THE ENDOCRINE SOCIETY

8401 CONNECTICUT AVENUE, SUITE 900 ■ CHEVY CHASE, MARYLAND ■ 20815-5817 ■ TELEPHONE 301.941.0200 ■ FAX 301.941.0259 ■ www.endo-society.org

The Endocrine Society Statement to Providers in Response to the Article Published in *The Lancet* on Glycemic Control

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Several studies in the last two decades have shown that improved glycemic control reduces complications in Type 1 and Type 2 diabetes both during the period of intensive treatment and for years thereafter (the "legacy" effect). Indeed, until two years ago there appeared to be evidence that both micro- and macrovascular outcomes were positively affected by tight glycemic control. However, several recent prospective, randomized controlled (RCT) trials (ACCORD, ADVANCE, and VADT) have cast doubt on the benefit of aggressive glycemic management on cardiovascular outcomes and mortality. The study by Currie et al. published on line on January 27, 2010 in the Lancet raises additional questions about how aggressive glycemic management should be in patients with Type 2 diabetes. In this retrospective data base analysis using information on almost 50,000 patients contained in the United Kingdom's General Practice Research Database (GPRD), they found that there was a U-shaped relationship between A1c and all-cause mortality and cardiovascular events, i.e. both the lowest deciles (median A1c 6.4%; range 3.3-6.72%) and highest (median A1c 10.5%; range 9.85-18.8%) had significantly higher risk of death or events than those at the lowest risk (median A1c 7.5%; range 7.41-7.68%). In an analysis of two separate cohorts – one group who were only on oral agents (metformin and sulfonylureas) and another group whose regimen was insulin-based (which may have also included oral agents) – they found similar U-shaped trends but a higher mortality rate in the lowest decile of achieved A1c in those taking insulin.

While provocative, this study is by no means definitive and by its very nature cannot answer questions about causality. There are many unknown factors that may have contributed to these results such as why patients were selected to be on one treatment or another, what the reporting requirements to the data base were, the duration of each treatment prior to an event or death, the frequency and severity of hypoglycemia (if any), the concomitant treatment with anti-hypertensive and lipid-lowering therapy, among others. In addition, these results may not be extrapolated to all patients with Type 2 diabetes since the patients in this study had a high prevalence of smoking (63% in both cohorts), may have been using first generation sulfonylureas, and already had evidence of either macrovascular disease (22%) or microvascular disease (18% in the oral agent cohort and 32% in the insulin-based cohort).

A retrospective study such as Currie et al.'s provides a much lower level of evidence than prospective, RCTs. In fact, some RCT's, e.g. the UKPDS and ACCORD (as well as some earlier retrospective studies [EDIC-Norfolk and CHARM]) have shown a linear relationship of cardiovascular outcome benefit (but not mortality) from tight glycemic control. However, because Currie et al.'s mortality results are consistent with those of the ACCORD study which was terminated early because of an increased mortality rate in those intensively controlled, diabetes care providers may want to reassess the glycemic (as well as blood pressure and lipid) goals for their patients on an individual basis using known risk factors. The exact effect of these risk factors on A1c goals of therapy will be the subject of much discuss, debate, and study

in the future. Providers should not lose sight of the fact that virtually all studies have shown reduction in microvascular complications with intensive glycemic control.

The Endocrine Society has not endorsed any specific A1c goals for diabetes therapy, and does not recommend that any wholesale change in glycemic goals be implemented at this time based on the report by Currie et al. Rather, we strongly recommend that patients discuss these issues with their diabetes care providers.