糖質制限ダイエットは心房細動に関連する (Abstract 19-A-13205)

糖質制限は心房細動の発生率を増加させる

Restriction of carbohydrates increases incidence of atrial fibrillation

毎日のカロリーを穀物、果物およびデンプン質の多い野菜から摂取する割合の低い人々は、心房細動（AFib）を発生する可能性が有意に高い、とAmerican College of Cardiology's 68th Annual Scientific Session で発表された。研究では、約 14,000 人の 20 年以上にわたる医療記録を分析した。研究者らは、対象者を炭水化物の摂取量により低、中等度、高摂取群に分類した。低摂取群では AFib 発生率が、中等度摂取群に比べ 18% 高い傾向にあり、高摂取群に比べ 16% 高い傾向にあった。

Full Text

Low-carb diets are all the rage, but can cutting carbohydrates spell trouble for your heart? People getting a low proportion of their daily calories from carbohydrates such as grains, fruits and starchy vegetables are significantly more likely to develop atrial fibrillation (AFib), the most common heart rhythm disorder, according to a study presented at the American College of Cardiology's 68th Annual Scientific Session.

The study, which analyzed the health records of nearly 14,000 people spanning more than two decades, is the first and largest to assess the relationship between carbohydrate intake and AFib. People with AFib are five times more likely to have a stroke than people without the condition. It can also lead to heart failure.

Restricting carbohydrates has become a popular weight loss strategy in recent years. While there are many different low-carbohydrate diets including the ketogenic, paleo and Atkins diets, most emphasize proteins while limiting intake of sugars, grains, legumes, fruits and starchy vegetables.

"The long-term effect of carbohydrate restriction is still controversial, especially with regard to its influence on cardiovascular disease," said Xiaodong Zhuang, MD, PhD, a cardiologist at the hospital affiliated with Sun Yat-Sen University in Guangzhou, China, and the study's lead author. "Considering the potential influence on arrhythmia, our study suggests this popular weight control method should be recommended cautiously."

The findings complement previous studies, several of which have associated both low-carbohydrate and high-carbohydrate diets with an increased risk of death. However, while previous studies suggested the nature of the non-carbohydrate component of the diet influenced the overall pattern observed, the new study did not.

"Low carbohydrate diets were associated with increased risk of incident AFib regardless of the type of protein or fat used to replace the carbohydrate," Zhuang said.

Researchers drew data from Atherosclerosis Risk in Communities (ARIC), a study overseen by the National Institutes of Health that ran from 1985-2016. Of the nearly 14,000 people who did not have AFib when they enrolled in the study, researchers identified nearly 1,900 participants who were subsequently diagnosed with AFib during an average of 22 years of follow-up.

Study participants were asked to report their daily intake of 66 different food items in a questionnaire. The researchers used this information along with the Harvard Nutrient Database to estimate each participant's daily carbohydrate intake and the proportion of daily calories that came from carbohydrates.

On average, carbohydrates comprised about half of calories consumed. The Dietary Guidelines for Americans recommend that carbohydrates make up 45 to 65 percent of total daily calorie intake.

Researchers then divided participants into three groups representing low, moderate and high carbohydrate intake, reflecting diets in which carbohydrates comprised less than 44.8 percent of daily calories, 44.8 to 52.4 percent of calories, and more than 52.4 percent of calories, respectively.

Participants reporting low carbohydrate intake were the most likely to develop AFib. These participants were 18 percent more likely to develop AFib than those with moderate carbohydrate intake and 16 percent more likely to develop AFib than those with high carbohydrate intake.

Several potential mechanisms could explain why restricting carbohydrates might lead to AFib, Zhuang said. One is that people eating a low-carbohydrate diet tend to eat fewer vegetables, fruits and grains—foods that are known to reduce inflammation. Without these foods people may experience more inflammation, which has been linked with AFib. Another possible explanation is that eating more protein and fat in lieu of carbohydrate-rich foods may lead to oxidative stress, which has also been associated with AFib. Finally, the effect could be related to an increased risk of other forms of cardiovascular disease.

Zhuang said that while the research shows an association, it cannot prove cause and effect. A randomized controlled trial would be needed to confirm the relationship between carbohydrate intake and AFib and assess the effect in a more ethnically diverse population. In addition, the study did not track participants with asymptomatic AFib or those who had AFib but were never admitted to a hospital, nor did it investigate different subtypes of AFib, so it is unknown whether patients were more likely to have occasional episodes of arrhythmia or persistent AFib. The study did not account for any changes in diet that participants may have experienced after completing the questionnaire.

The ARIC study is supported by the National Heart, Lung, and Blood Institute. Collaborating researchers also received support from the National Natural Science Foundation of China and Natural Science Foundation of Guangdong Province.

ACC2019特集

フィットネスレベルが高いほど高齢者の寿命を延ばす可能性がある (Abstract 19-A-15898)

フィットネスは 70 歳以上の人々に対し従来の心血管系リスク因子より有益である

Fitness may be more informative than traditional cardiovascular risk factors for people older than 70

70 歳以上の人々の間では、フィットネスは従来の心血管系リスク因子の数よりも、生存のより優れた予測因子であることが、American College of Cardiology's 68th Annual Scientific Session で明らかにされた。最大のフィットネスを行う人は、最小のフィットネスを行う人に比べ、10 年後生きている確率が倍以上であった。対照的に、患者の心血管系リスク因子の総数は、彼らの死亡リスクとは関連がなかった。研究者らは、いつもの運動について簡単に聞くことによってフィットネスを評価することは、リスク層別化を改善できる低コストで活用されていない手段である、と示唆している。

Full Text

Researchers have uncovered one more reason to get off the couch and start exercising, especially if you're approaching your golden years. Among people over age 70, physical fitness was found to be a much better predictor of survival than the number of traditional cardiovascular risk factors in a study being presented at the American College of Cardiology's 68th Annual Scientific Session.

While hypertension, hyperlipidemia, diabetes and smoking are closely linked with a person's chance of developing heart disease, these factors are so common in older people that the total number of risk factors becomes almost meaningless for predicting future health, researchers said. The new study suggests doctors can get a better picture of older patients' health by looking at how fit they are, rather than how many of these cardiovascular risk factors they have.

"We found fitness is an extremely strong risk predictor of survival in the older age group—that is, regardless of whether you are otherwise healthy or have cardiovascular risk factors, being more fit means you're more likely to live longer than someone who is less fit," said Seamus P. Whelton, MD, MPH, assistant professor of medicine at Johns Hopkins School of Medicine and the study's lead author. "This finding emphasizes the importance of being fit, even when you're older."

Previous studies have shown that quitting smoking and controlling blood pressure, cholesterol and diabetes can reduce heart disease risk. However, most studies of cardiovascular risk factors have focused on middle-aged people, leaving a knowledge gap regarding the importance of these risk factors in older people, Whelton said.

The team analyzed medical records from more than 6,500 people aged 70 years and older who underwent an exercise stress test at a Henry Ford Health Systems-affiliated medical center between 1991 and 2009. They assessed fitness based on patients' performance during the exercise stress test, which required patients to exercise on a treadmill as hard as they could. They divided patients into three groups reflecting their fitness based on the number of METs (metabolic equivalents, a measure of exercise workload) they achieved during the test: most fit (10 or more METs), moderately fit (six to 9.9 METs) and least fit (six or fewer METs). For this study, the researchers grouped patients with zero, one, two, or three or more cardiovascular risk factors.

On average, participants were 75 years old when they underwent the stress test. Researchers tracked the patients for an average of just under 10 years, during which time 39 percent of them died. Over this period, the researchers found higher fitness was associated with significantly increased rates of survival. The most fit individuals were more than twice as likely to be alive 10 years later compared with the least fit individuals.

In contrast, a patient's total number of cardiovascular risk factors was not associated with their risk of death and patients with zero risk factors had essentially the same likelihood of dying as those with three or more risk factors.

Whelton said the findings demonstrate that fitness level is an important indicator of an older patient's health that doctors could benefit from considering more often. While an exercise stress test using a treadmill or stationary bicycle provides the most precise way to measure fitness, doctors can also get a general idea of a patient's fitness level by asking about their exercise routine.

"Assessing fitness is a low-cost, low-risk and low-technology tool that is underutilized in clinical practice for risk stratification," Whelton said.

The study did not account for any changes in fitness level that the participants may have experienced over time. However, previous studies have suggested that improving fitness can help improve heart health, even late in life.

"People who aren't exercising or are sedentary would likely benefit from starting a routine of low- to moderate-intensity exercise, though they should talk with their physician first," Whelton said.

ACC2019特集

外科手術リスクの低い患者に対するTAVRは外科手術と同様に優れている(Abstracts 19-LB-19883 and 19-LB-19835)

大いに期待されていたトライアルは、全てのリスク群に対し TAVR は外科手術と同等あるいは優れていることを示した

Highly anticipated trials show TAVR equal to or better than surgery across all risk groups

American College of Cardiology's 68th Annual Scientific Session で取り上げられた 2 つのスタディの結果、経カテーテル大動脈弁置換術（TAVR）が外科手術リスクの低い大動脈弁狭窄症患者に拡大された。1 つ目のスタディでは、後遺症を伴う脳卒中または総死亡を合計した発現率が、TAVR を施行された低リスク患者において 5.3% であったのに対し、外科的大動脈弁置換術（SAVR）では 6.7% であった。もう 1 つのスタディ PARTNER-3 では、TAVR は 1 年後の一次エンドポイントである死亡、脳卒中および再入院を 46% と、有意に減少させた。このスタディ結果は同時に *New England Journal of Medicine* に掲載された。

Full Text

Results from two studies featured at the American College of Cardiology's 68th Annual Scientific Session open transcatheter aortic valve replacement (TAVR) up to patients with aortic stenosis at low surgical risk. Both trials were simultaneously published online in the *New England Journal of Medicine* at the time of presentation. Currently, TAVR is used for treatment of severe aortic valve stenosis in patients at intermediate and high risk for complications associated with surgery. Results from these trials open the use of TAVR in low risk patients to a class I guideline indication on par with surgery.

In one trial, comparing self-expanding transcatheter aortic valve replacement (TAVR) to standard open-heart surgery for valve replacement—this time in patients with severe aortic stenosis who are considered low surgical risk—found no difference in the combined rate of disabling stroke or death from any cause at two years. These events occurred in 5.3 percent of TAVR patients and 6.7 percent of patients undergoing traditional surgery.

TAVR, which involves threading a replacement valve through a catheter in the groin or chest, is at least as safe and effective as surgery in these patients; these results echo what was found in an earlier trial of intermediate risk patients, researchers said.

"We now have a minimally invasive procedure that is as good as or better than surgery, while at the same time allowing most patients to be out of the hospital within a few days and be back to their normal activities within a week, and that's pretty important," said Michael J. Reardon, MD, professor and Allison Family Distinguished Chair of Cardiovascular Research at Houston Methodist Hospital and the study's senior author.

This randomized, prospective study included 1,468 patients with severe, symptomatic aortic stenosis from 86 centers in Australia, Canada, France, Japan, the Netherlands, New Zealand and the United States who were deemed to be at low risk of surgery. Low risk was defined as a predicted 30-day mortality of 3 percent or less for 30 days post-surgery and was based on a combination of clinical judgment from the local heart team and an independent screening committee.

A total of 725 patients received TAVR with one of three types of self-expanding devices and 678 patients underwent surgical aortic valve replacement (SAVR) with bioprosthetic surgical valves. The TAVR arm of the trial started with first- and second-generation valves (3.6 percent received CoreValve and 74.1 percent Evolut R); the new third generation Evolut Pro valve was introduced late in the trial and was implanted in 22.3 percent of patients enrolled.

Both groups were well-matched in terms of baseline characteristics such as hypertension, coronary disease and lung disease. Unlike earlier intermediate- and high-risk trials that included a 50-50 split of men and women, this trial was two-thirds men and one-third women. Reardon said this might be because women tend to be smaller, require smaller surgical valves at surgery and are deemed at higher surgical risk.

At 30 days, TAVR was statistically superior to SAVR in terms of the combined rate of all-cause mortality or disabling stroke (0.8 vs. 2.6 percent). Taken by itself, death at one month was not statistically different between the groups, but there were fewer for TAVR; deaths occurred in 1.3 percent of surgical patients and 0.5 percent of TAVR patients, which Reardon said is clinically meaningful. TAVR patients also had significantly better quality of life and hemodynamics at 30 days, which are important factors, especially in younger, more active patients.

"TAVR beat surgery at 30 days for mortality or disabling stroke, quality of life and time in the hospital. In other words, you're more likely to be alive without a disabling stroke, get out of the hospital sooner—in half the time—and have a better quality of life one month after getting a new valve," Reardon said, adding that hospital stays were twice as long for patients undergoing surgery than they were for TAVR, 6.2 days vs 2.6 days on average. "The mean age of patients in this study was 74, so while this is still not a young group of patients, many of them are very active and whether it be in their professional or social lives, getting back to full range of daily activities is very important to them."

By 12 months, TAVR was still superior to open heart surgery for major stroke, occurring in 0.8 percent of TAVR patients and 2.4 percent of surgical patients. TAVR had lower rates of all-cause mortality (2.4 vs 3 percent), but it was not statistically significant. Hospitalization for heart failure occurred in 3.2 percent of TAVR patients and 6.5 percent of surgical patients at one year.

"At one year, patients with TAVR were more likely than surgery patients to be alive, without a disabling stroke and without a hospital admission for heart failure," Reardon said.

Quality of life assessments were done using the Kansas City Cardiomyopathy Questionnaire (KCCQ), allowing patients to report their functional ability and wellness. This was performed at baseline, one and six months, and yearly thereafter. For the KCCQ, a five-point increase is considered a small improvement in quality of life, 10 points is moderate, and 20 points is large. Patients receiving TAVR reported significantly better quality of life, 20 vs. 9.1 at one month post-procedure. By one year, both TAVR and surgery had similar improvements in quality of life, 22.2 and 20.9, respectively.

Based on an analysis of echocardiograms, Reardon said there was some indication that the TAVR valve worked better; TAVR had a better orifice (2.2 cm2 vs 2.0 cm2) and lower mean gradients than surgery at all time points in the trial. Similar to earlier studies, TAVR has more pacemakers and more moderate to severe paravalvular leak. The TAVR group also had major vascular injury, including dissection, cardiac perforation or access site injury. There were more cases of atrial fibrillation, transfusions and acute kidney injury in the surgery arm.

"We've now looked at a broad risk spectrum of patients—those at high, intermediate and low surgical risk—and these series of trials have shown that TAVR is better than or as good as surgery in terms of disabling strokes and deaths from all causes. When we look at secondary outcomes of quality of life and functional recovery, these seem to favor TAVR at this point," Reardon said. "Given this data, it now seems reasonable to consider moving TAVR in low risk patients to a class I guideline indication on par with surgery for patients with severe aortic stenosis."

Reardon said this and PARTNER 3 are probably the final trials that will randomize TAVR against surgery given the positive outcomes and patient preference for less invasive therapy. His team plans to follow patients for 10 years, which should yield important long-term data about TAVR compared with surgically implanted valves, as well as the valves themselves. They will also do a cost-effectiveness analysis.

A key study limitation is the relatively short follow up time. Because patients with bicuspid aortic valves and those with anatomic incompatibility for TAVR valves were excluded, as were patients needing other major cardiac surgical procedures such as mitral valve repair, researchers cannot say how these patients might fare.

The study received funding from Medtronic.

In a second trial among patients with severe, symptomatic aortic stenosis who were at low surgical risk, transcatheter aortic valve replacement (TAVR) using the SAPIEN 3 valve compared with conventional surgery significantly reduced the primary endpoint of death, stroke and re-hospitalizations by 46 percent at one year, according to data from the latest PARTNER trial presented at the American College of Cardiology's 68th Annual Scientific Session. In addition, the rates of death from any cause, stroke and repeat hospitalizations independently favored TAVR at 30 days and at one year, researchers said.

Unlike open surgery, TAVR involves threading a replacement valve through a catheter in the groin. TAVR is currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of severe aortic valve stenosis in patients at intermediate and high risk for complications associated with surgery.

PARTNER 3 is the fifth randomized trial of the PARTNER series of studies, which collectively includes over 9,000 patients with severe aortic stenosis, a problem that occurs when the valve in the heart's main artery doesn't open fully, forcing the heart to work harder to pump blood. The earliest trials evaluated TAVR in the "sickest" patients—many of whom cannot be treated with surgery—with subsequent research moving down the spectrum of risk. This study was performed in patients at low surgical risk, which comprise the majority of patients who are candidates for surgery to have their aortic valve replaced.

"This is a landmark study because it involves 80 percent of the people who are currently being treated with surgery for aortic stenosis. Our hope was that TAVR would be non-inferior or comparable to surgery, and we were surprised to find an almost 50 percent reduction in the primary endpoint, from 15.1 percent in the surgical group to 8.5 percent with TAVR," said Martin B. Leon, MD, director of the Center for Interventional Vascular Therapy at New York-Presbyterian/Columbia University Irving Medical Center, professor of medicine at Columbia University Vagelos College of Physicians and Surgeons and lead author of the study. "This is beyond anything we could have expected, mostly because surgery is so good in treating aortic stenosis in these low risk patients."

PARTNER 3 included 1,000 patients with severe aortic stenosis at 71 centers in the U.S. and several other countries with over 95 percent of patients enrolled at U.S. sites. Participants were carefully screened to be low risk for either TAVR or surgery and were randomly assigned to receive the SAPIEN 3 TAVR valve, the newest generation technology, or surgical valve replacement. Compared with the earlier PARTNER trials with intermediate- and high-risk surgical patients, this low-risk group was younger (73 years on average), had fewer co-morbid conditions and had fewer symptoms. There were also more men than women enrolled (67.5 percent vs. 32.5 percent, respectively).

The primary endpoint was the combined rate of all-cause death, any stroke and re-hospitalizations (those related to the valve, the procedure or heart failure) at one year after the procedure.

"Taken by themselves, each component of the primary endpoint also favored TAVR, which is confirmatory evidence of the outcome," Leon said.

A total of 16 patients died during follow up. Of these, 11 were in the surgery group and five were in the TAVR group, so the one-year mortality rate was 1 percent for TAVR and 2.5 percent for surgery. Twenty patients suffered a stroke, 14 of which occurred in the surgery group (3.1 percent) and six in TAVR (1.2 percent). Patients in the surgical group were also more likely to go back to the hospital compared with those in the TAVR group (11 percent and 7.3 percent, respectively).

Several secondary endpoints were also analyzed. The length of hospital stay was reduced from seven to three days with TAVR. Patients in the TAVR group also had more rapid 30-day functional recovery based on six-minute walk tests and other self-reported quality of life measures.

"Surgery eventually catches up to TAVR in terms of functional recovery and quality of life, but it takes several months," Leon said. "TAVR is a less invasive procedure, so we expect an earlier return to normal daily activities compared with surgery. There has also been an evolution of TAVR technology, increased operator experience and enhanced procedural techniques, all of which combine to lower complications after TAVR especially in the lowest risk patients."

Post-operative or new onset atrial fibrillation was found in almost 40 percent of the surgical patients compared with only 5 percent of those receiving TAVR. Major vascular complications were similar between the groups, as was the need for new permanent pacemakers (4 percent after surgery vs 6.5 percent after TAVR). However, Leon said that the incidence of new left bundle block was higher with TAVR, which may be a predictor of needing a new pacemaker in future. Moderate or severe paravalvular leaks, leaks around the valve, were similar in the two groups.

"The results of this trial in low risk patients indicates that the choice of TAVR versus surgery for severe aortic stenosis should be independent of surgical risk profile assessments," Leon said. "The combined rate of death and disabling stroke at one year was only 1 percent with TAVR, which was an unexpectedly favorable outcome. Based on these findings, the choice of TAVR versus surgery should be a shared decision-making process that respects patient preferences and considers some of the knowledge gaps, especially in treating young patients."

There are two major limitations to the PARTNER 3 trial. First, the data are limited to one-year follow-up and longer-term follow-up is needed to be certain that the transcatheter valves are as durable as surgical valves. The patients in this trial will be followed for 10 years. Second, certain patients were excluded in this study, such as patients with bicuspid aortic valve disease and those with poor anatomy such that the valve couldn't be threaded through the femoral artery in the groin.

The study was funded by Edwards Lifesciences.

ACC2019特集

二尖弁性大動脈弁狭窄に対する治療選択肢は開心術のみではない(Abstract 19-LB-20683)

経カテーテル弁置換術は弁の解剖学的異常を有する患者において安全である

Transcatheter valve replacement safe in those with unusual valve anatomy

典型的な大動脈三尖弁を有する患者に比べ、大動脈二尖弁患者においては、経カテーテル大動脈弁置換術(TAVR)施行後の死亡率は同等であるが、脳卒中の確率は高かった、とAmerican College of Cardiology's 68th Annual Scientific Session で発表された。研究者らは大動脈二尖弁を有する患者 2,691 人と同人数の大動脈三尖弁患者を比較した。30 日間および 1 年間の総死亡率は 2 群間で同等であった。このスタディは、大動脈弁狭窄症を来した大動脈二尖弁患者において、TAVR を施行することの正当性を裏付けるものである。

Full Text

Compared with patients who had a typical tricuspid aortic valve, patients with a more unusual bicuspid aortic valve had a similar rate of death but a higher likelihood of stroke after undergoing a transcatheter aortic valve replacement (TAVR), according to research presented at the American College of Cardiology's 68th Annual Scientific Session.

While most people are born with a tricuspid aortic valve, some are born with two of the flaps fused together, creating a bicuspid valve. This is the most common congenital anomaly of the heart, present in up to 1 percent of the general population.

The study, which focused on patients for whom open heart surgery would pose an intermediate or high risk, bolsters the case for performing transcatheter aortic valve replacement (TAVR) in those with a bicuspid valve who suffer from stenosis, researchers said.

"Based on this study, patients with bicuspid aortic valve stenosis who are at intermediate or high risk for open heart surgery can be safely treated by balloon-expandable TAVR with an acceptable risk," said Raj Makkar, MD, associate director of Cedars-Sinai Heart Institute and the study's lead author. "Our study supports the notion that carefully selected patients with bicuspid aortic stenosis can avoid surgery and be treated with this less invasive option."

Previous studies have shown TAVR to be better than or as good as conventional surgery for patients at high and intermediate cardiovascular risk, which typically includes older patients and those with multiple health problems. Research is underway to determine whether TAVR's benefits extend to younger and often healthier people, in whom open heart surgery is less risky.

Determining TAVR's risks and benefits in people with a bicuspid aortic valve is key to answering this question because a bicuspid valve is the most common cause of aortic stenosis in younger patients. While some previous studies have examined TAVR in those with a bicuspid valve, they were smaller and used older types of replacement valves. Most TAVR trials have excluded patients with bicuspid aortic stenosis, leading to a paucity of data in this patient population.

For the new study, researchers analyzed data from the STS/ACC TVT registry of more than 80,000 patients who underwent TAVR between 2015 and 2018. They matched 2,691 patients who had a bicuspid valve with an equal number of patients with a tricuspid valve based on 25 variables and compared outcomes between the two groups.

Rates of death from any cause were similar between the two groups at 30 days and one year after the procedure, with 2.6 and 2.4 percent of those in the bicuspid and tricuspid groups, respectively, dying within 30 days and 10.8 and 12.1 percent of those in the bicuspid and tricuspid groups, respectively, dying within a year. There were also no significant differences between the two groups in terms of how well the replacement valve functioned.

Patients with a bicuspid valve showed a 50 percent higher risk of any type of stroke at 30 days, which occurred in 2.4 percent of these patients compared with 1.6 percent in the tricuspid group. While this is a significant difference, the stroke rate of 2.4 percent is still considered relatively low, according to the researchers.

"The results indicate that survival, stroke and valve function were very acceptable and similar to tricuspid aortic stenosis, which is the more common type of aortic stenosis," Makkar said.

While procedural complication rates were low overall, patients with a bicuspid valve were significantly more likely to have their procedure converted from TAVR to open heart surgery due to problems encountered during the procedure, which occurred in 0.9 percent of those in the bicuspid group and 0.4 percent of those in the tricuspid group. Makkar said that further research is needed to understand why these complications were more common in those with a bicuspid valve.

"Using a CT scan prior to the procedure to predict which bicuspid valves should be triaged to surgery rather than TAVR is a crucial area of research," Makkar said.

The study included only patients who were considered at intermediate or high risk for open heart surgery. Determining the risks and benefits of TAVR in younger, lower-risk patients with bicuspid aortic stenosis would require a randomized trial, Makkar said.

ACC2019特集

ベンペド酸は12週後のLDLコレステロールを低下させる (Abstract 19-LB-20667)

CLEAR：スタチンへの追加治療は高リスク患者における LDL コレステロール降下のもう 1 つの選択肢である

CLEAR: Statin add-on may offer another option for reducing LDL in high risk patients

スタチンに加えベンペド酸を併用した心筋梗塞または脳卒中の高リスク患者は、12 週後の LDL コレステロール値が有意に低かった、と American College of Cardiology's 68th Annual Scientific Session で発表された。12 週の治療後、この治験薬を投与された患者の LDL コレステロール値は、プラセボ群に比べ 17.4% 低かった。このコレステロール値低下は 52 週持続し、重篤な有害事象および筋肉関連副作用を含む有害事象に差はなかった。筆者らは、動脈硬化性心血管疾患の高リスク患者に対し、この薬剤が既存の治療への追加治療の選択肢となり得る、と述べている。

Full Text

Patients at high risk for a myocardial infarction or stroke who took an investigational drug in addition to a statin had significantly lower LDL cholesterol after 12 weeks compared to similar patients who took a placebo in addition to statin therapy, according to research presented at the American College of Cardiology's 68th Annual Scientific Session.

LDL cholesterol levels in patients who received the investigational drug, known as bempedoic acid, were reduced by 17.4 percent after 12 weeks of treatment and the reduction was sustained at 52 weeks of treatment, compared with patients who received a placebo, with no differences in overall adverse effects, including serious adverse events and muscle-related side effects, said Anne C. Goldberg, MD, professor of medicine at Washington University School of Medicine in St. Louis and lead author of the study.

"These findings—taken together with other recently reported results of large randomized trials of bempedoic acid—indicate that this agent may add to the armamentarium of treatment options for high- risk patients with atherosclerotic cardiovascular disease whose LDL cholesterol remains uncontrolled despite taking a maximally tolerated statin," Goldberg said.

Studies have shown statins to be highly effective at lowering cholesterol levels and reducing the risk of a myocardial infarction or stroke. These drugs work primarily by blocking an enzyme that the liver uses to make cholesterol, but they also inhibit cholesterol production in muscles. Some patients develop muscle pain and must limit the statin dose they take, or in some cases, discontinue taking a statin to avoid this side effect. About 10 percent of patients taking high-dose statins experience muscle pain as a side effect, Goldberg said.

The Blood Cholesterol Guideline published in 2018 by the ACC and the American Heart Association recommends treating patients with atherosclerotic cardiovascular disease (ASCVD) with the highest tolerated dose of a statin, with the goal of reducing LDL cholesterol levels by at least 50 percent.

Bempedoic acid also blocks the liver from making cholesterol, but unlike statins it does not block cholesterol production in muscles. For this reason, Goldberg said, researchers think that bempedoic acid may be less likely than statins to cause muscle pain and thus may promote further reduction of LDL cholesterol levels in patients who must limit their statin doses or not take a statin at all because of this adverse effect.

A total of 779 patients were enrolled in the study. Their average age was 64 years and more than 60 percent were men. At study entry, all patients had LDL cholesterol levels of at least 100 mg/dL and were already taking the highest tolerated dose of a statin. A subset of 77 patients was not able to tolerate any dose of a statin.

In addition to ASCVD, 80 percent of the patients had high blood pressure and 30 percent had diabetes. Six percent had familial hypercholesterolemia, which causes high LDL cholesterol and elevates risk for a heart attack from an early age.

Patients were randomly assigned to take either bempedoic acid 180 mg tablet once a day or an identical placebo tablet once a day as an add-on to the statin they were already taking. Because this was a double- blind study, neither the patients nor their doctors knew which one they received. Two-thirds of the patients received the study drug and one-third took the placebo.

The study's primary endpoint was the percentage change in LDL cholesterol levels after 12 weeks. Patients continued to take the study medications for a year so that researchers could monitor the safety of bempedoic acid and the durability of treatment effects.

At 12 weeks, LDL cholesterol levels had declined to 97.6 mg/dL from an average of 119.4 mg/dL at study entry for patients taking bempedoic acid. Over the same period, LDL cholesterol levels among patients in the placebo group were essentially unchanged (122.8 mg/dL at 12 weeks vs 122.4 at study entry). In the subgroup of patients who were not taking a statin at study entry, LDL cholesterol levels were reduced by 22 percent at 12 weeks.

At one year, patients in the bempedoic acid group had an average LDL cholesterol level of 99.6 mg/dL, while for those in the placebo group the average was 116.9 mg/dL. Major adjudicated cardiovascular events (5-point MACE) were reported by 6.1 percent of patients taking bempedoic acid and by 8.2 percent of those taking the placebo, a non-statistically significant difference, Goldberg said. Rates of worsening diabetes were similar in the two groups.

"The effect of bempedoic acid was durable at one year and we observed no increase in adverse effects from the addition of bempedoic acid to statin therapy," Goldberg said.

Results of a randomized, double-blinded trial involving 2,230 patients, announced in May 2018, found that bempedoic acid reduced LDL cholesterol by 18.1 percent on top of maximally tolerated statin therapy at 12 weeks with no increase in adverse events compared with the placebo arm.

A global randomized, double-blinded, placebo-controlled trial is now underway to determine whether treatment with bempedoic acid decreases the risk of heart attacks, strokes and death from heart or blood- vessel disease in patients who can tolerate less than the lowest approved daily starting dose of a statin. This trial, which will enroll an estimated 12,600 patients in about 30 countries, is expected to be completed in 2022.

This study was funded by Esperion Therapeutics, Inc.

ACC2019特集

AFibとACSを有する患者に対するアスピリンを用いない2剤併用療法は最も安全である(Abstract 19-LB-19653)

AUGUSTUS：AFib と ACS を有する患者に対するアピキサバンと P2Y12 阻害薬の併用は最も有効であり有害事象が最も少ない

AUGUSTUS: Apixaban plus P2Y12 inhibitor most effective with fewest adverse events for patients with both AFib and ACS

心筋梗塞、脳卒中および血栓のリスクが高く、アピキサバンとクロピドグレルなどの抗血小板薬で治療された患者は、ワルファリンなどの古いタイプの抗凝固薬を投与された患者に比べ、出血および入院のリスクが有意に低かった、と American College of Cardiology's 68th Annual Scientific Session で発表された。さらに、アスピリンを併用せずクロピドグレルを投与された患者は出血リスクが 47% 低く、MI、脳卒中または血栓のイベントは増加しなかった。このスタディ結果は公表と同時に *New England Journal of Medicine* オンライン版に掲載された。

Full Text

Patients at high risk for myocardial infarction (MI), strokes and blood clots who were treated with a novel blood thinner (apixaban) and an antiplatelet drug such as clopidogrel had a significantly lower risk of bleeding and being hospitalized compared with patients who received an older blood-thinning medication such as warfarin, according to research presented at the American College of Cardiology's 68th Annual Scientific Session. In addition, patients who received clopidogrel without concurrent aspirin, which has been standard for these patients, had an additional 47 percent reduction in bleeding events with no increase in MI, strokes or blood clots when compared with patients who received aspirin.

The lowest rates of bleeding, with no increase in deaths or hospitalizations, were seen in patients who did not receive aspirin and were treated with apixaban plus a drug such as clopidogrel. In addition to the significant reduction in risk for bleeding and lower rates of stroke, patients treated with these two medications had no increase in MIs or blood clots.

"We have shown that when it comes to treating this high-risk patient population, less may be more," said Renato D. Lopes, MD, PhD of the Duke Clinical Research Institute at Duke University School of Medicine in Durham, North Carolina, and the study's lead author. "Our findings show that the combination of apixaban and a drug such as clopidogrel—without aspirin—is the safest treatment regimen for this difficult-to-treat group of patients, without significantly increasing ischemic events such as myocardial infarctions (MI), strokes and blood clots. These results should reassure clinicians that it's okay not to treat most of these patients with aspirin."

Patients in the trial, known as AUGUSTUS, had both atrial fibrillation (AFib), heart failure and other heart complications, and acute coronary syndrome (ACS). ACS may take the form of an MI or unstable angina that may signal an imminent MI. Choosing the optimal treatment for patients with both AFib and ACS is challenging, Lopes said. These patients need to take a blood thinner to prevent stroke and blood clots, but blood thinners have not been shown to prevent blood clots in stents (stent thrombosis) and are usually not recommended for patients with ACS. Treatment with aspirin plus clopidogrel or a similar dual antiplatelet therapy (DAPT) has been shown to reduce heart attacks and stent thrombosis in patients with ACS but not stroke associated with AFib. Moreover, combining a blood thinner with DAPT increases the risk of potentially life-threatening bleeding.

Most AFib treatment trials have excluded patients with ACS, while most ACS treatment trials have excluded patients with AFib, Lopes said, creating a gap in researchers' understanding of how best to treat patients who have both conditions. Among the unanswered questions: whether a next-generation blood thinner such as apixaban is more effective than warfarin, the standard treatment, for reducing episodes of bleeding in this group of patients and whether these patients fare better if they take aspirin plus a medication such as clopidogrel in addition to a blood thinner.

The AUGUSTUS trial was designed to answer both questions. It is the first randomized, double-blinded, placebo-controlled trial to test the effect of withdrawing aspirin from the treatment regimen for a patient population at high risk for bleeding as well as for MIs, strokes and blood clots, Lopes said.

The trial enrolled 4,614 patients in 33 countries, including the United States, Canada, Mexico, the United Kingdom, and other countries in Europe, Asia and South America. Patients' median age was 70 years and 71 percent were men. All patients had AFib requiring long-term treatment with a blood thinner, had experienced a recent episode of ACS and/or were having a stent inserted in a blocked artery.

All the patients had an indication to take medications to reduce the risk of blood clots in the arteries by inhibiting platelets. More than 92 percent were taking clopidogrel at baseline; the rest were taking one of the similar drugs (e.g., prasugrel, ticagrelor).

Within 14 days of an ACS episode or stent insertion, patients underwent random assignment twice: first, to receive either apixaban or warfarin and, second, to receive either a daily baby aspirin or a matching placebo. The aspirin-or-placebo treatment assignments were double blinded, meaning that neither the patients nor their doctors knew who was receiving which treatment. The apixaban-or-warfarin treatment assignments were not blinded because of the need for patients taking warfarin to get regular blood tests to check the drug's effect on blood clotting.

All patients were treated for six months. This follow-up period was selected because most bleeding episodes, MIs, strokes and blood clots occur during the first six months after an ACS episode, insertion of a stent or initiation of a blood-thinning medication, Lopes said.

The trial's primary endpoint was major or clinically relevant nonmajor bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH). The ISTH definition includes bleeding that results in death; occurs in a critical organ; or results in hospitalization, medical treatment or surgery for bleeding or a change in the patient's anti-blood-clotting treatment. Secondary endpoints included a composite of death or hospitalization and a composite of death or stroke, MI, stent thrombosis or urgent treatment to unblock an artery.

Results for the primary safety endpoint showed that patients taking apixaban had a 31 percent reduction in risk compared with patients taking warfarin and that patients taking a placebo instead of aspirin had a 47 percent reduction in risk compared with those taking aspirin. The proportion of patients who had a bleeding episode was highest among patients treated with clopidogrel, warfarin and aspirin (18.5 percent), and lowest among those treated with clopidogrel, apixaban and placebo (7.3 percent).

The proportion of patients who died or were hospitalized was highest for patients treated with clopidogrel, warfarin and aspirin (27.5 percent) and lowest for those treated with clopidogrel, apixaban and placebo (22 percent). Patients treated with apixaban also had 50 percent lower risk of stroke compared with those taking warfarin.

A limitation of the study, Lopes said, is that it was not large enough to detect potential small differences in clinically important but rare outcomes such as stent thrombosis for individual patients.

The study was funded by Bristol-Myers Squibb and Pfizer, Inc.

It was simultaneously published online in the *New England Journal of Medicine* at the time of presentation.

ACC2019特集

生体吸収性エンベロープはデバイス関連感染症を減少させる(Abstract 19-LB-20224)

WRAP-IT：抗菌性のエンベロープは心臓デバイス関連感染症のリスクを著明に低下させる

WRAP-IT: Antibiotic envelope markedly cuts risk of cardiac device-related infection

ペースメーカーや除細動器などの心臓デバイスを生体吸収性の抗菌性エンベロープで包むことにより、1 年以内の重大なデバイス関連感染リスクが 40% 減少し合併症は増加しない、と American College of Cardiology's 68thAnnual Scientific Session で発表され、同時に *New England Journal of Medicine* に掲載された。25 か国の患者計 6,983 人が WRAP-IT トライアルに参加した。この抗菌性エンベロープを挿入された患者のうち、25 人（0.7%）が 1 年以内に重大なデバイス感染を発症したのに対し、コントロール群では 42 人（1.2%）であった。

Full Text

Encasing cardiac devices such as pacemakers or defibrillators in an "envelope" —a mesh sleeve embedded with antibiotics—reduces the risk of major device-related infection by 40 percent within one year with no increase in complications, according to research presented at the American College of Cardiology's 68th Annual Scientific Session.

The Worldwide Randomized Antibiotic EnveloPe Infection PrevenTion Trial (WRAP-IT), which involved nearly 7,000 patients in 25 countries, is the first rigorously designed randomized study to demonstrate the safety and effectiveness of this antibiotic-permeated and bioabsorbable envelope, said Khaldoun G. Tarakji, MD, MPH, associate section head of cardiac electrophysiology at the Cleveland Clinic Heart and Vascular Institute and the study's lead author. It's also one of the largest global randomized controlled trials of a cardiac implantable electronic device ever conducted, he said.

Roughly 1.5 million patients receive a cardiac implantable electronic device worldwide every year. While these devices have improved and extended the lives of millions of patients, infection remains a major, potentially life-threatening complication.

Most infections occur during the first year following implantation, but the risk is not limited to the initial device implantation, Tarakji said. Patients are exposed to this risk every time they need additional device procedures, such as for generator replacement when the battery is depleted, when they need an upgrade of their device or to revise some leads. Therefore, infection is a risk over a lifetime.

When an infection is confirmed, it usually requires the removal of the device and the leads in addition to an extended course of antibiotic therapy. Complication rates with transvenous lead extraction are low, but when they occur, they can be fatal, especially in leads that have been implanted for many years. In addition to the risk of extraction, patients go through prolonged hospitalizations, leaving them vulnerable to additional complications.

"Studies show that even when the device infection is managed properly with successful extraction procedure and the proper antibiotic therapy, short- and long-term mortality remain high in this group of patients," Tarakji said. "Prevention is the cornerstone for addressing device infection. Until now, in addition to adhering to strict sterile surgical techniques, preoperative antibiotics have been the only intervention proven in randomized controlled trial to minimize infection risk. Knowing the consequences, minimizing risk isn't good enough—our goal should be to get the infection rate as close to zero as we can."

A total of 6,983 patients in 25 countries took part in the WRAP-IT trial, which began in 2015. The patients' average age was 70 years and 72 percent were men. Most patients (83 percent) were undergoing a revision, replacement or upgrade of an existing implanted cardiac device, while the rest were receiving their first biventricular pacemaker-defibrillator.

Patients were assigned at random to have their device encased in the antibiotic envelope or not. The antibiotic envelope, made of fully bioabsorbable mesh, is embedded with two antibiotics, rifampin and minocycline, that are slowly released into the pocket where the device is placed over seven days. The envelope itself is fully absorbed by the body at eight to nine weeks after implantation. It comes in two sizes, one for use with pacemakers and one for use with defibrillators. All patients were followed up for one year after their procedure and then every six months until the end of the study. The average length of follow-up was 20.7 months.

To minimize infection risk, all patients—both those receiving the antibiotic envelope and those in the control group—were treated with preoperative antibiotics. Additionally, all surgical teams participating in the study were required to use strict, sterile surgical techniques for every procedure.

The study's primary endpoint was a major device-related infection—defined as an infection resulting in extraction or revision of the device system, long-term antibiotic treatment, or death—within one year of the procedure. Among patients who received the antibiotic envelope, 25 (0.7 percent) developed a major device infection within one year, compared with 42 patients (1.2 percent) in the control group.

"The overall infection rate was lower than expected. This is great news for all electrophysiologists and a testament for the quality of all participating centers in adhering to best practices to minimize infection," Tarakji said. "Even so, using the antibiotic envelope led to an additional 40 percent reduction in major device-related infection during the first year after implantation. And we saw no increase in complications with the use of the envelope, indicating that it is safe to use."

Use of the antibiotic envelope should not replace standard protocols for procedure safety, sound patient selection, the use of preoperative antibiotics and proper surgical techniques. However, the envelope is an additional tool to help drive down the risk of infection after the implantation of a cardiac device, Tarakji said.

The researchers plan to conduct a follow-up study of the cost-effectiveness of using the antibiotic envelope. The large, global patient database that was developed for the WRAP-IT trial may also help to answer other important questions related to device infections, Tarakji said. These questions include whether variations in practice such as the management of different blood-thinning medications and the use of different practices and surgical techniques have any effect on rates of infection.

"We now have a wonderful and rich source of information that we can use to educate ourselves about the association of different practices and variables with device infection," Tarakji said.

The antibiotic envelope, manufactured by Medtronic, Inc., has been on the market since its approval by the U.S. Food and Drug Administration in 2013. This study was funded by Medtronic, Inc.

This study was simultaneously published online in the *New England Journal of Medicine* at the time of presentation.

ACC2019特集

ダパグリフロジンは駆出率の低下した患者に有益である (Abstract 19-LB-20165)

DECLARE-TIMI 58：糖尿病治療薬は広範な心不全に対し有効である

DECLARE-TIMI 58: Diabetes drug effective against heart failure in wide spectrum of patients

糖尿病治療薬ダパグリフロジンの心血管系に対する有益性は広範な患者に認められ、特に駆出率の低下した患者において顕著である、と American College of Cardiology's 68th Annual Scientific Session で発表され、同時に *Circulation* に掲載された。研究者らは、ダパグリフロジンが駆出率やスタディ開始時の心不全の有無に関係なく、全ての患者を通じて心不全による入院を減少させたことを明らかにした。しかし、この薬剤が心血管死亡率および総死亡率を有意に減少させたのは、駆出率の低下した患者においてのみであった。この結果は DECLARE-TIMI 58 から得られたものである。

Full Text

The cardiovascular benefits of the diabetes drug dapagliflozin extend across a wide spectrum of patients and are especially pronounced in those with reduced ejection fraction according to research presented at the American College of Cardiology's 68th Annual Scientific Session.

The findings stem from the DECLARE-TIMI 58 trial, which reported in 2018 that dapagliflozin, part of a class of drugs known as SGLT2 inhibitors, reduced the composite primary endpoint of cardiovascular death and heart failure hospitalizations, which was mainly driven by the reduction in hospitalization for heart failure. The new analysis is the first to examine whether dapagliflozin's benefits can be predicted based on left ventricular ejection fraction (LVEF), a measure of how effectively the heart's left ventricle squeezes blood out of its chamber.

Low ejection fraction can be evidence of heart failure, though many patients have heart failure with normal, or preserved, ejection fraction. Researchers found dapagliflozin decreased heart failure hospitalizations across all patients, regardless of ejection fraction or whether or not they had heart failure at the start of the study. However, the drug significantly decreased rates of death from cardiovascular causes and death from all causes only among those who had a lower ejection fraction.

"The use of the SGLT2 inhibitor dapagliflozin is beneficial in reducing hospitalizations for heart failure in patients with a broad range of left ventricular ejection fraction, but patients with reduced ejection fraction may derive an even greater benefit," said Eri T. Kato, MD, PhD, a cardiologist at Kyoto University Hospital and the study's lead author. "The clinical implication of this finding is that ejection fraction is a strong tool to identify those who are at highest risk and may derive particular benefit from SGLT2 inhibitors."

SGLT2 inhibitors improve the body's ability to remove glucose from the bloodstream, helping to regulate blood sugar in people with diabetes. DECLARE-TIMI 58, conducted at 882 sites in 33 countries, enrolled more than 17,000 patients who had Type 2 diabetes, as well as either established cardiovascular disease or a high risk for cardiovascular disease. Patients were randomized to receive dapagliflozin or a placebo and followed for a median of just over four years.

Thirty percent of study participants (5,202 patients) had their LVEF documented at the start of the trial. Of these participants, 13 percent (671 patients) had heart failure with reduced ejection fraction (HFrEF), defined as an ejection fraction less than 45 percent, meaning that just 45 percent of the blood in the left ventricle is squeezed out with each heartbeat.

Researchers compared rates of heart failure hospitalizations, cardiovascular death and all-cause mortality among patients with HFrEF and those without HFrEF. They found patients with HFrEF who took dapagliflozin were 38 percent less likely to be hospitalized for heart failure or die of cardiovascular causes compared with those taking placebo, a significantly greater reduction than the 12 percent drop in the likelihood of these events among patients who did not have HFrEF.

Patients who had HFrEF also showed a significantly lower rate of cardiovascular death and death from any cause, rates of which dropped by 45 percent and 41 percent, respectively, among those taking dapagliflozin compared to those taking placebo. Researchers did not observe these benefits in patients without HFrEF. Taking dapagliflozin reduced the rate of heart failure hospitalizations among all patients, regardless of ejection fraction or heart failure status.

"The reduction in hospitalization for heart failure is remarkable because there have been very few therapies that have shown any benefit both in patients with heart failure with preserved ejection fraction and in patients with heart failure with reduced ejection fraction," Kato said. "Furthermore, there appears to be a benefit for heart failure reduction across a broad spectrum of patients with and without heart failure, suggesting that use of these agents could be beneficial in a very large population of patients with diabetes."

Patients who have heart failure with reduced ejection fraction generally face a higher risk for cardiovascular events and death compared to those with normal ejection fraction. In the trial, these patients also showed a benefit from dapagliflozin in terms of heart failure hospitalizations earlier than the other groups, while the benefits took a year or more to appear in other groups. Noting that the interplay between diabetes and heart failure is complex and multifactorial, Kato said further studies are needed to understand the mechanisms driving these differences.

Researchers plan to further analyze the DECLARE-TIMI 58 data to understand dapagliflozin's effects on metabolic, renal and cardiovascular outcomes. Other ongoing trials are investigating SGLT2 inhibitors in patients with heart failure, which should shed further light on the benefits observed in this study, Kato said.

DECLARE-TIMI 58 was funded by AstraZeneca.

This study was simultaneously published online in *Circulation* at the time of presentation.

ACC2019特集

ステント留置後の患者においてDAPTを中止することにより予後が改善する(Abstract 19-LB-19719[STOPDAPT-2] and 19-LB-20276[SMART-CHOICE])

STOPDAPT-2:より短期間の DAPT 後に P2Y12 阻害薬単剤療法を継続することにより 1 年後の予後が改善する

STOPDAPT-2: Shorter DAPT followed by P2Y12 inhibitor monotherapy improves outcomes at one year

ステント留置 1 か月後にアスピリン服用を中止したが P2Y12 阻害薬クロピドグレル服用を継続した患者は、併用投与を続けた患者に比べ 1 年後の予後が有意に良好であった、と American College of Cardiology's 68th Annual Scientific Session で発表された。STOPDAPT-2 トライアルでは、アスピリンの早期中止はトライアルの主要評価項目(心血管死、心筋梗塞、ステント血栓症、脳卒中および大出血の複合)の観点から優れていることが示された。また、アスピリン中止により、出血は減少し虚血性イベントは増加しなかった。もう 1 つのトライアル SMART-CHOICE において、ステント留置後 3 か月後にアスピリンを中止し P2Y12 阻害薬服用を継続した患者においても、同様の結果が得られた。

Full Text

Patients who stopped taking aspirin one month after receiving a stent but continued taking the P2Y12 inhibitor clopidogrel fared significantly better after one year compared with those who followed the standard practice of continuing both medications, according to research presented at the American College of Cardiology's 68th Annual Scientific Session. Stopping aspirin early was found to be superior in terms of the trial's primary endpoint, a composite of death from cardiovascular causes, myocardial infarction, clotting near the stent, stroke and major bleeding.

The trial sheds new light on the optimal way to balance the risk of clotting and bleeding in patients who undergo procedures to clear blocked arteries. Giving these patients antiplatelet medications that reduce the body's ability to clot blood can reduce the chance of clot-related problems such as myocardial infarctions and stroke, but these medications can also lead to uncontrolled bleeding.

The newest generation of stents release drugs that prevent new blockages from forming around the stent. While current guidelines recommend patients take aspirin and a P2Y12 inhibitor such as clopidogrel for at least 12 months after receiving a stent, a strategy known as dual antiplatelet therapy (DAPT), doctors have sought to determine whether this is the best combination of drugs to use with newer drug-eluting stents. The new trial assessed whether stopping aspirin after one month but continuing clopidogrel alone for 12 months might be a better approach.

"Standard 12-month DAPT is currently recommended by the guidelines, and one-month DAPT has not yet been implemented in daily clinical practice," said Hirotoshi Watanabe, MD, research associate at Kyoto University Graduate School of Medicine and the study's lead author. "According to our findings, one-month DAPT followed by clopidogrel monotherapy could be a good option after drug-eluting stent implantation with an advantage of fewer bleeding events."

The trial, known as STOPDAPT-2, enrolled 3,009 patients who received a drug-eluting stent at 89 medical centers in Japan. Patients who were taking oral anticoagulants, could not tolerate clopidogrel or had a history of bleeding in the brain were excluded. Half of the patients were randomly assigned to receive standard DAPT. The other half took aspirin plus clopidogrel or prasugrel (another P2Y12 inhibitor) for the first month and took clopidogrel only after that, with patients who took prasugrel initially switching to clopidogrel after the first month.

In the one-month DAPT group, aspirin was stopped at one month in 96 percent of patients, while DAPT was continued up to one year in 88 percent of patients in the standard 12-month DAPT group. Overall, stopping aspirin after one month reduced the risk of adverse events by 36 percent. After one year, 2.4 percent of patients who stopped aspirin after one month experienced the composite primary endpoint compared to 3.7 percent among those following standard DAPT.

An analysis of secondary endpoints revealed stopping aspirin after one month significantly reduced the rate of bleeding. Overall, 0.4 percent of those stopping aspirin experienced major bleeding compared to 1.5 percent among those following standard DAPT. Furthermore, stopping aspirin after one month did not increase the events related to clotting, known as ischemic events, in a secondary endpoint that included a composite of death from cardiovascular causes, heart attack, clotting around the stent or stroke.

"One-month DAPT followed by clopidogrel monotherapy as compared with standard 12-month DAPT reduced the bleeding events and did not increase the ischemic events," Watanabe said. "That lead to a net clinical benefit for both ischemic and bleeding outcomes."

One limitation of the study is that most of the participants were at low or intermediate risk for ischemic events. Watanabe said it is unknown whether the study can be extrapolated to apply in higher-risk patients. To answer this question, the researchers are continuing to enroll patients in the trial who have acute coronary syndrome, a group that is at higher risk for ischemic events.

The study received funding from Abbott Vascular Japan, Co., Ltd.

In another study at the American College of Cardiology's 68th Annual Scientific Session, patients who stopped taking aspirin three months after receiving a stent but continued taking a P2Y12 inhibitor—clopidogrel, prasugrel or ticagrelor—did not experience higher rates of death from any cause, myocardial infarction (MI) or stroke after a year compared with those receiving standard therapy. Furthermore, patients who stopped taking aspirin after three months had a significantly lower rate of bleeding.

The trial, known as SMART-CHOICE, assessed whether stopping aspirin after three months but continuing the P2Y12 inhibitor alone for 12 months would offer better results.

"Our study demonstrated that P2Y12 inhibitor monotherapy after a short duration of DAPT is a novel antiplatelet strategy balancing ischemic and bleeding risk in patients undergoing PCI," said Joo-Yong Hahn, MD, PhD, professor of medicine at Sungkyunkwan University School of Medicine in Seoul, South Korea and the study's lead author. "Even though this treatment strategy needs to be confirmed in other trials, aspirin may be discontinued in most patients receiving current-generation drug-eluting stents, especially in patients with bleeding risk or in those with stable ischemic heart disease."

The trial enrolled 2,993 patients who underwent PCI and received a drug-eluting stent at 33 medical centers in South Korea. Patients were randomly assigned to receive either standard DAPT for a year or aspirin plus a P2Y12 inhibitor for three months and continue with only the P2Y12 inhibitor for nine more months after that.

After one year, 2.9 percent of patients who stopped aspirin early experienced the primary endpoint, a composite of death from any cause, heart attack or stroke, compared to 2.5 percent among those following standard DAPT. Based on thresholds determined before the trial began, these rates indicate that stopping aspirin early was not inferior to DAPT in terms of the trial's primary endpoint.

In addition, stopping aspirin early was found to reduce the risk of bleeding by about 40 percent. Overall, 2 percent of those stopping aspirin experienced major bleeding compared to 3.4 percent among those following standard DAPT. Taken together, the net rate of all adverse clinical events (death from any cause, MI, stroke or bleeding) was not significantly different between the two groups.

A little more than three-quarters of the study participants took clopidogrel, the most common P2Y12 inhibitor, with the rest taking either prasugrel or ticagrelor. Hahn said that the trial's inclusion of different P2Y12 inhibitors distinguishes it from other trials investigating alternatives to DAPT.

"The SMART-CHOICE trial has a unique design to include all kinds of P2Y12 inhibitors, including clopidogrel, prasugrel and ticagrelor," Hahn said. "Therefore, we believe that the SMART-CHOICE trial, compared with several ongoing trials on P2Y12 inhibitor monotherapy after PCI, provides more generalizable answers to the concept of P2Y12 inhibitor monotherapy across a broad spectrum of patients receiving current-generation drug-eluting stents."

One limitation of the study is that a considerable proportion of patients in the group assigned to stop aspirin early in fact received aspirin after three months, although a more detailed analysis suggested this discrepancy did not undermine the overall findings. Another limitation is that the trial allowed patients to know which medications they had been assigned to take, rather than giving some patients a placebo.

The researchers will further analyze the data to determine whether the type of P2Y12 inhibitor used or variables reflecting patients' physiological response to the P2Y12 inhibitor may affect outcomes. In addition, they are investigating whether the risk of ischemic events varied among patients with acute coronary syndrome versus stable ischemic heart disease.

This study received funding from the Korean Society of Interventional Cardiology, Abbott Vascular, Biotronik and Boston Scientific.

ACC2019特集

PCIにおける橈骨動脈アプローチと大腿動脈アプローチとは生存率に関しては同等である(Abstract 19-LB-20218)

SAFARI-STEMI：インターベンション医は PCI に対し橈骨動脈および大腿動脈アプローチを用いるが、予後は同等である

SAFARI-STEMI: Interventionalists use radial and femoral access for PCI with similar outcomes

ST 上昇型心筋梗塞（STEMI）を呈する患者における経皮的冠動脈インターベンションは、橈骨動脈または大腿動脈いずれのアプローチでも安全に施行することができる、と American College of Cardiology's 68th Annual Scientific Session で発表された。早期終了されたこのスタディは、橈骨動脈および大腿動脈アプローチは 30 日死亡リスクの点で同等であることを示唆した。STEMI 再発、ステント血栓症および出血性合併症など、その他の転帰は 2 群間で有意差がなかった。

Full Text

Doctors can use either a radial or femoral approach to safely perform percutaneous coronary intervention (PCI) on patients presenting with a myocardial infarction (MI), according to research presented at the American College of Cardiology's 68th Annual Scientific Session. The research, which was stopped early, suggests the radial and femoral approach are equivalent in terms of the risk of death at 30 days.

"Based on these findings, we feel you can achieve similar results with either approach if you have an efficient system for getting patients into the procedure quickly and a good team to perform it," said Michel Le May, MD, director of the STEMI program at the University of Ottawa Heart Institute and the study's lead author. "Furthermore, we believe it is important for interventionists to be familiar with both radial and femoral access in order to be able to shift gears from one strategy to the other without hesitation."

Le May said that while some operators may prefer the radial or the femoral approach, it can become necessary to switch approaches for certain patients, sometimes in the middle of a procedure. For this reason, it is valuable for operators to routinely practice both methods.

"I think it will be important for medical training programs to emphasize the need to be proficient at both the radial and femoral access," Le May said. "It is possible to become deskilled at doing one of the procedures, and a consistent emphasis on one approach over the other can lead to an increase in complications."

When PCI was first developed, doctors accessed the heart using the femoral approach. With the advent of smaller surgical equipment, it became feasible to use smaller-diameter arteries, leading some doctors to use the radial approach instead. Previous trials have suggested the radial approach may reduce the risk of bleeding and improve survival. However, no large, randomized trial has provided definitive evidence on which approach is superior in terms of survival in patients presenting with an acute heart attack.

This study, which sought to fill that void, aimed to enroll nearly 5,000 patients at five medical centers across Canada but stopped after enrolling 2,2929. All patients underwent PCI after ST-elevation myocardial infarction (STEMI). Half were randomly assigned to radial access and half to femoral access. Most of the patients received bivalirudin and ticagrelor.

The SAFARI-STEMI study was stopped early after an analysis indicated it would not be possible to reach the primary endpoint, an expected 1.5 percent difference in mortality at 30 days, as survival rates between the radial and femoral approaches were roughly equal (1.5 percent in the radial access group and 1.3 percent in the femoral access group, an absolute difference of 0.2 percent). Rates of other outcomes including subsequent MI, stent thrombosis and bleeding complications were not significantly different between the two groups either.

One unique aspect of the design of this study was the inclusion of a homogenous population of STEMI patients, according to researchers. It is possible that patients without STEMI, or certain STEMI patient subgroups, may see different benefits from the two approaches. The trial also used updated procedure protocols in terms of medications and surgical equipment compared to previous trials.

The study received funding from the Canadian Institutes of Health Research.

ACC2019特集

心内膜炎に対する抗菌薬の経口投与への切り替えは失敗ではない(Abstract 19-LB-20241)

POET:感染性心内膜炎において部分的経口抗菌薬治療は安全かつ有効である

POET: Partial oral antibiotic therapy safe and effective in infectious endocarditis

静注抗菌薬治療から経口抗菌薬治療に切り替えられた心内膜炎患者は、従来の静注抗菌薬治療を継続された患者に比べ、長期生存率が良好であり合併症が少なかった、と American College of Cardiology's 68th Annual Scientific Session で発表され、同時に *New England Journal of Medicine* に掲載された。追跡期間中央値 3.5 年後、主要評価項目イベントを来したのは部分的経口治療を受けた患者では 26.4% であり、静注治療群では 38.2% で、統計学的に有意な差があった。今回のトライアルでは、一定の細菌種により引き起こされた左心系感染性心内膜炎患者のみが組み入れられた。

Full Text

Patients with endocarditis who were switched from intravenous to oral antibiotic therapy had better long-term survival and fewer complications than similar patients who remained on conventional intravenous antibiotic therapy, according to research presented at the American College of Cardiology's 68th Annual Scientific Session.

While initial six-month data had shown that partial treatment with oral antibiotics was similar in efficacy and safety to conventional intravenous therapy for left-sided infectious endocarditis, longer follow-up (median of 3.5 years) demonstrates this therapeutic approach is better for patients, said Henning Bundgaard, MD, PhD, DMSc, professor of cardiology at the Heart Center at the National University Hospital in Copenhagen, Denmark, and the study's lead author.

"In stabilized patients with left-sided infectious endocarditis, a switch from intravenous to oral antibiotic therapy showed superior efficacy and safety compared with continued intravenous treatment," he said. "These findings clearly support a change in the standard of care for this condition."

People with pre-existing heart valve disease, previous endocarditis, prosthetic heart valves or other implanted cardiac devices have an elevated risk for infectious endocarditis. The condition most often occurs on the left side of the heart in the mitral or aortic valve. Men are diagnosed with infectious endocarditis about twice as often as women.

The current study, known as POET, is the largest randomized trial of patients with infectious endocarditis, and was designed to test whether oral antibiotic therapy for left-sided infectious endocarditis was at least as effective and safe as intravenous treatment.

Clinical guidelines from several professional organizations currently recommend treating left-sided infectious endocarditis with intravenous antibiotics for up to six weeks. During the initial treatment phase, patients often need intensive care and close monitoring. Because intravenous antibiotics are logistically difficult to administer outside of a hospital, most patients remain in the hospital for the duration of their treatment.

Studies have suggested that intravenous treatment during long hospital stays may put patients at increased risk for complications. Oral antibiotics would allow patients to leave the hospital sooner and complete their treatment at home. Studies in other conditions have shown that patients with shorter hospital stays generally had better outcomes.

A total of 400 patients (average age 67 years; 77 percent male) with left-sided infectious endocarditis were enrolled in the study. Study participants had to be in stable condition and to have had a satisfactory response to at least 10 days of intravenous antibiotic treatment before randomization. They were then randomly assigned to either continue with intravenous antibiotics or switch to oral treatment for an average of 17 days after they were diagnosed. Intravenously-treated patients remained in the hospital until they completed antibiotic therapy. Patients who switched to oral treatment were discharged from the hospital a median of three days after making the switch.

The study's primary endpoint was a composite of death from any cause, unplanned cardiac surgery, embolic events (e.g., stroke) and relapse of infection with the same pathogen from the time of randomization until the end of follow-up.

After a median of 3.5 years of follow-up, 53 patients (26.4 percent) in the group receiving partial oral treatment had a primary-endpoint event, compared with 76 patients (38.2 percent) in the intravenously treated group, a statistically significant difference. Eighty-seven patients died; of these, 54 (27.1 percent) were treated intravenously and 33 (16.4 percent) were treated with oral medications, a significant difference. No significant differences in outcome were seen for relapse of infection, unplanned cardiac surgery or embolic events. The magnitude of the difference between the two groups is sufficient to conclude that oral treatment is superior to intravenous treatment, Bundgaard said.

Only patients with left-sided infectious endocarditis caused by certain bacterial species were enrolled in the trial, Bundgaard said, and the results may not apply to the approximately 25 percent of patients whose conditions are caused by other bacteria. In addition, although patients with antibiotic-resistant bacteria were not excluded from the trial, none were enrolled. Bundgaard and his colleagues plan to conduct additional analyses to compare quality of life and treatment costs in the groups receiving intravenous and partial oral treatment.

This study was funded by the Danish Heart Foundation and the Danish Capital Regions Research Foundation.

This study was simultaneously published online in the *New England Journal of Medicine* at the time of presentation.

ACC2019特集

進行した心不全において新たなLVADは転帰をより良好にする(Abstract 19-LB-20223)

MOMENTUM-3：最大規模の LVAD トライアルの結果、最新世代のデバイスの臨床的有意性が示された

MOMENTUM-3: Largest LVAD trial demonstrates the clinical superiority of the newest generation device

進行した心不全で、新型の左心補助人工心臓（LVAD）を装着された患者は、旧型で既存の心臓ポンプを使用された患者に比べ、2 年後の脳卒中、ポンプ血栓症および出血エピソードが有意に少なかった、と American College of Cardiology's 68th Annual Scientific Session で発表され、*New England Journal of Medicine* に掲載された。2 年後、主要エンドポイント（後遺症を伴う脳卒中、または再装着あるいは装置の不具合による除去がないこと）に達したのは HeartMate 3 を装着された患者の 74.7% であり、HeartMate II を装着された患者では 60.6% であった。リスクは 40% 低下した。

Full Text

Severely ill patients with advanced heart failure who received a novel heart pump—the HeartMate 3 left ventricular assist device (LVAD)— suffered significantly fewer strokes, pump-related blood clots and bleeding episodes after two years, compared with similar patients who received an older, more established LVAD, according to research presented at the American College of Cardiology's 68th Annual Scientific Session and simultaneously published online in the *New England Journal of Medicine* at the time of presentation.

Based on these final findings, the HeartMate 3 LVAD should now be considered the standard of care for patients with advanced heart failure who do not respond to guideline-directed medical therapy, said Mandeep R. Mehra, MD, medical director of the Heart and Vascular Center, Brigham and Women's Hospital in Boston and lead author of the study.

"These final results from what is by far the largest LVAD trial ever conducted demonstrate the clinical superiority of the HeartMate 3 compared with its predecessor, the HeartMate II," Mehra said. "We have shown a decrease in adverse events that uniquely occur due to the interface between the patient and the mechanical pump. These include a consistent and reliable reduction in strokes of all kinds and severity with the HeartMate 3 but also a remarkable reduction in the rate of pump-related blood clots and significant reductions in all types of bleeding, especially gastrointestinal bleeding. In addition to having significantly lower rates of adverse events, patients who received the HeartMate 3 had a lower rate of readmission to the hospital and spent fewer days in the hospital when they were readmitted."

The HeartMate 3 is the first implantable mechanical heart pump to use fully magnetic levitation technology—which makes the pump frictionless without mechanical bearings—to push blood through the device and into the aorta, the body's central artery.

The trial, known as MOMENTUM-3, enrolled 1,028 patients at 69 centers in the U.S. Patients' median age was 60 years and 78 percent were men. All had severe heart failure that left them unable to engage in usual physical activity without discomfort. Most had symptoms of fatigue or shortness of breath even when resting. Most (85 percent) were receiving intravenous heart failure medication because pills alone no longer worked or caused intolerable adverse effects.

Some patients in the study needed an LVAD to sustain them until they were able to receive a heart transplant. Others, because of age or other health problems, were not candidates for a transplant and relied on an LVAD as lifelong therapy. Patients were randomly assigned to have either a HeartMate 3 or a HeartMate II surgically implanted. All patients received blood-thinning medications following surgery and were also taking 81 to 325 mg of aspirin daily. The trial was designed to include two pre-specified interim analyses and then a final analysis. The first interim analysis reported six-month outcomes in the first 294 patients and the second analyzed two-year outcomes for the first 366 patients enrolled; this data was presented at ACC's 2018 Annual Scientific Session.

The primary endpoint for the final analysis was survival at two years free of disabling stroke or reoperation to replace or remove a malfunctioning device. The principal secondary endpoint was the rate of device replacement at two years.
At two years, 74.7 percent of patients who received the HeartMate 3 met the primary endpoint, compared with 60.6 percent of those who received the HeartMate II, a 40 percent reduction in risk favoring the HeartMate 3. The rate of pump replacement at two years was 2.3 percent for patients receiving the HeartMate 3 and 11.3 percent for those who received the HeartMate II.

Pump clotting occurred in 1.4 percent of HeartMate 3 patients compared with 13.9 percent of HeartMate II patients. Five percent of HeartMate 3 patients experienced a disabling stroke compared with 7.5 percent of HeartMate II patients. Significantly fewer HeartMate 3 patients experienced episodes of any type of bleeding (43.7 percent) or gastrointestinal bleeding (24.5 percent) compared with HeartMate II patients (55 percent for any type of bleeding, 30.9 percent for gastrointestinal bleeding).

HeartMate 3 patients spent more days on LVAD support outside of hospital (a median of 48 more days in the Heartmate 3) and spent fewer days in the hospital after being readmitted (a median of 13 days, compared with a median of 18 days for HeartMate II patients).

Patients continued to be at increased risk for infections at two years of follow-up, Mehra said. He said that he and his colleagues are engaging with infectious disease experts to try to find ways of reducing susceptibility to infection in patients with advanced heart failure.

The research team plans to continue to follow the MOMENTUM-3 patients for at least another three years to monitor their long-term survival. Additionally, they are developing a new trial that will examine how to optimize medical therapy for patients with advanced heart failure—for example, whether bleeding episodes might be further reduced by discontinuing daily aspirin or switching from the traditional blood thinner warfarin to newer blood-thinning medications.

The MOMENTUM-3 study was funded by Abbott, Inc.

ACC2019特集

高純度オメガ3製剤は心血管イベントを著明に減少させる (Abstract 19-LB-19844)

REDUCE-IT：心血管系リスクの高い人々に対し、イコサペント酸エチルはこれまで報告されていたよりも保護効果が高い可能性がある

REDUCE-IT: Icosapent ethyl may be more protective than previously reported for people at high cardiovascular risk

高用量のイコサペント酸エチル（オメガ 3 脂肪酸の処方薬）を服用することで、スタチンを内服していても心血管リスクの高い人々において初回、再発および全ての虚血性イベントが有意に低下する、と American College of Cardiology's 68th Annual Scientific Session で発表され、同時に *Journal of the American College of Cardiology* に掲載された。プラセボに比べ、イコサペント酸エチルにより初回およびその後の心血管死、非致死性 MI、脳卒中、冠動脈インターベンション、または不安定狭心症による入院が 30% 減少し、この薬剤が過去に報告されていたよりも保護効果が高い可能性があることが示された。

Full Text

Taking a high dose of icosapent ethyl—a pure and stable prescription form of the omega-3 fatty acid known as EPA—significantly reduces the occurrence of first, subsequent and total ischemic events, including myocardial infarction (MI), strokes and related deaths, among people at high cardiovascular risk despite already being on statin therapy, according to research presented at the American College of Cardiology's 68th Annual Scientific Session.

Compared with placebo, icosapent ethyl cut the combined rate of first and subsequent cardiovascular deaths, nonfatal heart attacks or strokes, procedures for coronary artery disease such as stenting, or hospitalizations for unstable angina (the study's primary endpoint) by 30 percent, demonstrating the drug may be more protective than previously reported. Earlier analyses of the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT), which were primarily focused on the first occurrence of a major adverse cardiovascular event, found a 25 percent reduction. This latest analysis aimed to determine the extent to which the drug reduced the total burden of first and subsequent cardiovascular events.

"In looking at the totality of events—not just the first ones, but subsequent ones too—we see that the drug provides even greater reductions in ischemic events. By looking only at first events, we underestimate the true underlying treatment benefit offered," said Deepak L. Bhatt, MD, MPH, executive director of interventional cardiovascular programs at Brigham and Women's Hospital, professor of medicine at Harvard Medical School and the study's lead author. "From a patient's perspective certainly, and from a physician's point of view, icosapent ethyl's impact on total events is what matters most."

Bhatt said that patients with high triglycerides who also have atherosclerosis or diabetes are especially vulnerable to repeat cardiovascular complications, so finding ways to prevent subsequent events is important and potentially lifesaving. Over a median follow-up period of approximately five years, there were nearly 3,000 events; 1,606 first events and 1,303 subsequent events, which included 762 second events, 272 third events and 269 fourth or more events. For patients taking icosapent ethyl, first events were reduced by 25 percent, second events by 32 percent, third events by 31 percent and fourth or more events were cut nearly in half (48 percent). The drug also prevented 1 in 5 cardiovascular-related deaths, as previously reported.

"With this drug, we are not only preventing that first heart attack but potentially the second stroke and maybe that third fatal event," Bhatt said. "Prevention of such subsequent cardiovascular events could improve patient outcomes and quality of life and may lower the total cost burden of medical care."

REDUCE-IT included 8,179 patients with elevated cardiovascular risk who were already being treated with statins. Patients with well-controlled LDL-cholesterol (>40 and ≤100 mg/dL) and with elevated triglycerides (135 to 499 mg/dL) and other cardiovascular risk factors were enrolled at 473 sites in 11 countries between 2011 and 2016. About 70 percent of patients in the study had established cardiovascular disease and the rest had diabetes without known cardiovascular disease but with at least one additional cardiovascular risk factor. At baseline, median triglyceride levels were 216 mg/dL and median LDL-cholesterol was 75 mg/dL.

Patients were randomized in double-blinded fashion to receive either 2 grams icosapent ethyl twice daily or a placebo and were followed for a median of 4.9 years. The main outcomes were total (first and subsequent) primary composite endpoint events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization or hospitalization for chest pain related to blockages) and total key secondary composite endpoint events (cardiovascular death, nonfatal myocardial infarction or nonfatal stroke). Follow-up visits were at four months, 12 months and annually thereafter.

The primary endpoint occurred in 17.2 percent of patients taking icosapent ethyl versus 22 percent of patients taking the placebo—an absolute risk reduction of 4.8 percent. For every 1,000 patients treated for five years with icosapent ethyl vs. placebo, about 159 events could be prevented, including 12 cardiovascular-related deaths, 42 heart attacks, 14 strokes, 76 coronary revascularizations and 16 hospitalizations for unstable angina.

"That's a striking impact not only for that individual, but also if we consider the public health implications and potentially cost-effective ways to lower risk, this could be an appealing strategy," Bhatt said. "We were surprised by how large an effect size there is and how much of an impact the drug is having on these patients over time, especially in the context of patients who are already well treated with background therapy."

Baseline use of antiplatelet therapy, ACE-inhibitors/ARBs, beta blockers, aspirin and statins were all very high in REDUCE-IT, which Bhatt said provides reassurance that icosapent ethyl is providing separate and incremental benefits. "These are not undertreated patients, but they are really well treated and still remain at high cardiovascular risk," he said, adding that this drug could potentially benefit tens of millions of patients worldwide.

Researchers also reported consistent cardiovascular benefits across subgroups of patients, including across a range of triglycerides levels, such as those with baseline or achieved triglycerides above or below 150 mg/dL, which is considered the threshold for normal by current guidelines. Bhatt said this suggests there are likely additional cardioprotective effects unique to icosapent ethyl besides triglyceride-lowering, including anti-inflammatory properties, anti-thrombotic mechanisms and cell membrane stabilization. As previously reported, the drug had a good safety profile albeit with an increased incidence of atrial fibrillation and numerically more patients with serious bleeding episodes; however, Bhatt said the overall rates were low. He reported there was no increase in the risk of stroke, the most serious complication of atrial fibrillation, but rather a statistically significant 28 percent reduction with icosapent ethyl versus placebo, as well as significant reductions in heart attacks, cardiac arrest and sudden cardiac death.

The study received funding from Amarin Pharma, Inc.

This study was simultaneously published online in the *Journal of the American College of Cardiology* at the time of presentation.

ACC2019特集

閉鎖不全を有する弁の修復はQOLを改善する (Abstract 19-LB-20344)

COAPT：経カテーテル僧帽弁修復は心不全および 2 次性僧帽弁閉鎖不全を有する患者の QOL を改善する

COAPT: Transcatheter mitral valve repair improves quality of life for patients with heart failure and secondary mitral regurgitation

心不全及び 2 次性僧帽弁閉鎖不全を有する患者は、経カテーテル僧帽弁置換術（TMVR）施行後に体調がよく心不全症状が減少したと報告した、と American College of Cardiology's 68th Annual Scientific Session で発表され、*Journal of the American College of Cardiology* に掲載された。トライアル開始時、参加者の QOL 評価スコアは 100 点中 52 点であり、QOL は比較的低いことを示していた。1 か月後、TMVR を施行された患者は、標準治療を受けた患者に比べ、スコアが 16 点改善した。2 年後、TMVR 群のスコアは標準治療群のスコアに比べ 13 点高かった。

Full Text

Patients with heart failure and secondary mitral regurgitation reported feeling better and experiencing fewer heart failure symptoms if they underwent a procedure to repair their valve than patients who received standard treatment alone, according to research presented at the American College of Cardiology's 68th Annual Scientific Session. The study was simultaneously published online in the *Journal of the American College of Cardiology* at the time of presentation.

The findings are the latest to come from the COAPT trial, which investigated the use of a procedure called transcatheter mitral valve repair (TMVR) in patients with secondary mitral regurgitation. In 2018, COAPT researchers reported that patients undergoing TMVR had significantly better rates of survival at two years compared with those receiving standard medical therapy. For the new study, researchers further analyzed data from the trial to determine whether the valve repair also improved patients' quality of life.

"In patients with heart failure and secondary mitral regurgitation, TMVR resulted in early, substantial and sustained improvement in health status compared with standard care," said Suzanne Arnold, MD, a cardiologist at Saint Luke's Mid America Heart Institute, associate professor of medicine at the University of Missouri–Kansas City and the study's lead author. "These outcomes are incredibly important to patients. Showing that TMVR improves patients' symptoms and quality of life adds further support to the use of TMVR in these patients."

It is estimated that at least a quarter of heart failure patients also have secondary mitral valve regurgitation. People with both conditions commonly suffer symptoms such as shortness of breath, swelling and fatigue.

COAPT enrolled 614 patients treated at 78 medical centers in the U.S. and Canada and randomly assigned them to receive TMVR or standard medical therapy, which typically includes diuretics, beta blockers, other medications, and sometimes cardiac resynchronization therapy. All participants had heart failure and moderate to severe secondary mitral regurgitation at the start of the trial. Researchers assessed participants' quality of life with the Kansas City Cardiomyopathy Questionnaire (KCCQ), a tool designed to assess the symptoms, functional limitations, social limitations and quality of life of people with heart failure.

At the start of the trial, participants scored 52 out of 100 on the KCCQ summary score, on average, which reflects a relatively poor quality of life. Patients' heart failure symptoms significantly limited their daily activities, causing shortness of breath or fatigue when walking on level ground or doing light housework, Arnold said.

After one month, patients who underwent TMVR reported a 16-point greater improvement in their average KCCQ score compared with those on standard therapy, an improvement considered moderate to large. Patients potentially still had shortness of breath or fatigue when walking briskly or up an incline but were no longer limited in their ability to do less vigorous activities, such as shopping or walking at a normal pace.

By the end of two years, those undergoing TMVR had an average KCCQ score 13 points higher, on average, than those on standard therapy.

"The durability of the finding was a bit surprising given that these patients had pretty severe heart failure at baseline," Arnold said. "You might expect that the benefit might wane over time, and the fact that we didn't see much reduction over time was encouraging."

Although deaths were common in both treatment groups owing to advanced age, comorbidities and underlying heart failure, a higher proportion of patients who were randomized to TMVR were alive with significant improvement in health status at every follow-up time point. For example, at two years, 36 percent of patients treated with TMVR were alive with a moderate improvement in health status compared with only 17 percent in the standard care arm.

The study was limited by the fact that it was not a blinded trial; patients knew if they had undergone valve repair. In addition, because a relatively large proportion of patients died before the end of the two-year follow-up, the loss of the more severely ill patients, who likely had the poorest quality of life, may have biased the average quality of life over time in a slightly upward direction. It is also unclear whether the results are generalizable beyond the specific patient group included in the trial, Arnold said.

The study was funded by Abbott.

ACC2019特集

全ての心停止に対し緊急のインターベンションが必要なわけではない(Abstract 19-LB-20652)

非STEMI患者において心停止後の血管造影のタイミングは生存率に影響しない

Timing of angiography does not impact survival after cardiac arrest for non-STEMI patients

ST 上昇型心筋梗塞（STEMI）の所見のない心停止からの蘇生後の患者において、緊急冠動脈造影は数日後に冠動脈造影を施行した場合に比べ、90 日間の生存率を改善しなかった、と American College of Cardiology's 68th Annual Scientific Session で発表された。両群ともに生存率は予測よりも良好であり、心停止後 90 日の生存率は緊急冠動脈インターベンションを施行された群で 64.5% であり、インターベンションを遅れて施行された群で 67.2% であった。このスタディ結果は発表と同時に *New England Journal of Medicine* オンライン版に掲載された。

Full Text

In patients resuscitated after cardiac arrest who do not show evidence of ST-segment elevation myocardial infarction (STEMI), receiving immediate coronary angiography did not improve survival at 90 days compared to waiting a few days before undergoing the procedure, based on findings presented at the American College of Cardiology's 68th Annual Scientific Session.

For people who are resuscitated from cardiac arrest due to STEMI, it is common practice to immediately proceed with coronary angiography. If blockages are found, the medical team inserts a stent. However, it has been unclear whether this practice is beneficial for people who suffer cardiac arrest without STEMI. This study is the first randomized controlled trial to shed light on the optimal timing of coronary angiography in these patients.

"It is an important trial for the entire cardiac arrest team," said Jorrit Lemkes, MD, a cardiologist at Amsterdam University Medical Centre in the Netherlands and the study's lead author. "The question of whether or not to immediately send the patient for catheterization comes up routinely in this group of patients. This trial gives us more information on that question, suggesting patients who do not show ST-segment elevation on the electrocardiogram do not require an immediate invasive strategy after cardiac arrest."

The trial enrolled 552 patients who were treated at 19 medical centers in the Netherlands after suffering cardiac arrest outside of a hospital. All patients were evaluated with an electrocardiogram upon arrival at the emergency department and found not to have evidence of STEMI. Half of the patients were randomly assigned to immediately proceed to the cardiac catheterization laboratory, where they underwent coronary angiography and subsequent PCI if needed. The other half was transferred to the intensive care unit for standard post-resuscitation care. These patients underwent coronary angiography and PCI, if needed, only after they awoke and showed signs of neurological recovery, which typically occurs after a few days.

The results showed no significant difference between the two groups in terms of survival at 90 days, the trial's primary endpoint. Survival was better than expected in both groups, with 64.5 percent of those receiving immediate intervention and 67.2 percent of those receiving delayed intervention alive 90 days after their cardiac arrest. Researchers say the findings may reflect the fact that clearing the arteries with PCI sooner after cardiac arrest does not necessarily reduce the likelihood of long-term brain damage, which is a key factor in survival after cardiac arrest.

"We'd hoped that sending these patients for immediate catheterization would improve outcomes, but I think there are some explanations for why we found what we found," Lemkes said. "One is that the primary cause of death in this patient group is neurological injury, and it is difficult to imagine how immediate catheterization would address that."

Previous trials have suggested cooling the body can improve outcomes for patients after cardiac arrest. An analysis of secondary outcomes revealed patients who received delayed intervention achieved the target body temperature more quickly, after an average of 4.7 hours compared to 5.4 hours in the group receiving immediate intervention. However, this trend did not translate to a significant survival benefit.

The timing of angiography did not appear to make difference in regard to other secondary outcomes relevant to the degree of brain damage, kidney problems, bleeding and other common complications after cardiac arrest.

Lemkes said that the study's moderate sample size and the higher-than-expected survival rate may have limited the study's statistical power. In addition, the trial's findings are relevant only to non-STEMI patients after cardiac arrest, not to STEMI patients or those experiencing cardiogenic shock. He added that the results of several other ongoing trials may shed more light on the optimal timing of angiography in non-STEMI patients or help to identify subgroups who may be more likely to benefit from immediate intervention.

The study received funding from Biotronik, AstraZeneca and the Netherlands Heart Institute.

This study was simultaneously published online in the *New England Journal of Medicine* at the time of presentation.

ACC2019特集

CardioMEMSセンサーは入院を半分以下に減少させる (Abstract 19-LB-20163)

ワイヤレス心不全センサーは全ての駆出率範囲にわたり性別に関係なく入院を減少させた

Wireless heart failure sensor reduces hospitalizations across all ejection fraction ranges and both genders

CardioMEMS 心不全センサー（ワイヤレスで肺動脈圧をモニターするようにデザインされている）植え込み後 1 年間に、心不全入院が 58% 減少した、と American College of Cardiology's 68th Annual Scientific Session で発表された。患者の駆出率が保持されているか（>50%）、低下しているか（<40%）、またはミッドレンジ（41 ～ 50%）かにかかわらず、このセンサーにより入院を予防することができた。女性や少数人種および民族においても明らかに有益であった。植え込み型除細動器または心臓再同期療法除細動器を植え込まれている患者とそうでない患者、および虚血性または非虚血性心筋症の患者いずれにおいても、この CardioMEMS センサーにより入院率低下が認められた。

Full Text

In the year following placement of a CardioMEMS heart failure sensor—designed to wirelessly measure and monitor pulmonary artery pressures that can signal worsening heart failure—patients experienced a 58 percent reduction in hospitalization for heart failure, according to research presented at the American College of Cardiology's 68th Annual Scientific Session. Reductions in hospitalizations were seen in both men and women, across all ejection fraction ranges and regardless of race.

CardioMEMS is a small sensor that is placed directly into a patient's pulmonary artery. In a minimally invasive outpatient procedure, doctors use the femoral vein in the groin to thread the sensor up to the heart. Once implanted, the device can detect rising pressures in the pulmonary artery, which can be an early warning of pending congestive heart failure even before symptoms of shortness of breath or weight gain are reported. Pressures are recorded and transmitted electronically from a patient's home to a secure website so health care providers can review the readings and proactively adjust medical therapies to keep patients at their target pressures.

This prospective, open-label trial was initiated as a post-approval study to evaluate the efficacy and safety of the CardioMEMS sensor in clinical practice per U.S. Food and Drug Administration (FDA) mandates. The device was approved by the FDA in May 2014 for use in patients who have New York Heart Association (NYHA) Class III heart failure that limits daily life and who have been hospitalized for heart failure in the previous year. The study included 1,200 patients at 104 clinical sites in the U.S. Participants were an average of 69 years old and included 38 percent women, 17 percent non-white, 30 percent with preserved ejection fraction (HFpEF) and 53 percent with reduced ejection fraction.

"This study was done in a large number of patients with substantial representation of women and minorities and showed the device to be not only safe but markedly effective in keeping people out of the hospital," said David Shavelle, MD, associate professor at Keck School of Medicine of USC and the study's lead author. "Our findings further validate the concept that remote monitoring of pulmonary artery pressures, which is a surrogate to a patients' volume status, allows adjustment of medical therapy in a timely manner to prevent future heart failure hospitalizations. This represents an important advance in heart failure management, as these patients are at very high risk of hospitalizations and complications."

The primary efficacy endpoint was heart failure hospitalization rates in the year after the sensor was implanted compared to the year before. Heart failure is among the top conditions that result in hospitalizations among people age 65 years and older. Patients in the study had an average of 1.24 heart failure hospitalizations in the year prior to implant and 0.52 hospitalizations in the year after having the device implanted. This translated to a 58 percent reduction in heart failure-related hospitalizations, researchers said. Similar reductions in hospitalizations were seen in patients with the greatest burden of hospitalizations (more than two hospitalizations in the previous year).

"Having the device cut the risk of hospitalizations by more than half," Shavelle said. "The benefits of lower hospitalizations were seen across all subgroups of patients, and we also validated that this treatment can decrease hospitalizations in patients with HFpEF."

The sensor prevented hospitalizations regardless of patients' ejection fraction, preserved ejection fraction (50 percent or higher), reduced ejection fraction (<40 percent) or mid-range ejection fraction (41-50 percent). There were also clear benefits for females and racial/ethnic minorities. Females had a 61 percent reduction in heart failure hospitalization and blacks had a reduction of 53 percent.

Additionally, patients with or without an implantable cardioverter defibrillator or cardiac resynchronization therapy defibrillator and those with an ischemic or non-ischemic cardiomyopathy also saw lower rates of hospitalizations with the CardioMEMS sensor.

Moreover, having the device also appeared to reduce all-cause hospitalizations for conditions like pneumonia, chronic obstructive pulmonary disease or arrhythmias by 28 percent. Other analyses showed the combined rate of heart failure-related hospitalizations or death also dropped by 44 percent after the sensor was placed.

"If you can maintain more normal cardiac filling pressures and less heart stress, you are less likely to be seriously affected and need hospitalization for other conditions such as lung disease or liver disease, which are affected by heart function," Shavelle said. "We believe that having the sensor monitored by their care team also encourages patients to follow their medication plan and gives them a sense of security that is particularly important for those living far away from a hospital."

The CardioMEMS sensor also met its safety endpoint—freedom from device or system-related complications or sensor failure at one year. To assess safety, researchers tracked whether there were any device or system-related complications and episodes of sensor failure where they were unable to get pressure readings from the device even after troubleshooting the external electronics. Based on the data, only four patients had device- or system-related complications, and there was only one episode of sensor failure, Shavelle said. Reported another way, at one year post-implant, study participants had 99.7 percent freedom from device/system-related complications and 99.9 percent freedom from sensor failure.

An ongoing study is evaluating the use of the CardioMEMS sensor for patients with other classes of heart failure (NYHA Class II and IV) and for patients at risk but without a prior hospitalization for heart failure.

This study was funded by Abbott Vascular.

ACC2019特集

高齢者において降圧は脳損傷の悪化を予防する (Abstract 19-LB-20271)

INFINITY：高齢者においてより積極的な降圧治療は脳機能を維持するのに役立つ可能性がある

INFINITY: More aggressive hypertension treatment could help preserve brain function in elderly

高血圧を有する高齢者で3年間にわたり薬物投与を受け、24時間の収縮期血圧を130mmHgに維持した者は、収縮期血圧を145mmHg程度に維持した者に比べ、有害な脳病変の蓄積が有意に少なかった、とAmerican College of Cardiology's 68th Annual Scientific Sessionで発表された。しかし、核磁気共鳴画像検査（MRI）において明るい白い斑点として見えるこの脳病変の減少は、可動性および認知機能の有意な改善を示すわけではなかった。そのような有益性が明らかになるには3年間は短すぎる可能性がある、と研究者らは述べている。

Full Text

Elderly people with hypertension who took medicine to keep their 24-hour systolic blood pressure around 130 mm Hg for three years showed significantly less accumulation of harmful brain lesions compared with those taking medicine to maintain a systolic blood pressure around 145 mm Hg, according to research presented at the American College of Cardiology's 68th Annual Scientific Session. However, the reduction in brain lesions, visible as bright white spots on a magnetic resonance imaging (MRI) scan, did not translate to a significant improvement in mobility and cognitive function. Researchers said it is likely that three years was too short a time for such benefits to become apparent.

The study, called INFINITY, is the first to demonstrate an effective way to slow the progression of cerebrovascular disease, a condition common in older adults that restricts the flow of blood to the brain. The study is also unique in its use of around-the-clock ambulatory blood pressure monitors, which measured participants' blood pressure during all activities of daily living, rather than only in the medical care environment. In addition to seeing beneficial effects in the brain, those who kept their blood pressure lower also were less likely to suffer major cardiovascular events, such as a heart attack or stroke.

"I think it's an important clinical finding, and a very hopeful one for elderly people who have vascular disease of the brain and hypertension," said William B. White, MD, professor of medicine at the University of Connecticut School of Medicine's Calhoun Cardiology Center and one of the study's principal investigators. "With the intensive 24-hour blood pressure treatment we reduced the accrual of this brain damage by 40 percent in a period of just three years. That is highly clinically significant, and I think over a longer time period intensive reduction of the ambulatory blood pressure will have a substantial impact on function in older persons, as well."

By reducing blood flow to the brain, cerebrovascular disease causes a gradual buildup of lesions that represent areas with damaged nerve cells in the brain's white matter. Older people with more of these lesions tend to have slower reflexes, problems with mobility and more signs of cognitive decline.

Having high systolic blood pressure over a long period of time is known to exacerbate damage to small arteries in the deep regions of the brain, but it was not previously known whether the process could be stopped or slowed by controlling ambulatory blood pressure. The new findings suggest keeping the 24- hour systolic blood pressure around 130 mm Hg is a safe and effective way to slow the progression of the disease, White said.

The trial enrolled 199 people who were an average age of 81 years old. All participants had hypertension at the start of the trial, with an average systolic blood pressure around 150 mm Hg, as well as evidence of some cerebrovascular disease on an MRI scan. Half of the participants were randomly assigned to receive standard blood pressure control and half were assigned to receive more intensive blood pressure control.

Doctors worked closely with each patient to manage their medications until they achieved the target blood pressure. They used ambulatory blood pressure monitors to guide blood pressure treatment. Since blood pressure measurements taken in the clinical environment may not be truly representative of the out-of- office blood pressure, ambulatory blood pressure monitoring is known to provide a more accurate picture of blood pressure behavior, White said.

Patients receiving standard blood pressure control maintained an average systolic blood pressure of 146 mm Hg, close to the study's target level of 145 mm Hg. Patients receiving the more intensive treatment had an average systolic blood pressure of 131 mm Hg, close to the target level of 130 mm Hg.

After three years, those maintaining the lower systolic blood pressure level had about a 40 percent relative reduction in the accumulation of the white matter lesions, the study's first co-primary endpoint, than those with higher blood pressure. However, the groups showed no significant difference in gait speed, a marker of mobility function and the other co-primary endpoint.

A sensitivity analysis showed that 60 percent of the patients maintained their target blood pressure throughout the full three years. An analysis of data from these patients revealed even more pronounced differences in the number of brain lesions among participants with higher versus lower blood pressure. Because this reduction in accrual of brain lesions was so significant, it is reasonable to expect that those in the more intensive treatment group would begin to show benefits over the standard treatment group in mobility and cognitive function after a few more years, White said.

"The average 80-year-old without a major illness such as cancer or heart failure can expect to live about 13 more years, and if you cut back the accrual of vascular damage over the course of that timeframe it could substantially improve a person's quality of life," White said. "In addition, this benefit would likely be amplified in people with more severe or longer-duration hypertension."

Intensive blood pressure control also brought cardiovascular benefits. Even in this small group of 199 patients, participants in the standard therapy group were four times as likely to suffer a major non-fatal cardiovascular event compared with those in the intensive treatment group.

Having blood pressure that is too low can cause a person to faint or have falls with injury. However, the rates of fainting and falling were the same in both treatment groups, suggesting that the 24-hour systolic blood pressure target of 130 mm Hg was not an unacceptably low target, White said.

White said that the study was limited by its relatively small size and the likelihood that three years was not enough time to show measurable cognitive benefits.

The study was funded by the National Institute of Aging of the National Institutes of Health and the Lowell Weicker General Clinical Research Center at the University of Connecticut.

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