of lowering LDL-C with statins alone vs statins plus ezetimibe on common CIMT in patients with type 2 diabetes and no known prior cardiovascular events. The SANDS Trial was a randomized, open labeled, blinded to outcomes, 3-year trial examining the effects of aggressive goals for LDL-C (≤70 mg/dL) non-high-density lipoprotein cholesterol (<100 mg/dL) and blood pressure (<115/75 mm Hg) reduction vs standard goals of <100 mg/dL, <130mg/dL, and <130/80 mm Hg, respectively, in 499 Native American patients with type 2 diabetes. The primary outcome was change in CIMT after 36 months of treatment.

Ezetimibe is an antihyperlipidemic medication used to lower cholesterol levels. It acts by decreasing cholesterol absorption in the intestine and can be used alone or with other cholesterol-lowering medications. It is generally indicated for use when cholesterol levels cannot be controlled with statins alone.

The authors compared CIMT levels for 36 months in diabetic individuals aged >40 years receiving statins plus ezetimibe vs statins alone. The CIMT changes in both aggressive subgroups were compared with changes in the standard subgroups. LDL-C was reduced by 31 mg/dL (range, 23-37 mg/dL) and 32 mg/dL (range, 27-38 mg/dL) in the aggressive group by statins plus ezetimibe and statins alone, respectively. This was compared with changes of 1 mg/dL (range −3 to 6 mg/dL) in the standard group vs both aggressive subgroups ($P < .0001$). Within the aggressive group, mean CIMT at 36 months regressed in the ezetimibe and nonezetimibe subgroups but progressed in the standard treatment arm (−0.025, −0.012, and 0.039 mm, respectively; $P < .0001$).

Comment: CIMT is considered a marker of future cardiovascular risk and thus can serve as a short-term surrogate for potential long-term cardiovascular events. The current trial has, therefore, two potential significant implications. The first is that ezetimibe does not provide any advantage over a statin alone in reducing long-term cardiovascular risk. The results would therefore seem to confirm the Enhanced Trial (N Engl J Med 2008;358:1431-43) of 720 patients with familial hypercholesterolemia where there was no statistically significant difference in the primary end point of mean increase in CIMT over 24 months in the patients treated with statins alone vs statin plus ezetimibe. The second point is that it does appear possible to actually reduce surrogate markers of future atherosclerosis by aggressively lowering cholesterol beyond standard target levels. In its early stages, atherosclerosis may be a reversible disease.

Evaluation of Wells Score and Repeated D-Dimer in Diagnosing Venous Thromboembolism

Ljungqvist M, Soderberg M, Moritz P, et al. Eur J Intern Med 2008;19:285-8.

Conclusion: A normal pretest probability score using Wells criteria and a normal D-dimer level safely excludes venous thromboembolism (VTE) in emergency department patients.

Summary: Evaluation of possible VTE is common in the emergency department. Overall, <25% of the patients evaluated for VTE in the emergency department will actually have the disease. The authors sought to determine if a low pretest probability score (PTP) using Wells criteria, together with a normal D-dimer level, could safely exclude VTE in outpatients and if a follow-up D-dimer study would add additional information to the initial evaluation. Excluded were 177 patients (54% women) with D-dimer levels >0.5 mg/dL and a PTP of ≥1.5. Of these, 25% had VTE. The study included 151 patients (68% women) with suspected VTE and who had a PTP <1.5 and a D-dimer test (TinaQuant) result <0.5 mg/L but who underwent no further initial diagnostic investigations. A follow-up D-dimer test was conducted 3 to 7 days after the initial hospital visit. If this test result was abnormal, further diagnostic investigations were made.

A follow-up D-Dimer test was conducted in 101 of 151 patients (67%), and 13 had elevated D-dimer levels. None of these patients were diagnosed with VTE or had persistent symptoms. After 3 months, all 151 of these patients were contacted and none had clinical signs of VTE.

Comment: These data support the use of a clinical algorithm that includes both the Wells criteria PTP score and D-dimer levels to reduce the number of ultrasound investigations in patients with a low risk of VTE. There were no symptomatic VTEs ≤3 months in 151 patients with low PTP and a normal D-dimer level. A follow-up D-dimer test did not add clinically important information. There are many assays for D-dimer. The data here apply only to that assay used in this study.

Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes

Duckworth W, Abraira C, Moritz T. N Engl J Med 2009;360;129-39.

Conclusion: In patients with previously poorly controlled type 2 diabetes, use of intensive glucose control vs standard glucose control did not affect rates of major cardiovascular events, death, or microvascular complications.

Summary: The authors sought to determine the effects of intensive glucose control on cardiovascular events in patients with longstanding type 2 diabetes. There were 1791 veterans (mean age, 60.4 years), all of whom had suboptimal response to therapy for type 2 diabetes, randomized to either standard or intensive glucose control. All other cardiovascular risk factors were treated the same in both groups. The diagnosis of diabetes was present for a mean of 11.5 years, and 40% had sustained a previous cardiovascular event. An absolute reduction of 1.5 percentage points in the hemoglobin A_{1C} level was the goal for the intensive therapy group compared with the standard therapy group. Primary outcome was time from randomization to the occurrence of the first major cardiovascular event, defined as composite of myocardial infarction, stroke, death from cardiovascular causes, congestive heart failure, surgery, or intervention for vascular or coronary disease, and amputation for ischemic gangrene.

Median follow-up was 5.6 years. Median hemoglobin A_{1C} was 8.4% in the standard-therapy group and 6.9% in the intensive-therapy group. The primary outcome occurred in 264 patients in the standard-therapy group and 235 patients in the intensive-therapy group (0.88; 95% confidence interval [CI], 0.74-1.05; $P = .14$). Between the two groups, there were no differences in the occurrence of any components of the primary outcome or in the rate of death from any cause (hazard ratio, 1.07; 95% CI, 0.81-1.42; $P = .62$). There was also no difference in microvascular complications between the two groups. Adverse events, predominantly hypoglycemia, occurred in 17.6% of the standard-therapy and 24.1% in the intensive-therapy groups respectively.

Comment: Many interventions can affect prognosis in patients with type 2 diabetes, including lifestyle changes, control of blood pressure and lipids, and use of antiplatelet agents. Blood pressure control appears to have better benefit than glucose control (BMJ 1998;317:703-13). Previously, there had been mixed results about whether glucose control can independently reduce cardiovascular complications in patients with advanced type 2 diabetes. The UK Prospective Diabetes Study (BMJ 1998;317:703-13), the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) Trial (N Engl J Med 2008;358:2560-72), and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial (N Engl J Med 2008;358:2545-59) all studied the effects of intensive glucose control in patients with diabetes. None of these studies, and now the current study, provided significant evidence for favorable effects of intensive glucose control in controlling cardiovascular events in patients with diabetes. Some, in fact, even suggested harm from this approach. At this point we can say that intensive glucose control early in the course of patients with diabetes may be of benefit; however, in patients with well-established diabetes, it appears that management of other cardiovascular risk factors, such as hypertension and increased lipids, is a more effective approach to preventing cardiovascular morbidity and mortality than tight glucose control.

The Obesity Paradox in Patients With Peripheral Arterial Disease

Galal W, van Gestle YRBM, Hoeks SE, et al. Chest 2008;134:925-30.

Conclusion: The presence of chronic obstructive pulmonary disease (COPD) may partly explain the "obesity paradox" of increased mortality rate among underweight patients with peripheral arterial disease (PAD).

Summary: There is a paradox in patients with PAD with respect to weight. In the population with PAD, overweight or obese patients have a better survival rate than those patients of normal weight, with the highest mortality seen in the so-called underweight patient (Am J Cardiol 2007;99:1485-90). COPD is emerging as an independent risk factor for cardiovascular death (Eur Respir J 2006;28:1245-57). Given that COPD is a potential independent risk factor for cardiovascular death, the authors sought to investigate whether the presence of COPD may partly explain the so-called obesity paradox of increased mortality in underweight patients with PAD.

The study included 2392 patients who underwent major vascular surgery at a single teaching institution in The Netherlands from January 1990 to November 2006. Patients were classified according to COPD status and body mass index (BMI) as underweight, normal, overweight, and obese. Cox regression analysis was used to determine relationships between variables and all-cause mortality. Median follow-up was 4.37 years (interquartile range, 1.98-8.47 years).

Overall mortality rates among the underweight, normal, overweight, and obese patients were 54%, 50%, 40%, and 31%, respectively ($P < .001$). Distribution of COPD severity class showed increased prevalence of moderate to severe COPD in underweight patients. BMI as a continuous variable was associated with increased mortality in the entire population (hazard ratio [HR], 0.96; 95% confidence interval [CI], 0.94-0.98). Patients classified as being underweight were also at increased risk for high mortality (HR, 1.42; 95% CI, 1.0-2.01). After adjusting for COPD severity, however, the relationship between underweight and cardiovascular mortality was no longer significant (HR, 1.29; 95% CI, 0.91-1.93).

Comment: Why there should be an inverse relationship between BMI and death is uncertain. Underweight patients may have higher metabolic rates, lower antioxidant capacity in skeletal muscles, and perhaps increased systemic inflammatory responses that may contribute to the combination of lower BMI and morbidity. It is important to note spirometry, which was used routinely in this study to classify COPD, is not routinely obtained in vascular disease patients. That 50% of the patients in this study had COPD when examined with spirometry and only 10% to 15% of patients were