should not be prescribed gatifloxacin; alternative antibiotics are preferable (levofloxacin should be used with caution). When gatifloxacin is prescribed, remember to warn the patient of the signs and symptoms of hypo- and hyperglycemia, and consider having the patient's blood glucose monitored during at least the first week of treatment with the drug.

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IN THE LITERATURE

Does pioglitazone prevent macrovascular events in patients with type 2 diabetes?

Dormandy JA, Charbonnel B, Eckland DJ, et al; the PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005;366:1279-89.

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Background: Most patients with type 2 diabetes have, in addition to their hyperglycemia, a myriad of other metabolic and vascular abnormalities associated with insulin resistance. These metabolic disturbances increase the risk of macrovascular disease. Patients who have type 2 diabetes are at increased risk of myocardial infarction and stroke, whether fatal or nonfatal. Pioglitazone is a member of the thiazolidinedione class of oral glucose-lowering agents that are peroxisome proliferator–activated receptor gamma (PPARγ) agonists. Laboratory research has shown that insulin resistance is reduced by means of this action, which results in improved glucose control. Moreover, several studies suggest that pioglitazone confers additional clinical benefits, such as improved dyslipidemia and reduced vascular inflammation.[1] Given these benefits, pioglitazone has the potential to prevent cardiovascular events as well as to improve glycemic control.

Design: A large, double-blind, multicentre, randomized controlled trial, the PROactive study was conducted between 2001 and 2005 in 321 centres in 19 European countries. The investigators enrolled 5238 people 35–75 years of age with type 2 diabetes that was managed with diet or oral glucose–lowering drugs (combinations of oral

Table 1: Incidences and hazard ratios of primary and secondary outcomes in patients with type 2 diabetes managed with diet or oral glucose-lowering drugs, who were treated with pioglitazone versus placebo

Outcome	Group; no. (%) of patients		Hazard ratio (95% CI)	*p* value
	Pioglitazone *n* = 2605	Placebo *n* = 2633		
Primary: a composite of all-cause mortality, nonfatal myocardial infarction, stroke, acute coronary syndromes, endovascular or surgical intervention in the coronary or leg arteries, or amputation above the ankle	514 (19.7)	572 (21.7)	0.90 (0.80-1.02)	0.095
Secondary: a composite of all-cause mortality, nonfatal myocardial infarction and stroke	301 (11.6)	358 (13.6)	0.84 (0.72-0.98)	0.027

Note: CI = confidence interval.

agents and insulin were permitted) and a history of macrovascular disease. Patients with type 1 diabetes who required insulin as sole diabetic therapy were excluded, along with patients who had New York Heart Association (NYHA) class II–IV heart failure, hepatic dysfunction or ischemic leg ulcers; required dialysis; or were already receiving pioglitazone or other thiazolidinediones. Patients were randomly assigned to receive, in addition to existing therapy, pioglitazone (as a forced titration from 15 mg to 30 or 45 mg, depending on the patient's tolerance) or placebo. The primary end point of the study combined all-cause mortality, nonfatal myocardial infarction, stroke, acute coronary syndromes, endovascular or surgical intervention in the coronary or leg arteries, and leg amputation above the ankle. Secondary end points included a composite of all-cause mortality, myocardial infarction and stroke.

Results: Mean length of study participation was 34.5 months; only 2 patients were lost to follow-up. During the study, 93% of participants received 45 mg daily of either pioglitazone or placebo, with 95% compliance with medication. Patients receiving pioglitazone experienced a significantly greater reduction in hemoglobin A_{1c}, triglyceride and blood pressure measurements and ratio of low-density to high-density lipoproteins (LDL:HDL) than did those in the control group, and greater rises in LDL and HDL cholesterol concentrations. There was no significant difference between the groups in the primary end point (Table 1). The absolute risk reduction of 2.0% in the principal secondary end point was significant (Table 1); the relative risk reduction was 15%. Heart failure was reported in 281 patients receiving pioglitazone (10.8%) and in 198 patients receiving placebo (7.5%; $p < 0.0001$). Heart failure that led to hospital admission was reported in 149 patients taking pioglitazone (5.7%) and 108 taking placebo (4.1%; $p = 0.007$).

Commentary: The possible benefit suggested by the data on secondary outcomes is certainly interesting; it nevertheless may have occurred by chance, and therefore bears further investigation. Moreover, despite the exclusion of patients with known NYHA class II–IV heart failure, patients who took pioglitazone had a 3.3% higher likelihood of heart failure and 1.6% higher chance of heart failure requiring hospital admission. One of the side effects of treatment with thiazolidinediones is edema and possible fluid retention. These results are consistent with those of previous reports of a higher risk of heart failure among patients with type 2 diabetes treated with thiazolidinediones.[2,3]

Clinical implications: The PROactive findings confirm the metabolic benefits of pioglitazone in a high-risk population. They do not, however, provide clear evidence of reduced cardiovascular outcomes in people with type 2 diabetes who are at high risk, despite some encouraging results. Moreover, it raises unresolved concerns about heart failure. The cardiovascular benefits and risks of pioglitazone and other agents that lower glucose therefore require further study before a clear recommendation on cardiovascular risk reduction can be made.

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