# Findings

## Fewer Long-Term Cardiovascular Events with Intensive Glycemic Control

Ten years later, patients with type 2 diabetes assigned to intensive glucose-lowering therapy have fewer major adverse cardiovascular events but no reduction in cardiovascular mortality, according to a study in the *New England Journal of Medicine*.

The study reports extended follow-up data on patients enrolled in the Veterans Affairs Diabetes Trial. In that study of 1791 veterans with type 2 diabetes, intensive glucose-lowering therapy did not reduce the rate of major cardiovascular events at a median 5.6 years' follow-up. For the primary outcome of major cardiovascular events, follow-up (median, 9.8 years) was available for 703 patients assigned to intensive therapy and 688 assigned to standard therapy. For the secondary outcomes of cardiovascular and all-cause mortality, the analysis included 837 and 818 patients, respectively (median, 11.8 years).

The median glycated hemoglobin levels during the trial were 6.9 percent in the intensive therapy group and 8.4 percent in the standard therapy group. Three years after the study ended, the difference was only 0.2 to 0.3 percentage points. At long-term follow-up, the risk of major cardiovascular events was significantly lower in the intensive therapy group: hazard ratio 0.83, with an absolute risk reduction of 8.6 events per 1000 person-years.

Neither cardiovascular nor overall mortality was significantly different between groups. The effects of intensive glucose control were similar for patients at higher versus lower cardiovascular risk.

Intensive glucose control may reduce the long-term risk of major cardiovascular events in older patients with long-standing type 2 diabetes, the results suggest. However, there is no reduction in the risk of death, overall or from cardiovascular causes. The potential benefits of intensive glycemic control should be weighed against the burdens and side effects of the specific treatment being considered, the researchers conclude [Hayward RA, et al. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015; 372:2197–2206].

## "Simple Strategy" Reduces AKI Risk during Cardiac Surgery

A preoperative "remote ischemic preconditioning" step substantially lowers the risk of acute kidney injury (AKI) in high-risk cardiac surgery patients, reports a study in the *Journal of the American Medical Association*.

The randomized trial included 240 patients undergoing on-pump cardiac surgery at four German centers. All were considered at high risk for AKI based on a Cleveland Clinic Foundation score of 6 or higher. The intervention group underwent remote ischemic preconditioning, administered by blood pressure cuff inflation after the induction of anesthesia. The protocol consisted of three cycles of 5-minute ischemia and 5-minute reperfusion in one upper arm. Control individuals underwent a sham intervention.

Based on the Kidney Disease: Improving Global Outcomes criteria, AKI occurred in 37.5 percent of patients assigned to remote ischemic preconditioning versus 52.5 percent of control individuals. Preconditioning was also associated with less need for renal replacement therapy: 5.8 versus 15.8 percent, and less time in the intensive care unit, 3 days versus 4 days.

There was no difference in stroke, myocardial infarction, or death. The release of two AKI biomarkers, urinary insulin-like growth factor–binding protein 7 and tissue inhibitor of metalloproteinases 2, was reduced in the intervention group. There were no reported adverse events.

Remote ischemic preconditioning may activate natural defense mechanisms that can protect the kidney during subsequent inflammatory or ischemic stress. Previous small studies of remote ischemic preconditioning to prevent AKI have yielded conflicting results.

This multicenter trial showed a 15 percent absolute reduction in AKI among high-risk cardiac surgery patients undergoing remote ischemic preconditioning. The authors call for further study of this "simple and promising strategy" to protect the kidneys and improve postoperative outcomes [Zarbock A, et al. Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery: a randomized clinical trial. *JAMA* 2015; 313:2133–2141].

## Common Kidney Function Tests Predict AKI Risk

Widely assessed kidney function measures are consistently and strongly related to the risk of acute kidney injury (AKI), independently of other risk factors, according to a pair of meta-analyses in the *American Journal of Kidney Diseases*.

One analysis included eight general population cohorts and five chronic kidney disease (CKD) cohorts participating in the CKD Prognosis Consortium. Potential predictors of AKI hospitalization were evaluated, including diabetes and hypertension, estimated GFR (eGFR, calculated by the 2009 CKD Epidemiology Collaboration creatinine equation), and urine albumin-to-creatinine ratio (ACR).

With and without diabetes or hypertension, low eGFR and high ACR were associated with higher AKI risk. Diabetic patients were generally at higher AKI risk than were nondiabetic patients at any level of eGFR, although the difference was less pronounced in the lower range of eGFR. A similar pattern was noted for ACR. Hypertensive patients were at higher risk than were patients without hypertension, although the risks were comparable at eGFR levels less than 60 mL/min/1.73 $m^2$ and ACR values greater than 30 mg/g.

The second meta-analysis evaluated the AKI risk associated with eGFR and ACR in terms of age, race, and sex. Acute kidney injury occurred in 1.3 percent of the general population cohort members (mean follow-up time, 4 years) versus 2.6 percent of CKD cohort members (mean follow-up time, 1 year). Again, both test results were strongly associated with AKI. Older age and male sex were significant risk factors for AKI, although the associations were weaker in the presence of CKD. For African Americans, AKI risk was elevated at higher eGFR levels and at most ACR levels.

The results suggest that common laboratory measures of pre-existing kidney health could be the strongest predictors of AKI risk—even more so than diabetes, hypertension, age, race, and sex. The researchers conclude, "These results suggest the primacy of low eGFR and high ACR in AKI risk stratification—an observation that could guide preventative efforts" [James MT, et al. A meta-analysis of the association of estimated GFR, albuminuria, diabetes mellitus, and hypertension with acute kidney injury. *Am J Kidney Dis* 2015; doi:10.1053/j.ajkd.2015.02.338; and Grams ME, et al. A meta-analysis of the association of estimated GFR, albuminuria, age, race, and sex with acute kidney injury. *Am J Kidney Dis* 2015; doi:10.1053/j.ajkd.2015.02.337].

# Industry Spotlight

## Sanofi Tackles Diabetes

French drugmaker Sanofi recently reported on two developments in diabetes drug development: results of a successful clinical trial of a Sanofi drug combined with another drug to lower hemoglobin A1c levels and a new partnership that intends to create a stem cell–based drug to treat diabetes.

Sanofi's drug insulin glargine (Lantus) taken in combination with lixisenatide (Lyxumia, Zealand Pharma, Copenhagen) successfully lowered hemoglobin levels in patients with type 2 diabetes compared with either drug administered alone. The combination drug, called LixiL, is injectable.

According to Zealand, a global licensing agreement is in place with Sanofi that covers lixisenatide and any combination products that include lixisenatide, and specifies that Sanofi is responsible for all development and commercialization including the financing.

Sanofi is also teaming up with German biotech firm Evotec to develop stem cell–based treatments for diabetes, under a deal that could earn Evotec more than €300 million ($327 million), Reuters reported in early August.

Philip Larsen, MD, PhD, Sanofi's global head of diabetes research and translational science, noted: "Combining Sanofi's and Evotec's beta cell and stem cell expertise in drug discovery and development will enable optimal exploitation of the potential of stem cell–derived human beta cells for therapy and drug screening in diabetes."

Cord Dohrmann, MD, chief scientific officer of Evotec, said that the use of human stem cells in drug discovery and development is rising and "will increasingly shift the landscape from symptomatic treatments to disease-modifying therapies also in diabetes."

Under the agreement, Evotec will receive different tiers of payments depending on the firm's success in meeting targets set for development, regulatory. and commercialization purposes, Reuters noted.