HEALTHCARE GROUP

CENTRE FOR DIABETES & ENDOCRINOLOGY

CDE Academy - Diabetes Literature Review

70: 2022 QUARTER 2: 2022

Academy

Perioperative Statins and BP Control Reduce Mortality after CABG in Diabetes

Takeaway

Among people with diabetes, perioperative (3-month) systolic BP (SBP) control of <130 mmHg and statin therapy are independent cardiometabolic survival determinants at 5 years post-coronary artery bypass graft (CABG) surgery.

Why this matters

Some people with diabetes remain at significant risk for subsequent cardiovascular events despite successful CABG.

Data on the effect of cardiometabolic control in mitigating this risk are scant.

Study design

Single-institution retrospective study in 1273 low- to intermediate-risk people with diabetes who underwent CABG between January 2010 and June 2018.

Key results

At 5 years, 10% had died overall, with 5% of these deaths being from from cardiovascular causes.

In multivariable analysis, SBP of ≥130 mmHg was independently associated with all-cause mortality (HR, 1.573; P=.029) after adjustment for age (HR, 1.050; P<.001).

Perioperative statin prescription was associated with lower all-cause mortality (HR, 0.484; P=.007).

HbA1c was not associated with all-cause mortality (P=.301 and .083 for 6%-7% vs ≤6% and ≥7%, respectively).

For cardiovascular mortality, the HR for SBP of ≥130 mmHg was 2.023 (P=.009). After adjustment for age this was 1.035 (P=.020). Perioperative statin therapy again had a protective effect (0.459; P=.028), whereas HbA1c was again unrelated.

Limitations

Retrospective, potential bias. No data on adherence or therapy duration over time. Exclusion of people with new-onset diabetes.

Skendelas JP, Phan DK, Friedmann P, Rodriguez CJ, Stein D, Arbab-Zadeh A, Forest SJ, Slipczuk L. Perioperative Cardiometabolic Targets and Coronary Artery Bypass Surgery Mortality in Patients With Diabetes. *J Am Heart Assoc*. 2022;11(9):e023558. doi: 10.1161/JAHA.121.023558. PMID: 35475344

Dapagliflozin Curbs Albuminuria in CKD With or Without Diabetes

In patients with chronic kidney disease (CKD), with or without type 2 diabetes, the SGLT2 inhibitor dapagliflozin reduced albuminuria, according to data from the DAPA-CKD trial.

"The effect was greater in patients with type 2 diabetes compared to those without type 2 diabetes," Dr. Hiddo Heerspink of University Medical Centre Groningen in the Netherlands told Reuters Health by email. "The similar efficacy in patients with and without type 2 diabetes on clinical outcomes suggests that part of dapagliflozin's protective effect is mediated through pathways unrelated to albuminuria reduction."

As reported in *The Lancet Diabetes and Endocrinology*, the trial protocol defined CKD as an estimated glomerular filtration rate (eGFR) of 25 to 75 mL/min/1.73m^2 and a urinary albumin-to-creatinine ratio (UACR) between 200 and 5,000.

A total of 4,304 participants in 21 countries received dapagliflozin 10 mg or placebo once daily and were followed for a median of 2.4 years. The median UACR was 949.

Notably, the trial was stopped early for overwhelming efficacy based on a recommendation of the Independent Data Monitoring Committee.

In this prespecified analysis, overall, dapagliflozin reduced the geometric mean UACR by 29.3% compared to placebo.

In patients with type 2 diabetes, relative to placebo, treatment with dapagliflozin resulted in a geometric mean percentage reduction of 35.1%, versus a reduction of 14.8% in patients without type 2 diabetes.

Among 3,860 patients with a UACR of 300 or greater at baseline, dapagliflozin increased the likelihood of regression in UACR stage (hazard ratio, 1.81).

Among 3,820 patients with a UACR less than 3,000 at baseline, dapagliflozin decreased the risk of progression in UACR stage (0.41).

Larger reductions in UACR at day 14 of dapagliflozin treatment were significantly associated with attenuated eGFR decline during follow-up.

Dr. Katherine Tuttle of the University of Washington School of Medicine in Seattle, the author of a related editorial, commented in email to Reuters Health that the study "has firmly established SGLT2 inhibition as new standard of care for people with type 2 diabetes and CKD."

Using albuminuria to risk stratify and follow treatment response is "indisputable", she said, and treatment should be intensified if albuminuria occurs. With regard to using the EGFR slope, she noted, "it will be important to determine if the historical slope prior to starting a therapy predicts the future slope for assessment of therapeutic response."

Now that the benefits of SGLT2 inhibitors have been demonstrated, she added, "more education, coordination, and multidisciplinary/multispecialty care models are needed, as the number of patients who have an indication for CKD monitoring (albuminuria/eGFR) and treatment with SGLT2 inhibitors is enormous. Optimal care will clearly require team efforts."

The study was funded by Astra Zeneca. Dr. Heerspink and most of the coauthors have received funds from the company, as has Dr. Tuttle.

SOURCE: https://bit.ly/3ppM4CJ and https://bit.ly/3plMABP *Lancet Diabetes and Endocrinology*, online October 4, 2021.

"...the study has firmly established SGLT2 inhibition as new standard of care for people with type 2 diabetes and CKD"

Stem Cell-Derived Pancreatic Cells May Be Alternative to Islet Transplants

An ongoing first-in-human trial suggests that pancreatic cells grown from stem cells can be safely implanted into people with type 1 diabetes, and in some cases, begin producing insulin.

"I was surprised by how well the device implant and explant surgeries were tolerated by these patients, and to be able to measure human insulin in the blood in a third of (them)," Dr. A.M. James Shapiro of the University of Alberta told Reuters Health by email. Dr. Shapiro led the team that developed the Edmonton Protocol, a process that allows transplantation of donated insulin-producing islet cells into the portal vein of people with type 1 diabetes.

In the new study, PEC-01 cells were implanted subcutaneously in macroencapsulation devices (VC-02; ViaCyte) into 17 subjects (nine, male) ages 22-57, allowing for direct vascularization of the cells. All participants were negative for C-peptide at baseline.

The devices have ports in the membrane to allow the patient's vasculature to grow into the lumen and directly vascularize the engrafted cells, thereby enhancing cell survival via improved oxygenation and metabolic exchange. "These preliminary data from an ongoing first-in-human phase 1/2, open-label study provide proof-of-concept that pluripotent stem cell-derived pancreatic endoderm cells (PEC-01) engrafted in type 1 diabetes patients become islet cells releasing insulin in a physiologically regulated fashion," Shapiro and colleagues write in *Cell Reports*.

Engraftment and insulin expression were observed in 63% of the VC-02 units explanted from participants at three months to a year post-implant. Six (35.3%) showed positive C-peptide at six months. Most adverse events were related to the surgical implant or explant procedures (27.9%) or to side effects of immunosuppression (33.7%).

The authors conclude, "Initial data suggest that pluripotent stem cells, which can be propagated to the desired biomass and differentiated into pancreatic islet-like tissue, may offer a scalable, renewable alternative to pancreatic islet transplants."

Shapiro said, "The next step is to transplant similar cells that have been gene edited to prevent rejection and improve survival. This is already happening with ViaCyte, and we plan to initiate first-in-human studies (now approved) in the next few weeks."

The team will also continue its work on generating insulin-producing islet cells using cells from a person's own bloodstream. "A simple blood sample and some complex processing now allow us routinely to make human insulin -producing islets that are completely biocompatible with the same person, so no anti rejection drugs will be needed," he said. "There is a lot of work ahead to move this forward, but this is now possible and within reach."

Dr. Andrew Stewart, Director, Diabetes Obesity and Metabolism Institute at the Icahn School of Medicine at Mount Sinai in New York City commented in an email to Reuters Health, "This is one of a series of recent reports showing that the path for stem cell-derived beta cells is moving forward, but still faces challenges and requires solving a number of unsolved problems."

"It remains to be demonstrated that stem cell-derived beta cells can remain fully differentiated and functional - i.e., sensing glucose and producing normal amounts of insulin sufficient to maintain a normal blood glucose - for the long term, meaning years," he noted. "This study shows that it is possible to some degree in some people for at least a matter of months, but more work is needed in learning how to keep transplanted beta cells happy, health and fully functional over the long term."

"We still don't have a well-tolerated and perfectly safe method to prevent rejection of transplanted human islets or stem cell-derived beta cells," he added. "While many academic and commercial research labs are working on this, and progress is definitely being made, we are not completely done. More work is needed on developing safe, effective and well tolerated immunosuppressive drugs, and/or improved next-generation encapsulation devices."

"My own group is focused on the development of drug treatments that can induce the residual beta cells - present in essentially all people with T1D and T2D - to regenerate, without the need for transplant (or) surgical interventions," he noted. "We are closing in on the finish line on many fronts, but more work needs to be, and is being, done. The next several years will be exciting!"

The study did not receive commercial funding. However, seven coauthors are employees of ViaCyte and Dr. Shapiro and another coauthor are consultants to the company.

SOURCE: https://bit.ly/3FFG9Ok Cell Reports Medicine, online December 2, 2021.

"ongoing... first-in-human trial suggests that pancreatic cells grown from stem cells can be safely implanted into people with type 1 diabetes."

Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Older Adult

Abstract

Background

Aspirin is a well-established therapy for the secondary prevention of cardiovascular events. However, its role in the primary prevention of cardiovascular disease is unclear, especially in older persons, who have an increased risk.

Methods

From 2010 through 2014, we enrolled community-dwelling men and women in Australia and the United States who were 70 years of age or older (or ≥65 years of age among blacks and Hispanics in the United States). The participants did not have cardiovascular disease, dementia, or disability.

Participants were randomly assigned to receive 100 mg of enteric-coated aspirin or placebo.

The primary end point was a composite of death, dementia, or persistent physical disability; results for this end point are reported in another article in the Journal.

Secondary end points included major haemorrhage and cardiovascular disease (defined as fatal coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal stroke, or hospitalisation for heart failure).

Results

Of the 19,114 persons who were enrolled in the trial, 9525 were assigned to receive aspirin and 9589 to receive placebo.

After a median of 4.7 years of follow-up, the rate of cardiovascular disease was 10.7 events per 1000 person-years in the aspirin group and 11.3 events per 1000 person-years in the placebo group (hazard ratio, 0.95; 95% confidence interval [CI], 0.83 to 1.08).

The rate of major haemorrhage was 8.6 events per 1000 person-years and 6.2 events per 1000 person-years, respectively (hazard ratio, 1.38; 95% CI, 1.18 to 1.62; P<0.001).

Conclusions

The use of low-dose aspirin as a primary prevention strategy in older adults resulted in a significantly higher risk of major haemorrhage and did not result in a significantly lower risk of cardiovascular disease than placebo.

The study was funded by the National Institute on Aging and others; ASPREE ClinicalTrials.gov number, NCT01038583.

***N Engl J Med* 2018; 379:1509-1518. DOI: 10.1056/NEJMoa1805819**

" low-dose aspirin as a primary prevention strategy in older adults resulted in a significantly higher risk of major haemorrhage and did not result in a significantly lower risk of cardiovascular disease."