejected by two editorial offices because it was an open-label clinical trial and, therefore, perceived to be vulnerable to reliability degradation. The editorial office of the New England Journal of Medicine has occasionally accepted open-label clinical trials for publication. The faces of the co-authors came to my mind, and I plucked up the confidence to submit our article for publication. As we were absolutely confident of the results of the TOHO-LIP study, we also submitted it to the International Journal of Cardiology. The reply from the editorial office was that if a major revision was performed, it would be re-reviewed. To prove the authenticity of the results objectively, we added a new analysis with two new end points: major adverse cardiovascular events (MACE), defined as either a composite of cardiac death and nonfatal myocardial infarction (P=0.079), or as a composite of sudden death, heart failure requiring hospitalization, and transient ischemic attack (P=0.0096). The reviewers also required the submission of data on the mechanism. We conducted additional analyses and responded to the reviewers' comments. Finally, our manuscript was accepted and published in the International Journal of Cardiology in January 2020. Some reviewers may be reluctant to accept controversial or innovative research, or may not allow such research to be used as a basis for research funding. If we were not confident of the results, we might have given up submitting the manuscript. Confidence results from checking all the data, even if the authors have a hard time, and it is important that the authors are confident when submitting new data to journals with a high-impact factor.

## Significance of the TOHO-LIP Trial

The TOHO-LIP trial demonstrated that patients with hypercholesterolemia treated with pitavastatin (2 mg/day) experienced fewer cardiovascular events than those treated with atorvastatin (10 mg/day). This effect was

| | Subgroup | Patient' number | Events' number/patients' number | | HR (95%CI) | P value for interaction |
|---|---|---|---|---|---|---|
| | | | Pitavastation | Atorvastatin | | |
| A. Preventive efficacy for primary end point (sudden death, stroke, myocardial infarction, heart failure requring hospitalization) | | | | | | |
| | Overall | 622 | 9/312 | 25/310 | 0.364(0.169-0.785) | |
| Age | < 65 | 269 | 3/135 | 9/134 | 0.349(0.092-1.327) | 0.908 |
| | ≥ 65 | 353 | 6/177 | 16/176 | 0.425(0.082-2.197) | |
| Sex | Male | 336 | 7/168 | 16/168 | 0.441(0.181-1.076) | 0.496 |
| | Female | 286 | 2/144 | 9/142 | 0.247(0.051-1.204) | |
| Diabetes | Yes | 472 | 5/238 | 16/234 | 0.355(0.128-0.984) | 0.820 |
| | No | 150 | 4/74 | 9/76 | 0.413(0.125-1.367) | |
| Systolic blood pressure | < 140 mmHg | 501 | 6/258 | 17/243 | 0.453(0.185-1.109) | 0.479 |
| | ≥ 140 mmHg | 121 | 3/54 | 8/67 | 0.179(0.036-0.901) | |
| HDL-C | < 40 mmHg | 53 | 1/26 | 2/27 | 1.131(0.057-22.590) | 0.745 |
| | ≥ 40 mmHg | 569 | 8/286 | 23/283 | 0.352(0.156-0.793) | |
| BMI | < 25 kg/m$^2$ | 426 | 5/226 | 14/200 | 0.278(0.099-0.783) | 0.521 |
| | ≥ 25 kg/m$^2$ | 196 | 4/86 | 11/110 | 0.486(0.154-1.535) | |
| History of ACS and/or coronary revascularization | Yes | 162 | 3/77 | 10/85 | 0.307(0.082-1.150) | 0.714 |
| | No | 460 | 6/235 | 15/225 | 0.410(0.156-1.076) | |
| | | | | | Pitavastatin better / Atorvastatin better | |
| B. Preventive efficacy for secondary end point (primary end point + coronary revascularization for stable coronary artery disease) | | | | | | |
| | Overall | 622 | 14/312 | 40/310 | 0.344(0.186-0.635) | |
| Age | < 65 | 269 | 6/135 | 19/134 | 0.298(0.117-0.761) | 0.696 |
| | ≥ 65 | 353 | 8/177 | 21/176 | 0.644(0.159-2.615) | |
| Sex | Male | 336 | 11/168 | 26/168 | 0.422(0.208-0.857) | 0.340 |
| | Female | 286 | 3/144 | 14/142 | 0.204(0.056-0.737) | |
| Diabetes | Yes | 472 | 8/238 | 26/234 | 0.341(0.152-0.764) | 0.927 |
| | No | 150 | 6/74 | 14/76 | 0.394(0.150-1.035) | |
| Systolic blood pressure | < 140 mmHg | 501 | 10/258 | 27/243 | 0.417(0.205-0.849) | 0.356 |
| | ≥ 140 mmHg | 121 | 4/54 | 13/67 | 0.156(0.041-0.589) | |
| HDL-C | < 40 mmHg | 53 | 1/26 | 3/27 | 0.330(0.019-5.804) | 0.743 |
| | ≥ 40 mmHg | 569 | 13/286 | 37/283 | 0.338(0.179-0.641) | |
| BMI | < 25 kg/m$^2$ | 426 | 9/226 | 23/200 | 0.322(0.148-0.702) | 0.808 |
| | ≥ 25 kg/m$^2$ | 196 | 5/86 | 17/110 | 0.381(0.139-1.044) | |
| History of ACS and/or coronary revascularization | Yes | 162 | 7/77 | 19/85 | 0.354(0.145-0.863) | 0.902 |
| | No | 460 | 7/235 | 21/225 | 0.321(0.135-0.763) | |
| | | | | | Pitavastatin better / Atorvastatin better | |

Fig. 3 Subgroup analyses of the efficacy of pitavastatin vs atorvastatin for the primary end point and for a secondary composite end point (primary end point plus coronary revascularization) in prespecified subgroups. Numbers of patients with events were summarized for each subgroup within each treatment. Hazard ratios (HRs) were calculated within each subgroup level for the treatment effect of pitavastatin 2 mg/day relative to atorvastatin 10 mg/day. The P value was derived from an interaction test between the subgroup factors and the treatment effect of pitavastatin relative to atorvastatin. Horizontal bars indicate 95% confidence intervals (CIs). Coronary revascularization, as a component of the secondary composite end point, excluded target-lesion revascularization for lesions treated at the time of prior percutaneous coronary intervention. HRs for overall patients were adjusted for confounding factors, including ageN65 years, sex, diabetes, systolic blood pressure N140 mmHg, high-density lipoprotein cholesterol (HDL-C) b40 mg/dL, body mass index (BMI) N25 kg/m$^2$, and a history of acute coronary syndrome (ACS) and/or coronary revascularization. Figure 3 was drawn from Moroi et al. [4]

similar in all the subgroups. The cholesterol-lowering effect was the same for both the statins. LDL-C decreased by 37%, from 150 to 94 mg/dL, in the atorvastatin group and decreased by 36%, from 148 to 95 mg/dL, in the pitavastatin group.

In 1998, a study reported that patients with diabetes without a history of myocardial infarction had the same risk of developing myocardial infarction as patients without diabetes with a history of myocardial infarction.[5] Subsequently, patients with diabetes undergoing treatment for the primary prevention of CVD are considered to be at a lower risk of experiencing cardiovascular events than patients undergoing treatment for the secondary prevention of CVD.[6] In the US and Europe, secondary prevention programs for patients at risk of experiencing cardiovascular events aim to reduce patients' LDL-C levels as much as possible. In contrast, primary prevention programs for patients with diabetes aim to reduce LDL-C levels by 30–50%.[7] According to the guidelines for the prevention of atherosclerosis published by the Japan Atherosclerosis Society,[8] LDL-C levels should be less than 120 mg/dL for high-risk patients undergoing treatment for the primary prevention of atherosclerosis and less than 100 mg/dL for patients treated

for secondary prevention. Furthermore, LDL-C levels should be less than 70 mg/dL for patients with acute coronary syndrome. Patients with acute coronary syndrome were excluded from the TOHO-LIP trial, and both the pitavastatin and atorvastatin groups reached this target value. Therefore, the main message from the TOHO-LIP trial is that treatment with pitavastatin (2 mg/day) is recommended over atorvastatin (10 mg/day) for the primary prevention of cardiovascular events in patients with hypercholesterolemia who have diabetes or stable coronary artery disease.

Are there any other studies that support the TOHO-LIP trial results? There has been no report of a one-to-one randomized prospective clinical study of pitavastatin (2 mg/day) compared to atorvastatin (10 mg/day). Park et al. published a design paper for a one-to-one randomized prospective clinical trial of pitavastatin (4 mg/day) and atorvastatin (20 mg/day) in South Korea.[9] These results will be reported in the near future. Rosuvastatin (2.5 mg/day), which is currently used in Japan, has been shown to have the same effect as pitavastatin (2 mg/day) on reducing cholesterol levels.[10]

## Data Supporting the Results of the TOHO-LIP Trial

After the publication of the main results of the TOHO-LIP trial, a sub-analysis was conducted by Saiki et al.[11] They showed that the reduction in cardiovascular events observed in the trial was associated with the cardio-ankle vascular index (CAVI)-lowering effect of pitavastatin. The CAVI is a marker of the intrinsic stiffness of the aortic wall, independent of blood pressure at the time of measurement. Increased CAVI values were observed in patients with CVD or dyslipidemia and improvements in dyslipidemia were associated with reduced CAVI scores. The CAVI is independently associated with future cardiovascular events.[12] Evidence of a greater reduction of the CAVI with pitavastatin (2 mg/day) therapy compared with atorvastatin (10 mg/day) therapy could support the main results of the TOHO-LIP trial.

Another sub-analysis was performed by Nagayama et al.[13] They reported that patients in the pitavastatin group had an increased preheparin lipoprotein lipase (LPL) mass, which was associated with a greater reduction in cardiovascular events, whereas patients in the atorvastatin group did not have an increased preheparin LPL mass, despite the similar LDL cholesterol-lowering effects of both treatments. It has been reported that LPL mass is negatively correlated with coronary atherosclerosis.[14] Therefore, the results reported by Nagayama et al. could be seen to support the main results of the TOHO-LIP trial and may also suggest that pitavastatin is more effective in reducing CVD risk than atorvastatin.

## Pitavastatin's Potential Mechanisms of Action to Produce Effects Beyond Cholesterol Reduction

What mechanisms underlie the biological effects, beyond cholesterol reduction, that pitavastatin produces? In the TOHO-LIP trial, some patients in the pitavastatin group experienced greater reductions in C-reactive protein levels than those in the atorvastatin group. Pitavastatin may have a larger inhibitory effect on inflammation than atorvastatin. Recently, it has been reported that "statin monotherapy could potentially reduce any-organ- and colorectal cancer-related mortality".[15] Another sub-analysis of the TOHO-LIP trial showed that the incidence of new cancer cases over 240 weeks tended to be lower in the pitavastatin group than in the atorvastatin group.[16] Further investigations of these results may provide new insights into pitavastatin's mechanisms of action as an anticancer drug. Recently, Xu et al. reported that pitavastatin and capmatinib suppressed signaling of the MET proto-oncogene and consequently inhibited oral and esophageal cancer cell growth.[17] Pitavastatin may similarly inhibit arteriosclerosis-related cell growth more effectively than atorvastatin.

## Summary

The TOHO-LIP trial demonstrated that pitavastatin (2 mg/day) was more effective than atorvastatin (10 mg/day) for the prevention of cardiovascular events in patients with hypercholesterolemia who had one or more risk factors for arteriosclerotic CVD. The use of pitavastatin (2 mg/day) is recommended over atorvastatin (10 mg/day) in patients with hypercholesterolemia, especially those with diabetes, for the primary or secondary prevention of cardiovascular events. Further research into pitavastatin's exact mechanisms of action could lead to the development of new drugs. This article describes my own experience of the process of conducting the TOHO-LIP trial and provides a historical backdrop with my own opinion. What is the purpose of the study? Researchers should always ask themselves this question. All clinical

studies must focus on how the results can benefit the patients and not how they can benefit the researcher or provide commercial gains. Finally, I expect that researchers belonging to Toho University will disseminate clinically innovative information around the world.

**Conflicts of interest:** None declared.

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## Masao Moroi, Professor Curriculum Vitae

**Present academic rank and position:** Professor, Department of Cardiovascular Medicine, Toho University Ohashi Medical Center

**Education & professional positions:**

| | |
|---|---|
| 1984 | M.D., Toho University School of Medicine, Tokyo, Japan |
| 1984-1986 | Residency of Internal Medicine, Ohashi Hospital, Toho University, Tokyo, Japan |
| 1986-1987 | Clinical Fellow of Internal Medicine, Ohashi Hospital, Toho University |
| 1987-1988 | Research Fellow in Medicine, University of Tokyo, Tokyo, Japan |
| 1991 | Ph.D. (Dr. of Medical Science), Toho University School of Medicine |
| 1989-1992 | Clinical Fellow, Internal Medicine, Ohashi Hospital, Toho University |
| 1993-1995 | Instructor of Medicine, Toho University School of Medicine |
| 1995-1997 | Research Fellow in Cardiac Unit, Massachusetts General Hospital/ Harvard Medical School, Boston, USA |
| 1996-1997 | Research Fellow in the Center for Thrombosis and Vascular Research, KU Leuven, Leuven, Belgium. |
| 1997-2004 | Instructor of Medicine, Toho University |
| 2004-2010 | Assistant Professor, Department of Cardiovascular Medicine, Toho University Ohashi Medical Center |
| 2010-2012 | Chief, Department of Cardiology, National Center for Global Health and Medicine |
| 2012-2014 | Associate Professor, Department of Cardiovascular Medicine, Toho University Ohashi Medical Center |
| 2015-present | Professor, Department of Cardiovascular Medicine, Toho University Ohashi Medical Center. |

**Board certification:**

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|---|---|
| 1993 | Fellow, Japanese Society of Internal Medicine<br>Certificate # 2204 |
| 1993 | Fellow, Japanese Circulation Society<br>Certificate # 10550 |
| 1994 | Member, American College of Physicians<br>Reference # 01043528 |
| 1995 | Member, American Physiology Society |
| 1995 | Fellow, American College of Physicians<br>Reference # 01043528 |
| 2001 | Fellow, Japanese College of Cardiology |
| 2016 | Excusive Board member, Japanese Society of Medical Imaging |
| 2018 | Fellow of the Japanese Circulation Society<br>Certificate # 315 |
| 2020 | Fellow of Japanese Society of Hypertension<br>Certificate # 00977 |

**Medical Licensure:**

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| 1984 | Medical License of Japan (# 283692) |

**Professional memberships and societies:**

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|---|---|
| 1985- | Japanese Society of Internal Medicine |

1986- Japanese Circulation Society
1986- Japanese College of Cardiology
1987- Japanese College of Angiology
1988- Japanese Society of Circulation Research
1994- Japanese Society of Interventional Cardiology
1994- American College of Physicians
1994- American Heart Association
1994- American Physiological Society
2006- Japanese Society of Medical Imaging
2016- Japanese Society of Nuclear Cardiology
2016- Japanese Society of Sarcoidosis and Other Granulomatous Disorders

**Research interests:**

1. Atherosclerosis
2. Vascular biology: Vascular endothelial function: nitric oxide, endothelin, neointimal proliferation as response to injury
3. Cardiomyopathy (sarcoidosis, amyloidosis, Fabry disease)
4. Noninvasive cardiovascular imaging (CT, cardiac MRI, nuclear cardiology)

**Bibliography:**

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