

Editorial

How Does Bezafibrate Affect the Plasma LDL Cholesterol Levels?

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Bezafibrate is a widely used fibrate with a substantial triglyceride (TG)-reducing effect and high-density lipoprotein cholesterol (HDL-C)-raising effect. However, the effects of this lipid-lowering drug on the plasma LDL-C levels are not as clear as those on the TG or HDL-C levels. The J-BENEFIT (Japan BEzafibrate clinical Effectiveness and Tolerability) study was a prospective observational study comprising 6,407 dyslipidemic subjects with diabetes or hyperglycemia¹⁾. In that study, there were almost no changes in the LDL-C levels after bezafibrate treatment (**Table 1**). In both the St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) Study²⁾ and Bezafibrate Infarction Prevention (BIP) study³⁾, which were conducted in subjects with an average baseline TG level of <200 mg/dL, there were modest reductions in the LDL-C levels (**Table 1**).

In the current issue of *J Atheroscler Thromb*, the subgroup analysis of J-BENEFIT by Hirose *et al.*⁴⁾ showed that bezafibrate has a different effect on the LDL-C levels depending on the pre-treatment LDL-C or TG level. The higher the pre-treatment level of LDL-C, the greater the reduction of LDL-C produced by bezafibrate. On the other hand, the higher the pre-treatment level of TG, the lower the reduction of LDL-C, or the LDL-C level even increased.

Therefore, we are interested in knowing what happens in terms of the properties of LDL particles in those subjects with increased LDL-C levels after treatment with bezafibrate. Recent studies suggest that the increased LDL level associated with bezafibrate treatment may not necessarily be undesirable because this treatment causes a shift in the LDL subclass distribution toward larger particle species^{5, 6)}. In addition, our

previous findings showed that bezafibrate treatment is associated with an increase in the LDL-C level from 164 to 178 mg/dL in type IIb subjects⁷⁾. A detailed analysis of lipoproteins in that study showed that this change in LDL-C was explained by a 10% decrease in small- to medium-sized LDL cholesterol and a 16% increase in large-sized LDL. Considering the previous findings that small dense LDL is an important predictor of cardiovascular risk⁸⁻¹⁰⁾, the shift in the LDL particle size during treatment with bezafibrate is highly likely to be beneficial.

The BIP study showed that bezafibrate treatment causes cardiovascular event reductions in subjects with a plasma TG level of >200 mg/dL but not those with a TG level of <200 mg/dL at baseline. The authors presumed that the reduced TG and increased HDL-C levels induced by bezafibrate treatment contributed to this event reduction; however, they did not mention the changes in LDL-C in subjects with a plasma TG level of >200 mg/dL during the treatment. Given the present findings of Hirose *et al.*, it is possible that the LDL-C level was increased during bezafibrate treatment in the high TG subjects in the BIP study, although that study was conducted among subjects with a different race or ethnic background than the J-BENEFIT study. We assume that the changes in the properties of LDL-C instead of the concentration of LDL-C as well as the reduced TG and increased HDL-C levels contributed to the beneficial outcomes in the high TG subjects in the BIP study.

Conflicts of Interest

The author declares that he has no conflicts of interest associated with this manuscript.

References

- 1) Teramoto T, Shirai K, Daida H, Yamada N: Effects of bezafibrate on lipid and glucose metabolism in dyslipidemic patients with diabetes: the J-BENEFIT study. *Cardiovasc Diabetol*, 2012; 11: 29
- 2) Elkeles RS, Diamond JR, Poulter C, Dhanjil S, Nicolaides AN, Mahmood S, Richmond W, Mather H, Sharp P,

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Table 1. Effects of bezafibrate on the plasma LDL-cholesterol levels

Study	Number of subjects	Baseline TG mg/dL	Baseline LDL-C mg/dL	LDL-C reduction	reference
SENDCAP	83	P 185	P 153	P + 0.6%	2)
	81	B 198	B 141	B - 9.6%	
BIP	1542	P 145	P 149	P - 1.3 mg/dL	3)
	1548	B 145	B 148	B - 6.5 mg/dL	
J-BENEFIT	3316	332	125 (n=2226)	+ 1.6%	1)

P, placebo; B, bezafibrate

SENDCAP, St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention

BIP, Bezafibrate Infarction Prevention

- Feher MD: Cardiovascular outcomes in type 2 diabetes. A double-blind placebo-controlled study of bezafibrate: the St. Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) Study. *Diabetes Care*, 1998; 21: 641-648
- 3) The BIP study group: Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease; the bezafibrate infarction prevention (BIP) study. *Circulation*, 2000; 102: 21-27
- 4) Hirose T, Teramoto T, Abe K, Taneyama T and the J-BENEFIT study group: Determinants of bezafibrate-induced improvement of LDL cholesterol in dyslipidemic patients with diabetes: A subgroup analysis from the J-BENEFIT study. *J Atheroscler Thromb*, 2015; 22: 676-684
- 5) Ikewaki K, Noma K, Tohyama J, Kido T, Mochizuki S: Effects of bezafibrate on lipoprotein subclasses and inflammatory markers in patients with hypertriglyceridemia--a nuclear magnetic resonance study. *Int J Cardiol*, 2005; 101: 441-447
- 6) Ruotolo G, Ericsson CG, Tettamanti C, Karpe F, Grip L, Svane B, Nilsson J, de Faire U, Hamsten A: Treatment effects on serum lipoprotein lipids, apolipoproteins and low density lipoprotein particle size and relationships of lipoprotein variables to progression of coronary artery disease in the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT). *J Am Coll Cardiol*, 1998; 32: 1648-1656
- 7) Kawashiri MA, Kobayashi J, Nohara A, Noguchi T, Tada H, Nakanishi C, Inazu A, Mabuchi H, Yamagishi M: Impact of bezafibrate and atorvastatin on lipoprotein subclass in patients with type III hyperlipoproteinemia: result from a crossover study. *Clin Chim Acta*, 2011; 412: 1068-1075
- 8) Rizzo M, Pernice V, Frasheri A, Di Lorenzo G, Rini GB, Spinass GA, Berneis K: Small, dense low-density lipoproteins are predictors of cardio- and cerebrovascular events in subjects with the metabolic syndrome. *Clin Endocrinol (Oxf)*, 2009; 70: 870-875
- 9) Koba S, Hirano T, Ito Y, Tsunoda F, Yokota Y, Ban Y, Iso Y, Suzuki H, Katagiri T: Significance of small dense low-density lipoprotein-cholesterol concentrations in relation to the severity of coronary heart diseases. *Atherosclerosis*, 2006; 189: 206-214
- 10) Hirayama S, Miida T: Small dense LDL: an emerging risk factor for cardiovascular disease. *Clin Chim Acta*, 2012; 414: 215-224