viduals, even if LDL size is larger or in vitro susceptibility to oxidation is diminished. Statements to the contrary should be established by clinical trials before their acceptance for the care of patients with diabetes.

Improvement in insulin sensitivity in type 2 diabetes would be expected to improve the dyslipidemia associated with this syndrome. The relative role of this dyslipidemia versus LDL cholesterol concentrations in the etiology of CVD in diabetic individuals remains an unanswered question. Interventions aimed at investigating this issue are needed.

BARBARA V. HOWARD, PHD
WM. JAMES HOWARD, MD

From the Medlantic Research Institute (B.V.H.) and Washington Hospital Center (W.J.H.), Washington, DC.

Address correspondence to Barbara V. Howard, PhD, Medlantic Research Institute, 108 Irving St., NW, Washington, DC 20010. E-mail: bvh1@ mhg.edu.

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Response to Howard and Howard

Drs. Howard and Howard (1) express caution about the suggestion that the risk of an increase in LDL cholesterol, as observed during troglitazone treatment, may be offset by beneficial changes in LDL composition and LDL susceptibility to oxidation. Although we largely agree with the points they raise, we would like to add the following comments.

There is indeed firm evidence that the absolute plasma concentration of LDL cholesterol is the major determinant of cardiovascular morbidity and mortality in nondiabetic, as well as diabetic, populations and that lowering LDL cholesterol concentration is of clinical benefit. Regarding the susceptibility of LDL for in vitro oxidation, this evidence is less strong. A number of observations suggest that lipid peroxidation does occur in humans (2). Epitopes of oxidized LDL and autoantibodies against these epitopes can be detected in human plasma. Patients with coronary heart disease show an increased susceptibility of LDL to oxidation (3). Cross-sectional studies have reported an association between higher dietary antioxidant levels and reduced risk of CVD (4). However, only a few studies have reported on the relation between oxidation parameters and coronary heart disease, and there is only one randomized intervention trial suggesting a beneficial effect of vitamin E treatment on nonfatal myocardial infarction but not on total mortality (5). We found, in an animal model for familial hypercholesterolemia (Watanabe rabbit), that improving LDL susceptibility to oxidation by administration of vitamin E, without changing the absolute level of LDL cholesterol, had no effect on the progression of the atherosclerotic process (6). Thus, whether enhancing susceptibility of LDL to oxidation is of any clinical benefit is not (yet) supported by clinical evidence.

Regarding particle size and cardiovascular disease, the situation is complex. Small, dense LDL is part of the atherogenic lipoprotein phenotype, which is characterized by raised plasma triglycerides and low HDL cholesterol in addition to the presence of small, dense LDL particles. This so-called "pattern B" confers increased risk for coronary heart disease (7). Prospective studies have shown that the small, dense LDL particle predicts the risk of ischemic heart disease, an effect that may be partly independent of plasma lipoprotein concentrations (8). Studies showing a beneficial clinical effect of changes in particle size are currently lacking. Treatment with fibrates may shift the LDL particles to a subpopulation of intermediate density and larger size (9); treatment with gemfibrozil has a proven beneficial effect on cardiovascular mortality (10). Changes in LDL composition are difficult to dissect from changes in HDL and triglyceride metabolism. Therefore, it cannot be determined whether changing LDL composition alone (if at all possible) would change cardiovascular risk. The effects of troglitazone on lipids in larger trials show a small increase in HDL cholesterol and/or a decrease in triglyceride concentration (11,12). In our sample of 15 subjects, HDL cholesterol did not change during troglitazone; triglycerides tended to decrease, albeit not significantly.

The fact that our studies were performed in obese subjects is of methodological advantage; a short-term study like this, however, is not able to answer study questions regarding atherosclerosis-related cardiovascular events, no matter whether it is performed in obese or in diabetic subjects.

In summary, we agree that with currently available scientific evidence, the risk of the troglitazone-induced increase in LDL concentration is not necessarily offset by a more favorable LDL composition profile or an enhanced susceptibility of LDL to in vitro oxidation. However, evidence that LDL composition may be clinically relevant is emerging. Awaiting the results of formal clinical trials studying the effect of troglitazone on cardiovascular disease, clinical decisions will have to be based on available indirect evidence.

CEES J.J. TACK, MD
PAUL SMITS, MD
PIERRE N.M. DEMACKER, PHD
ANTON F.H. STALENHOEF, MD

From the Division of General Internal Medicine (C.J.J.T., P.N.M.D., A.F.H.S.), Department of Internal

Medicine, and the Department of Pharmacology (P.S.), University Hospital of Nijmegen, Nijmegen, the Netherlands.

Address correspondence to Cees J.J. Tack, PO Box 9101, 6500 HB Nijmegen, the Netherlands. E-mail: c.tack@aig.azn.nl.

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Erratum

Brown JB, Pedula K, Barzilay J, Herson MK, Latare P: Lactic acidosis rates in type 2 diabetes. *Diabetes Care* 21:1659–1663, 1998

Incorrect data were given in Table 1. The table is shown below, with the corrected data in bold.

Table 1—*Frequency of lactic acidosis*

	Mean age (years)	Person-years reviewed	Events reviewed	Identified lactic acidosis events: Confirmed	Possible	Borderline
KP-Northwest						
1993	63.5 ± 12.4	10,983	10	0	0	0
1994	63.7 ± 12.3	10,667	9	**1**	**0**	**1**
KP-Georgia						
1993	55.2 ± 8.5	3,803	6	**0**	**2**	—
1994	55.6 ± 8.7	4,027	12	**0**	**1**	—
KP-Hawaii						
1993	**62.6 ± 10.8**	4,710	13	**1**	**0**	**1**
1994	**64.3 ± 10.9**	7,236	25	**2**	**0**	**1**
Total						
1993	**61.7 ± 11.4**	19,506	29	**1**	**2**	**1**
1994	**62.4 ± 11.3**	21,930	46	**3**	**1**	**2**
Overall	—	41,436	75	4	3	3
Rate per 100,000 person-years	—	—	—	9.7	7.2	7.2
95% CI	—	—	—	0.2 to **19.1**	−1.0 to 15.4	−1.0 to 15.4

Data are means ± SD or *n*.