脳画像が扁桃体の活性と心臓発作のリスクを関連付ける (Abstract 1275M-03)

画像を用いたスタディにおいてストレス応答と心血管リスクの背後にあるメカニズムが初めて研究された

Study uses imaging to gain a first look into mechanisms behind stress response and cardiovascular risk

脳内のストレス中枢が活性化されるほど動脈の炎症所見も多く有し、心筋梗塞、脳卒中および死亡などの心血管イベントリスクも高い、と第65回American College of Cardiology年次集会で発表された。PET/CT画像を調査することで研究者らは、脳ストレス活性測定値が1単位増加するごとに心血管イベントリスクが14倍上昇することを明らかにした。5年間で、ストレス中枢の活性が高い患者の35%が心血管イベントを発症したのに対し、ストレス中枢の活性が低い者におけるその割合は5%であった。

Full Text

New research shows that individuals with a greater degree of activity in the stress center of the brain also have more evidence of inflammation in their arteries and were at higher risk for cardiovascular events, including myocardial infarction (MI), stroke and death, according to a study presented at the American College of Cardiology's 65th Annual Scientific Session.

While there has been mounting evidence of the strong link between stress and heart disease, relatively little is understood about the mechanisms behind this stress response and what might put someone at risk for cardiovascular disease. This is the first study to use medical imaging to show a possible association between biochemical activity in the brain and arterial inflammation. Arterial inflammation is a key component of atherosclerotic disease and is highly predictive of future cardiovascular events and stroke.

"Our study illuminates, for the first time, a relationship between activation of neural tissues – those associated with fear and stress – and subsequent heart disease events," said Ahmed Tawakol, M.D., co-director of the cardiac MR PET CT program at Massachusetts General Hospital and co-author of the study. "There is a need to develop greater knowledge in terms of the mechanism that translates stress into cardiovascular disease risk, given the prevalence and potency of stress as a risk factor."

Data show the more activity occurring in the amygdala – the stress center of the brain – the more inflammation patients had in their arteries and the greater the likelihood of having cardiovascular events. There was also a corresponding activation of the bone marrow. Bone marrow releases immune cells called monocytes that can trigger inflammation in other parts of the body.

Researchers examined PET/CT scans for 293 patients (average age of 55 years) who originally received the test between 2005 and 2008 for cancer evaluation but were found to be free of active disease. The scans allowed researchers to objectively measure activity in regions of the brain, as well as the bone marrow and arteries. Patients were excluded if they had evidence of cancer, established cardiovascular disease or were younger than 30 years old. An hour before the scan, patients were injected with a radioactive atom attached to a glucose molecule as a tracer; tissues that were more active would metabolize more of the glucose and glow more brightly on the scan. A radiologist who had no knowledge of the patient's history or identifying characteristics measured the images. Activity in the amygdala was compared to other regions in the brain. Researchers then grouped patients based on the relative magnitude of brain stress activity.

After correcting for age, gender and other cardiovascular risk factors using the Framingham Risk Score, there was a 14-fold greater risk of cardiovascular events for every unit increase in measured brain stress activity. Over the approximately five-year study period, 35 percent of the patients in the high stress center activity group later suffered a cardiovascular event, compared to just 5 percent of the low stress center activity group.

Tawakol and his colleagues found the subjects' amygdala activity – as seen on brain scans – indicated whether they would suffer a major cardiac event in the near future. Increased amygdala activity corresponded to greater activity in the bone marrow and increased inflammation in arteries.

The researchers further observed that activation of the brain's fear centers, bone marrow activation and arterial inflammation may together contribute to a mechanism that provokes cardiovascular events. Tawakol said this points to the need for future studies to test whether interrupting this mechanism reduces the burden of cardiovascular disease associated with stress.

"Over the past several years, it's become clear that stress is not only a result of adversity but may itself also be an important cause of disease. The risks of heart disease linked to stress is on par with that for smoking, high blood pressure, high cholesterol and diabetes, yet relatively little is done to address this risk compared to other risk factors," Tawakol said. "We are hopeful studies like this bring us closer to understanding how stress may lead to heart disease."

While researchers were able to objectively measure stress activity in the brain, the retrospective nature of the study meant that they could not compare it to subjective measures of patients' stress levels. Additionally, the patient population is limited to individuals who received PET/CT scans to screen for cancer.

Still, Tawakol said the study findings prompt the question of whether treating stress and reducing the activation of the fear center of the brain may lead to less atherosclerotic inflammation and, ultimately, reduce cardiovascular events. Larger prospective studies are needed.

Doctors need to be aware of the heart-health consequences of current events such as the Syrian crisis and this week's terror attacks in Brussels, said Dr. Richard Becker, director of cardiovascular health and disease at the University of Cincinnati College of Medicine. He is also director of the university's Heart, Lung & Vascular Institute.

"After there's an earthquake or a tsunami, the incidence of heart attacks over the next six to eight weeks increases substantially," said Becker, an American Heart Association spokesman, citing prior research. "The same thing happens with human disasters, with terrorism, particularly if it's on a large scale."

ACC2016特集

心疾患患者においてうつ病は予後不良と関連している (Abstract 1275M-05)

うつ病の冠動脈疾患患者は心筋梗塞および死亡のリスクが高い可能性がある

Depressed patients with coronary artery disease may be at higher risk for myocardial infarction and death

うつ病の冠動脈疾患（CAD）患者はうつ病でないCAD患者に比べ、心筋梗塞（MI）または死亡のリスクが高い可能性がある、と第65回American College of Cardiology年次集会で発表された。安定CADの診断後のうつ病発現率は18.8%であった。うつ病のCAD患者はうつ病でないCAD患者に比べ、総死亡率が83%高く、MIで来院する確率が36%高かった。CADの診断後90～180日にうつ病と診断された患者は、リスクがより高かった。

Full Text

Patients with coronary artery disease (CAD) who are depressed may have a much higher risk of myocardial infarction (MI) or death compared to those who are not depressed, according to research presented at ACC.16, the American College of Cardiology's 65th Annual Scientific Session.

The study, conducted by Natalie Szpakowski, M.D., and colleagues, from the Sunnybrook Health Sciences Centre and Institute for Clinical Evaluative Sciences (ICES) in Toronto, Canada included 22,917 patients who had been diagnosed with stable CAD following a coronary angiogram for chest pain. Results showed that the incidence of depression following a diagnosis of stable CAD was 18.8 percent. Patients who were female or who had more severe angina were more likely to be diagnosed with depression.

Further, depressed CAD patients were 83 percent more likely to die from any cause compared to those who were not depressed. They were also 36 percent more likely to present at a hospital for MI. Those who were diagnosed with depression 90 to 180 days following the diagnosis of CAD were at greatest risk.

According to the authors, these findings suggest that these patients may need to be screened for mood disorders, either by their family physician or their cardiologist.

"Based on these findings, there may be an opportunity to improve outcomes in people with coronary heart disease by screening for and treating mood disorders, but this needs to be further studied," says Szpakowski. "Stable chronic angina due to narrowing of the coronary arteries is common, and our findings show that many of these patients struggle with depression. Our follow-up was at most five years, so many more might be affected."

ACC2016特集

心疾患疑いの症状は男女で差がない (Abstract 1206M-03)

PROMISE：心疾患の危険因子に性差はあるが、過去の研究結果とは異なり症状は同様である

PROMISE: Risk factors for heart disease vary by gender but symptoms are similar despite findings from older research

心疾患が疑われる男女において最も一般的に訴えられる症状は胸痛と息切れであり、この結果は過去のデータとは対照的である、と第65回American College of Cardiology年次集会で発表され*JACC: Cardiovascular Imaging*に掲載された。このPROMISEトライアルにおいてはまた、女性の方が男性に比べ保有する危険因子は多いが、女性は医療従事者のみならず、客観的に測定し心疾患を予測するスコアにおいても、低リスクに分類されがちであることも明らかにされた。

Full Text

Chest pain and shortness of breath are the most common symptoms reported by both women and men with suspected heart disease, a finding that is in contrast to prior data, according to a study presented at the American College of Cardiology's 65th Annual Scientific Session and published in a special issue of *JACC: Cardiovascular Imaging* focused on imaging in women.

The study, which includes one of the largest cohorts of women ever enrolled in a heart disease study, also found that women had a greater number of risk factors for heart disease than men, yet these women were more likely to be characterized as lower risk not only by their health care providers, but also by scores that objectively measure and predict heart disease risk.

"The most important take-home message for women from this study is that their risk factors for heart disease are different from men's, but in most cases symptoms of possible blockages in the heart's arteries are the same as those seen in men," said Kshipra Hemal of the Duke Clinical Research Institute in Durham, North Carolina, and lead author of the study.

The finding that women have more risk factors for heart disease than men means measures to reduce risk need to be a priority for women, as well as men, Hemal said.

Some previous studies have suggested that women having a heart attack are less likely to have classic symptoms such as chest pain and more likely to have atypical symptoms such as back pain, abdominal pain and fatigue that may be less readily recognized as heart attack symptoms. Hemal and her colleagues sought to shed light on a different group of patients – those without a prior heart disease diagnosis who were being evaluated for symptoms suggestive of heart disease. Few studies, mostly several decades old, have examined sex differences in this group of patients.

The Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE), a randomized trial conducted at 193 centers in the United States and Canada, enrolled 10,003 patients, of whom more than 5,200 were women. Half of the patients were randomly selected to receive a heart CT scan that doctors can use to noninvasively assess the degree of narrowing. The rest received a functional or stress test – an exercise electrocardiogram, stress echocardiography or nuclear stress test. Hemal and her colleagues examined patient data to assess differences between women and men in age, race or ethnicity, risk factors, symptoms, evaluation and test results.

The study found that, compared with men, women were older (average age 62 vs. 59 for men), more often non-white, less likely to smoke or be overweight, and more likely to have high blood pressure, high cholesterol, a history of stroke, a sedentary lifestyle, a family history of early-onset heart disease and a history of depression. Chest pain was the primary symptom for 73.2 percent of women and 72.3 percent of men. The two sexes, however, described this pain differently – women were more likely to describe it as "crushing," "pressure," "squeezing" or "tightness, " whereas men were more likely to describe it as "aching," "dull," "burning" or "pins and needles." Equal proportions of women and men (15 percent) reported shortness of breath as a symptom.

Although women were more likely than men to have back pain, neck or jaw pain, or palpitations as their primary symptom, the percentage of patients of both sexes reporting these symptoms was very small (1 percent of women vs. 0.6 percent of men for back pain, 1.4 percent of women vs. 0.7 percent of men for neck or jaw pain, 2.7 percent of women vs. 2 percent of men for palpitations).

Women had lower scores than men on heart disease risk-assessment scores, suggesting a lower risk of heart disease, and before any diagnostic tests were conducted, health care providers were more likely to consider that women probably did not have heart disease. Nontraditional risk factors such as depression, sedentary lifestyle and family history of early-onset heart disease – risk factors that in this study were more commonly found in women than in men – are excluded from most risk-assessment questionnaires, however.

"For health care providers, this study shows the importance of taking into account the differences between women and men throughout the entire diagnostic process for suspected heart disease," Hemal said. "Providers also need to know that, in the vast majority of cases, women and men with suspected heart disease have the same symptoms."

Women were more likely than men to be referred for a stress echocardiography or nuclear stress test and less likely than men (9.7 percent vs. 15.1 percent) to have a positive test. Factors predicting a positive test differed for women compared with men. In women, body mass index and score on one of five risk-assessment questionnaires (the Framingham risk score) predicted a positive test, whereas in men scores on two risk-assessment questionnaires (the Framingham and modified Diamond-Forrester risk scores) predicted a positive test.

"The fact that this is one of the largest cohorts of women ever evaluated in a heart disease study lends validity to our findings," Hemal said. A limitation of the study is that it looks only at the diagnostic process and not at whether there are differences between women and men in numbers of heart attacks or in outcomes from heart attacks, she said.

"The next step in this research will be to examine whether and how the differences we have identified between women and men influence outcomes," she said.

The study was funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health. Pamela S. Douglas, M.D., led the study team.

ACC2016特集

午睡はメタボリック症候群のリスクを上昇させる (Abstract 1191-377)

午睡や眠気はメタボリック症候群リスク上昇と関連する

Daytime napping and sleepiness associated with increased risk of metabolic syndrome

日中の眠気に加え、40分以上の午睡はメタボリック症候群発症リスク上昇と関連する可能性がある、と第65回American College of Cardiology年次集会で発表された。307,237人のアジア人および欧米人を対象とした、21の観察研究のデータを解析したスタディにおいて、日中に40分以上午睡する者はメタボリック症候群のリスクが著しく上昇することが示された。90分の午睡は過剰な日中の疲労感と同様に、リスクを50%も上昇させるようであった。

Full Text

Napping for 40 minutes or longer during the day, along with daytime sleepiness, may be associated with an elevated risk of developing metabolic syndrome, according to research presented at the American College of Cardiology's 65th Annual Scientific Session.

The study, led by Tomohide Yamada, M.D., Ph.D., and colleagues from the University of Tokyo analyzed data from 21 observational studies involving 307,237 Asian and Western subjects who self-reported their daytime tiredness and napping habits. Researchers compared the participants' responses to their history of metabolic syndrome, type-2 diabetes and obesity.

The analysis revealed that subjects who napped for more than 40 minutes during the day showed a sharp increase in the risk of metabolic syndrome. Napping for 90 minutes appeared to increase the risk by as much as 50 percent, as did excessive daytime tiredness. The study also showed a slight decrease in risk of metabolic syndrome when participants napped for less than 30 minutes. Previous work by Yamada and his team showed that napping for longer than one hour corresponded to a 50 percent increase in type-2 diabetes.

The authors note that as the data was dependent on self-reporting by participants, the study's findings may not be representative of the world population. However, the results indicate a need for further study into how sleep habits influence metabolic syndrome and cardiovascular disease, especially considering that nap length appears to influence risk both upward and downward.

Moving forward, future research should focus on "clarifying the relationship between naps and metabolic disease," with the hope of offering a new strategy of treatment, says Yamada.

"Excessive weight and its associated increased risk for sleep apnea might be a potential mechanistic pathway to explain these results," adds Kim A. Eagle, M.D., MACC, editor-in-chief of *ACC.org*.

ACC2016特集

バイスタンダーによるCPRは生存率向上および神経学的転帰が良好であることと関連がある(Abstract 1189-355)

HeartRescue：バイスタンダーによるCPRおよび除細動は院外心停止後の予後を改善する

HeartRescue: Bystander CPR and defibrillation improves outcomes following out-of-hospital cardiac arrest

院外心停止患者に対するバイスタンダーによる心肺蘇生（CPR）およびファーストレスポンダーによる除細動は、生存率向上および神経学的転帰が良好であることと関連がある、と第65回American College of Cardiology年次集会で発表された。2010～2014年の間に、バイスタンダーによるCPRを施行された患者の割合は自宅および公共の場において有意に増加した一方で、ファーストレスポンダーによる除細動は自宅では増加したが公共の場では増加しなかった。退院時生存率は公共の場における心停止群において10.8%から16.8%に上昇し、自宅における心停止群では5.7%から8.1%に上昇した。神経学的転帰は自宅では改善の傾向がみられ（4.9%から6.1%；p=0.06）、公共の場においては有意に改善した（9.5% から14.7%；p=0.02）。

Full Text

Initiatives to improve bystander cardiopulmonary resuscitation (CPR) and first-responder defibrillation may be associated with improved survival and reduced brain injury in people with out-of-hospital cardiac arrest, according to research presented at ACC.16.

Christopher B. Fordyce, M.D., and colleagues at the Duke Clinical Research Institute analyzed 8,269 cases of cardiac arrest between 2010 and 2014 collected from the North Carolina Cardiac Arrest Registry to Enhance Survival. The statewide program, part of the HeartRescue Project, trained family members and bystanders to recognize the signs of sudden cardiac arrest, quickly call emergency responders, and use CPR or automated external defibrillators (AEDs). The study is the first to separately track the effects of such interventions on cardiac arrests in public places and private homes.

Results showed that the proportion of patients receiving bystander CPR increased at home from 28.3 percent to 41.3 percent (p<0.0001) and in public locations from 61.0 percent to 70.6 percent (p=0.007), while first-responder defibrillation increased at home from 42.2 percent to 50.8 percent (p=0.01) but stayed mostly the same in public locations (33.1 percent to 37.8 percent; p=0.16). There was not a statistically significant increase in non-EMS first-responder AED use in public places, which the authors attribute to timely defibrillation by EMS. The rate at which cardiac arrest patients survived until their discharge from the hospital rose from 10.8 to 16.8 percent for public cardiac arrests and from 5.7 to 8.1 percent for cardiac arrests in the home. The rate at which patients only suffered minor losses in brain function or regained it fully increased from 4.9 to 6.1 percent at home and from 9.5 to 14.7 percent in public.

The authors explain that these results are encouraging, but due to the low absolute survival rates, there is still room for improvement. They suggest that future research in this area include interventions such as deploying AEDs into more private homes when cardiac arrests occur and using mobile technology to notify nearby citizens trained in CPR who can initiate care quickly.

"Survival is notoriously worse in private homes, where the majority of cardiac arrests occur," says Fordyce. "Little is known about whether broader efforts to teach people to recognize cardiac arrest and act quickly also impact home cardiac arrests, where the bystander is typically a family member. What's interesting about this study is it's the first time a statewide intervention has improved both public and residential cardiac arrest outcomes," he adds.

ACC2016特集

マンモグラムは心疾患の新たなスクリーニング法となり得る (Abstract 1184-256)

乳房の石灰化と冠動脈石灰化との強力な定量的関連が認められた

Strong quantitative association found between breast arterial calcification and coronary artery calcification

定期的なマンモグラフィーは心疾患リスクのある女性の同定に役立ち、それにより早期介入が可能となる、と第65回American College of Cardiology年次集会で発表され、同時に*JACC: Cardiovascular Imaging*オンライン版に掲載された。全体で、マンモグラフィーで乳房石灰化（BAC）所見を有する女性の70%が、非造影胸部CTスキャンで冠動脈石灰化（CAC）も有していた。CACを有する60歳未満の女性においては、半数が乳房石灰化も有していた。BACを有する若年女性は、CACも有する確率が83%であった。

Full Text

Routine mammography – widely recommended for breast cancer screening – may also be a useful tool to identify women at risk for heart disease, potentially allowing for earlier intervention, according to a study presented at the American College of Cardiology's 65th Annual Scientific Session.

Data from this study show for the first time a link between the amount of calcium in the arteries of the breast – readily visible on digital mammography – and the level of calcium buildup in the coronary arteries. Coronary arterial calcification, or CAC, is considered a very early sign of cardiovascular disease. Importantly, the presence of breast arterial calcification also appears to be an equivalent or stronger risk factor for CAC than other well-established cardiovascular risk factors such as high cholesterol, high blood pressure and diabetes. Earlier research had shown a link between breast arterial calcification and atherosclerotic disease – even myocardial infarction, stroke and other cardiovascular disease events, but researchers said these data provide a more direct relationship between the extent of calcified plaque in the mammary and coronary arteries, as well as a comparison to standard risk evaluation.

"Many women, especially young women, don't know the health of their coronary arteries. Based on our data, if a mammogram shows breast arterial calcifications it can be a red flag – an 'aha' moment – that there is a strong possibility she also has plaque in her coronary arteries," said Harvey Hecht, M.D., professor at the Icahn School of Medicine and director of cardiovascular imaging at Mount Sinai St. Luke's hospital, and lead author of the study.

All told, 70 percent of the women who had evidence of breast arterial calcification on their mammogram were also found to have CAC as shown on a noncontrast CT scan of the chest. For women under 60 years of age with CAC, half also had breast arterial calcification – an important finding as very few would be thinking about or considered for early signs of heart disease. There were even fewer false positives among younger patients; researchers said that if a younger woman had breast arterial calcification, there was an 83 percent chance she also had CAC.

Notably, breast arterial calcification also appeared to be as strong a predictor for cardiovascular risk as standard risk scores such as the Framingham Risk Score, which underestimates women's risk, and the 2013 Cholesterol Guidelines Pooled Cohort Equations, which tends to overestimate risk, Hecht said. When researchers added 33 asymptomatic women with established CAD, breast arterial calcification was more powerful than both risk assessment formulas, which suggests the presence of subclinical atherosclerosis may be a more important indicator of heart disease than other risk factors.

"This information is available on every mammogram, with no additional cost or radiation exposure, and our research suggests breast arterial calcification is as good as the standard risk factor-based estimate for predicting risk," Hecht said. "Using this information would allow at-risk women to be referred for standard CAC scoring and to be able to start focusing on prevention – perhaps even taking a statin when it can make the most difference."

Multivariate analysis showed that early signs of a buildup of plaque in the coronary arteries were most strongly related to breast arterial calcification. While CAC was about two times as likely with advancing age or high blood pressure, it was three times more likely with breast arterial calcification.

"The message is if a woman is getting a mammogram, look for breast arterial calcification. It's a freebie and provides critical information that could be lifesaving for some women," Hecht said, adding he hopes these findings will prompt clinicians, who rarely report breast arterial calcification, to routinely report not just the presence or absence of breast arterial calcifications but also to estimate and note the amount.

"The more breast arterial calcification a women has, the more likely she is to have calcium in her heart's arteries as well. If all it requires is to take a closer look at the images, how can we ignore it?," he said.

A total of 292 women who had digital mammography and noncontrast CT scans within one year were included in the study. Of these, 124, or 42.5 percent, were found to have evidence of breast arterial calcification. Mammograms were reviewed by a second radiologist who was blinded to the CAC results. Women with breast arterial calcification were more likely to be older, have high blood pressure and chronic kidney disease, and less likely smokers. Women with established cardiovascular diseases were excluded. Breast arterial calcification was evaluated on a scale from zero to 12 by increasing severity, and CAC was measured on the CT using a validated 0-12 severity score. The overall accuracy of breast arterial calcification for the presence of CAC was 70 percent, and 63 percent of those with CAC also had breast arterial calcification.

To date, there is no consensus on using CAC as a screening test, though a very large outcome study of 39,000 subjects is underway in the Netherlands. Mammography, however, is widely used and accepted and, as Hecht said, may provide an opportunity to risk stratify asymptomatic women by breast arterial calcification who might have calcium in the coronary arteries and ordinarily would not have been readily considered for cardiovascular screening.

Another intriguing point that deserves additional study, according to the researchers, is that the nature of the atherosclerosis is different in breast arterial calcification and CAC, making it unclear why one should be related to the other.

Hecht stresses that these findings warrant further evaluation and validation in larger studies. Future prospective trials are needed to see what the prognostic significance of breast arterial calcification might be. Because the study involved women who received both mammography and CT scan for clinical indications, these women may have been more likely than the average woman to have coexisting conditions, although Hecht said these were unrelated to heart disease.
This study is being published simultaneously online in *JACC: Cardiovascular Imaging*.

In an accompanying editorial in *JACC: Cardiovascular Imaging*, Khurram Nasir, M.D., M.P.H., and John McEvoy, from the Center for Healthcare Advancement and Outcomes at Baptist Health South Florida, said that the report provides impetus to document breast arterial calcification in mammography reports, to improve education of primary care and radiology providers on the link with heart disease, and other actions to establish best practices for incorporating this research into care.

"Even by the conservative estimate of 10 percent, approximately 4 million women nationwide undergoing screening mammography will exhibit breast arterial calcification; with 2 to 3 million of them likely to have signs of premature coronary atherosclerotic disease," the authors said. "Whether the best use of breast arterial calcification is to trigger additional testing or to directly inform preventive treatment decisions, either by flagging high-risk women to their providers or by reclassifying traditional (heart disease) risk estimates, is worth further discussion."

The study was funded, in part, by the Flight Attendants Medical Research Institute.

ACC2016特集

スタチンの広範な使用がスタディにより支持された (LBCT 401-19)

HOPE-3：中等度の心血管疾患リスク患者においてスタチンを用いたコレステロール低下療法は有益である

HOPE-3: Lowering cholesterol with statins is beneficial in patients at intermediate risk of cardiovascular disease

平均的なコレステロール値および血圧レベルで心疾患リスクが中等度と考えられる人々において、スタチンを用いたコレステロール低下療法は有害心血管イベントを有意に低下させた、とのHOPE-3トライアルの結果が第65回American College of Cardiology年次集会で発表され、同時に*New England Journal of Medicine*に掲載された。スタチンの有益性は全ての民族集団および全てのLDLコレステロール基準値において同等であり、内服時のコレステロール値はスタチンの恩恵を得られるか否かの判断には重要でないことが示唆された。降圧薬は高血圧を有する人々にしか有益ではなかった。

Full Text

Lowering cholesterol with statins significantly reduced adverse cardiovascular events in people with average cholesterol and blood pressure levels who were considered to be at intermediate risk for heart disease, while the use of blood pressure-lowering medications was beneficial only in those with hypertension, according to three separate reports from the large HOPE-3 trial presented at the American College of Cardiology's 65th Annual Scientific Session and simultaneously published online in *The New England Journal of Medicine*.

Previous studies have focused on the impacts of cholesterol and blood pressure-lowering drugs for people with established cardiovascular or renal disease, diabetes, other high-risk conditions or in those with markedly elevated cholesterol or blood pressure levels. Current guidelines recommend the use of these drugs mainly in patients at high risk for cardiovascular disease.

The trial, called HOPE-3, is the first to assess outcomes of preventative treatment with cholesterol and blood pressure lowering drugs in a large, globally diverse population at intermediate risk for developing cardiovascular disease. Statins—alone or in combination with blood pressure-lowering drugs—were found to be superior to placebo for both the study's first co-primary endpoint, a composite of cardiovascular deaths, myocardial infarctions (MI) and strokes, and its second co-primary endpoint, a composite of those events plus heart failure, resuscitated cardiac arrest and revascularization procedures, such as bypass surgery or angioplasty. For these endpoints, blood pressure drugs were found to improve outcomes compared with placebo only in patients with elevated blood pressure; these drugs were associated with no improvements in patients without elevated blood pressure, and there was a trend toward worse outcomes in those with relatively low blood pressure.

"The implications for practice are huge—I think we certainly should consider using statins much more widely than we have used them thus far," said Salim Yusuf, M.B.B.S., D.Phil., professor of medicine at McMaster University, executive director of the Population Health Research Institute of McMaster University and Hamilton Health Sciences and a senior member of the research team. "In particular for patients with hypertension, our study suggests you can essentially double the benefit of lowering blood pressure in hypertensives if you also lower cholesterol simultaneously."

The trial included 12,705 people in 21 countries on six continents. All participants had at least one known cardiovascular risk factor, such as smoking, an elevated waist-to-hip ratio or a family history of heart disease, but none had been diagnosed with cardiovascular disease. The trial was designed to focus on preventing cardiovascular disease before it starts.

Participants were randomly assigned to receive either a cholesterol-lowering drug—10 milligrams of rosuvastatin—or a placebo pill daily and either a blood pressure lowering drug—a combination pill with 16 milligrams of candesartan and 12.5 milligrams of hydrocholothiazide—or a placebo pill daily. Through this randomization, patients were sorted evenly into four categories: those receiving both a cholesterol-lowering drug and a blood pressure-lowering drug, those receiving only a cholesterol-lowering drug, those receiving only a blood pressure-lowering drug and those receiving only placebo pills. Outcomes were tracked for a median of 5.6 years.

Cardiovascular death, MI or stroke occurred in 3.5 percent of patients receiving both drugs and in 5 percent of patients receiving only placebo. The relative risk reduction in those taking both drugs was 30 percent overall, 40 percent in those with elevated blood pressure and 20 percent in those without elevated blood pressure. The results for the study's second co-primary endpoint were identical for this analysis.

A separate analysis focusing on the use of statins alone showed 3.7 percent of participants who took statins experienced the first co-primary endpoint, a composite of cardiovascular deaths, heart attacks and strokes, a significant reduction compared with 4.8 percent among patients taking a placebo. Among patients taking statins, 4.4 percent experienced the second co-primary endpoint, a composite of the events in the first co-primary endpoint plus heart failure, resuscitated cardiac arrest and revascularization procedures, such as bypass surgery or angioplasty, a significant reduction compared with 5.7 percent among patients taking a placebo. Patients taking statins experienced, on average, a drop in low-density lipoprotein, or LDL, cholesterol of 39.6 mg/dL, about 25 percent, after 12 months.

The benefits of statins were similar across all ethnic groups and across all baseline LDL levels, suggesting that a person's starting cholesterol levels are not important in determining whether the person will benefit from statins. These findings suggest that many people who have average cholesterol and blood pressure levels and are at average risk for heart disease—and not just those with extremely high cholesterol or blood pressure levels—can benefit from statins. The treatment was also remarkably safe; although some patients reported muscle weakness or pain, these effects were generally alleviated by stopping the statins or reducing the dose.

"The take-home message is that statins are safe and effective, and that because benefits were similar irrespective of pretreatment cholesterol levels or levels of inflammatory markers, no baseline blood tests are required to identify the patients who will derive benefits from this treatment," said Jackie Bosch, Ph.D., associate professor of rehabilitation science at McMaster University and director of the prevention Program at the Population Health Research Institute, who led the report focused on rosuvastatin. "Our results were remarkably consistent across all subgroups."

An analysis focusing on the use of blood pressure lowering drugs alone revealed no significant improvements overall in those receiving the drugs compared with those receiving a placebo. However, in a pre-specified analysis, when the patients were stratified into thirds by baseline systolic blood pressure, an analysis of subgroups with the highest, middle and lowest starting systolic blood pressure revealed significant differences. Among the one-third of participants with the highest blood pressure, a starting systolic blood pressure above 143.5 mm Hg, 4.8 percent experienced the first co-primary endpoint and 5.7 percent experienced the second co-primary endpoint, significantly lower than 6.5 and 7.5 percent, respectively, among patients taking placebo.

"Overall in this population the blood pressure lowering drugs had no clear benefit, but in those with higher blood pressure before therapy—over 143.5 mm Hg—the treatment was effective. However, there was no benefit in those with lower blood pressure and even a tendency towards harm in those in the lowest third of the blood pressure distribution," said Eva Lonn, M.D., FACC, a cardiologist and professor of cardiology at McMaster University and senior scientist at the Population Health Research Institute, who led the report focused on blood pressure lowering medications. "These data suggest blood pressure-lowering medications are appropriate for people with hypertension but that people with lower blood pressure who have no other reasons to use blood pressure reducing drugs should avoid taking these drugs."

Treating high blood pressure can be a time-consuming and intensive process involving multiple visits to the doctor's office for blood tests to help adjust dosing. This itself has been a significant impediment to reducing risk in people with hypertension because many patients find it inconvenient to make multiple visits or use multiple drugs, especially at full doses, which carries a higher risk of side effects. Yusuf said the study findings point to the value of a more simplified approach, which places more emphasis on statins in the general population and adds low doses of combination blood pressure medications to the statins in patients with mild hypertension. In this study, combination therapy reduced risk among people with elevated blood pressure by 40 percent safely, without dose titration or the need for frequent blood tests.

"Most of the hypertension guidelines right now focus on what agents to use and what blood pressure to aim for, and there has been very little emphasis on the importance of statins in treating patients with hypertension," Yusuf said. "Our approach, which used a combination of moderate doses of two blood pressure lowering-drugs plus a statin, appears to produce the biggest 'bang,' in terms of reducing events, with few side effects."

One limitation of the study is that, while it tracked patients for more than five years—a long period of time compared to most clinical trials—it can take many more years or even decades to show the full improvements in outcomes from primary disease prevention interventions. It is possible that extending the study for a longer period of time may have revealed larger benefits.

Participants will be tracked for an additional three to five years. The researchers will continue to conduct additional analyses examining the effects on cognitive decline, erectile dysfunction and vision, along with detailed analyses of potential differences among ethnic groups and geographic regions.

The study was funded by the Canadian Institutes of Health Research and AstraZeneca, the manufacturer of the drugs tested. The study was independently designed and conducted by the Population Health Research Institute at McMaster University and Hamilton Health Sciences in Canada, which conducts epidemiologic studies and clinical trials in more than 50 countries. Yusuf, Lonn and Bosch have received institutional research grants from several pharmaceutical companies, and Yusuf and Lonn have served as consultants for several pharmaceutical companies.

ACC2016特集

中等度リスクの患者においてTAVRは手術に代わる妥当な代替療法である(LBCT 401-15)

PARTNER 2A：2年後の死亡率および脳卒中発症率は手術とTAVRとで同等である

PARTNER 2A: Rates of death and stoke equivalent for surgery and TAVR at two years

重度の大動脈弁狭窄を有し、非侵襲的経カテーテル大動脈弁置換術（TAVR）を施行された中等度リスク患者における2年後の死亡率および機能障害を残す脳卒中の発症率は、標準的な開心術による大動脈弁置換術を施行された患者と同等である、と第65回American College of Cardiology年次集会で発表され、同時に*New England Journal of Medicine*に掲載された。この非劣性試験の追加データから、経大腿動脈アプローチで施行された場合にはTAVRの方が優れている可能性があることが示唆された。TAVRを施行された患者はまた、手術を施行された患者に比べ入院期間が短く一部の主要合併症も少なかった。

Full Text

Intermediate-risk patients with severe aortic stenosis who receive minimally invasive transcatheter aortic valve replacement, known as TAVR, have similar rates of death and disabling strokes after two years compared with those undergoing standard open heart surgical replacement, according to a study presented at the American College of Cardiology's 65th Annual Scientific Session and simultaneously published online in *The New England Journal of Medicine*. Patients receiving TAVR also experienced shorter hospital stays and lower incidence of some major complications compared with those undergoing surgery.

Data from this non-inferiority trial—the first to evaluate TAVR in patients who are considered intermediate-risk—suggests TAVR is at least as safe and effective as surgery in these patients. Overall, the primary endpoint of all-cause death and disabling strokes was comparable at two years, 19.3 percent for TAVR and 21.1 percent for surgery. Among TAVR patients with transfemoral placement of the valve—the least invasive of two approaches in which the device is implanted through a small incision in the groin—the combined rate of death and disabling stroke was lower, 16.8 for TAVR compared with 20.4 percent for surgery (p-value=0.05).

"For the past five years, TAVR has been growing in use and acceptance largely based upon clinical evidence from multiple randomized controlled trials, but these have been limited to patients at the highest risk for surgery," said Martin B. Leon, M.D., professor of medicine and director of the Center for Interventional Vascular Therapy at Columbia University Medical Center-New York Presbyterian Hospital and co-principal investigator of the PARTNER trials. "Here, we demonstrate outcomes related to death and stroke, which are equivalent in these patients and may be superior in the transfemoral group."

To perform TAVR, a surgeon threads a replacement valve to the heart through a catheter placed in the groin or chest. TAVR is currently approved for patients with severe aortic stenosis whose health profile makes them ineligible or high-risk candidates for open-heart valve replacement surgery.

In this randomized controlled PARTNER 2A trial, outcomes using the SAPIEN XT valve were compared with open-heart surgery valve replacement among 2,032 intermediate-risk patients treated between December 2011 and November 2013 at 57 sites, all but two in the U.S. Patients were randomly assigned; 1,011 to TAVR and 1,021 to surgery. Of those in the TAVR group, 76 percent underwent transfemoral placement, and the rest had transthoracic placement in which the new valve is thread through a cut in the chest wall.

"When we compare transthoracic TAVR patients to those having surgery, they are about the same, so whatever benefit achieved related to lower rates of death and strokes was clearly in the transfemoral group," Leon said.

Researchers also found significant differences in secondary clinical endpoints looking at time in the hospital, valve function and major complications, some favoring TAVR, some surgery. For example, TAVR patients spent less time in the hospital overall—the average time in the ICU was two days with TAVR versus four days with surgery, and the average hospitalization for TAVR was six days compared to nine days with surgery. TAVR also appeared to improve the aortic valve areas more than surgery, meaning that the quality of the valve's performance was better as measured by echocardiography during follow-up points through two years.

Compared to surgery, TAVR also yielded significantly lower rates of acute kidney injury, severe bleeding events and new onset atrial fibrillation, a heart rhythm problem that is a common complication of open procedures. The surgery group, on the other hand, had fewer major vascular complications and leakage around the valve (para-valvular regurgitation).

The heart team discussed each individual case to determine if patients were indeed intermediate-risk. Baseline characteristics were comparable. All patients were followed for at least two years and will continue to be followed for five years.

"The two-year follow-up allows enough time to accurately assess the relative performance of these two valve replacement therapies," Leon said, adding that he suspects these findings will potentially affect clinical guidelines for TAVR in the future. "We know surgery is good, but it is still a major procedure and for many patients, a less-invasive approach may be the preferred alternative. As we continue to evolve the procedure and technology, it's important to know whether TAVR is an effective alternative in these lower risk patients."

The study was funded by Edwards LifeSciences.

The SAPIEN XT device used in this trial is an older model transcatheter. The same research team will present findings comparing the SAPIEN 3, the newest generation of the device, to surgery.

ACC2016特集

PCSK9阻害薬はスタチン不耐性患者のコレステロール値を低下させる(LBCT 404-10)

GAUSS-3：エボロクマブはLDL-Cコントロール不良でスタチン不耐性患者のコレステロール値を低下させる

GAUSS-3: Evolocumab dramatically reduces cholesterol in patients with both uncontrolled LDL-C levels and statin intolerance

前駆蛋白変換酵素サブチリシン／ケキシン9（PCSK9）阻害薬エボロクマブを用いて6か月間治療することにより、LDL-Cコントロール不良およびスタチン不耐性患者のLDL-C値を劇的に低下させることができる、と第65回American College of Cardiology年次集会で発表され、同時に*JAMA*に掲載された。24週間の治療期間後、スタチン不耐性が確認されエボロクマブを投与された患者では、スタディの主要エンドポイントの1つであるLDLコレステロール値が52.8%低下したのに対し、エゼチミブ内服患者においては16.7%の低下であった。エボロクマブを投与された患者のうち筋肉症状を訴えたものは少なかった。

Full Text

Six-month treatment with the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor evolocumab can dramatically reduce LDL-cholesterol levels in patients with both uncontrolled LDL-C levels and statin intolerance according to research presented at the American College of Cardiology's 65th Annual Scientific Session and simultaneously published online in *the JAMA*.

After a 24-week treatment period, patients with confirmed statin intolerance who were given evolocumab on average showed a 52.8 percent reduction in LDL cholesterol, one of the study's co-primary endpoints, compared with a 16.7 percent reduction for patients taking ezetimibe. For the study's other co-primary endpoint, the average change in LDL cholesterol for weeks 22 and 24, patients taking evolocumab showed a reduction of 54.5 percent and patients taking ezetimibe showed a reduction of 16.7 percent.

The GAUSS-3 trial is also the first major clinical trial to include a blinded, placebo-controlled "statin re-challenge" in patients with a history of muscle-related side effects sheds new light on statin-associated muscle symptoms. The study showed that 42.6 percent of 491 patients who had previously reported muscle pain with at least two different statins had a recurrence of symptoms during blinded administration of atorvastatin, but not while taking a placebo.

"These findings provide unique insights into the challenging clinical problem of muscle symptoms in statin treated patients," said Steven Nissen, M.D., MACC, chairman of Cardiovascular Medicine at Cleveland Clinic and the lead author of the trial. "Evolocumab substantially lowered LDL cholesterol with few patients experiencing muscle symptoms. The study has important implications for both guidelines and regulatory policy, because it provides strong evidence that muscle-related statin intolerance is a real and reproducible phenomenon."

The patients in the GAUSS-3 trial had very high levels of LDL cholesterol, averaging more than 210 mg/dL. Untreated high LDL cholesterol increases the risk of heart disease, and statins are the most effective drugs available, yet some patients report that that they are unable to tolerate statins, mostly due to muscle pain or weakness.

There has been considerable controversy about the prevalence of muscle-related statin intolerance because large randomized trials have reported low rates of muscle symptoms, while observational studies have suggested that 5 to 20 percent of patients experience muscle symptoms when taking statins.

"Statin intolerance has been one of the most vexing problems faced by cardiologists," Nissen said. "Patients with high levels of LDL cholesterol and a high risk of cardiovascular events are often reluctant or completely unwilling to take statins, the only cholesterol lowering drugs approved to reduce their risk of a cardiovascular event. This situation is extremely frustrating for both patients and physicians because there have not been good alternatives for treatment."

Evolocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, is a non-statin cholesterol-lowering drug administered by self-injection every two to four weeks. By binding to and inhibiting PCSK9, a protein that degrades LDL cholesterol receptors on the surface of the liver, the drug is designed to increase the number of LDL receptors on the liver, thus allowing the liver to remove LDL cholesterol from the blood more effectively. Ezetimibe, the existing drug used as a control in the trial, lowers blood cholesterol by decreasing the absorption of cholesterol in the small intestine.

The phase 3, randomized, double-blind GAUSS-3 trial enrolled 511 patients at 53 health care centers. Participants had high LDL cholesterol and a history of statin intolerance. A vast majority of participants—82 percent—had tried and failed to tolerate three or more statins.

Previous studies, including the trial's predecessor, GAUSS-2, have shown evolocumab reduces LDL cholesterol levels more effectively than ezetimibe.

Because the trial was intended to evaluate evolocumab in statin-intolerant patients, it included an initial statin re-challenge procedure designed to confirm that patients had reproducible muscle symptoms when taking a statin. Nineteen of the enrolled participants bypassed this initial segment because they were documented to have creatine kinase levels—a marker of muscle injury—at least 10 times higher than the upper limit of normal when taking a statin.

Those who participated in the statin challenge were given 20 milligrams of atorvastatin or a placebo daily for 10 weeks, then switched over and were given either a placebo or atorvastatin—whichever one they had not been given in the first phase—for 10 more weeks. Of the 491 participants, 209, or 42.6 percent, reported muscle-related side effects while taking atorvastatin but not while taking the placebo. More than a quarter, 26.5 percent, reported muscle pain while taking the placebo but not while taking atorvastatin, suggesting that although statin intolerance can be confirmed in a substantial proportion of patients with self-reported intolerance, there is also a significant proportion who experience muscle pain that cannot be attributed to taking statins.

After that initial phase, 218 patients with confirmed statin intolerance were enrolled in the trial's second segment, with 145 randomly assigned to receive evolocumab and 73 randomized to receive ezetimibe. Because evolocumab was administered through self-administered injections totaling 420 milligrams per month, and ezetimibe was administered through a 10-milligram daily pill, those randomized to receive evolocumab were given injections of evolocumab and daily placebo pills, and those randomized to receive ezetimibe were given placebo injections and a daily ezetimibe pill.

Participants in the study's second phase had an average baseline LDL cholesterol level of 220 mg/dl. After 24 weeks, those given evolocumab had an LDL cholesterol level of 104 mg/dl on average; 64.1 percent of patients taking evolocumab finished the trial with LDL cholesterol below 100 mg/dl, and 29.9 percent finished with LDL cholesterol below 70 mg/dl.

Treatment was discontinued during the trial for one patient given evolocumab and five patients given ezetimibe due to muscle-related adverse events.
Longer-term results from another evolocumab trial showing health outcomes may be available by the end of 2016.

The study's limitations included its modest size and relatively short duration, but Nissen said it was adequately powered to address its primary endpoint.

The trial was funded by Amgen. Nissen has served as a consultant for many pharmaceutical companies and has overseen clinical trials for Amgen, AstraZeneca, Cerenis, Eli Lilly, Novartis, Novo Nordisk, The Medicines Company, Orexigen, Takeda and Pfizer. However, he does not accept honoraria, consulting fees or other compensation from commercial entities.

ACC2016特集

心臓検査における性差(LBCT 416-08)

PROMISE：心機能の診断検査は女性と男性とでは異なって機能する

PROMISE: Diagnostic tests for heart disease function differently for women than men

冠動脈疾患の重症度の診断や評価に用いられる検査は女性と男性とで異なって機能する、と第65回American College of Cardiology年次集会で発表された。女性においてCT血管造影（CTA）は機能的負荷検査よりも将来の冠動脈イベントの予知能が高いことが示された。男性において、負荷検査は心疾患の陽性所見頻度がCTAよりも少なかったが、イベント予知能はCTAと負荷試験とでほぼ同等であった。

Full Text

Tests used to diagnose and assess the severity of coronary artery disease appear to function differently for women and men who have stable symptoms, according to research presented at the American College of Cardiology's 65th Annual Scientific Session. The finding adds new insights into the differences between men and women who are newly diagnosed with heart disease.

Analyzing data from the PROMISE study (Prospective Multicenter Imaging Study for Evaluation of Chest Pain), researchers previously found that for both women and men, myocardial infarctions (MI) and other events occurred at the same rate regardless of whether patients were assessed using a computed tomographic angiography (CTA) or a functional stress test.

However, since the frequency of a positive test differed between the two test types, the ability to predict an event based on test findings was not the same for CTA vs. stress testing.

More women had a positive stress test than a CTA, but given the same event rate, this meant that a smaller proportion who had a positive stress test went on to have a coronary event – death, MI or other heart problem leading to hospitalization. As a result, CTA proved to be more predictive than a stress test of a future coronary event among women.

For men, a stress test showed a positive finding for heart disease less often than CTA, but the predictive value of CTA and the stress testing for an event was roughly similar.

"In the main PROMISE study analysis, the rates of coronary events were similar whether patients were tested with CTA or a stress test," said lead author Neha Pagidipati, M.D. of from Duke Clinical Research Institute. "Our analysis delved a little deeper to determine if there were subtle differences between the sexes associated with using these diagnostic tests."

Pagidipati said the differences in women are statistically significant and could help guide test selection and the interpretation of test results, but do not yet provide a basis to recommend that all women undergo CTA instead of functional stress tests. Instead, she said, the findings point strongly to the need for a study specifically designed to answer that question.

In addition to Pagidipati, study authors include Kshipra Hemal, Adrian Coles, Daniel B. Mark, Rowena J. Dolor, Patricia A. Pellikka, Udo Hoffmann, Sheldon E. Litwin, James Udelson, Melissa A. Daubert, Svati H. Shah, Beth Martinez, Kerry L. Lee, and Pamela S. Douglas.

This project received support from the National Heart, Lung, and Blood Institute.

ACC2016特集

Evacetrapibトライアルは早期中断された(LBCT 404-08)

ACCELERATE：Evacetrapibはコレステロールには影響したものの主要有害心血管イベントは軽減しなかった

ACCELERATE: Evacetrapib fails to reduce major adverse cardiovascular events despite impacts on cholesterol

低比重リポ蛋白（LDL）を低下させ高比重リポ蛋白（HDL）を著明に増加させたにもかかわらず、コレステロール治療薬evacetrapibを調べる大規模臨床試験は予備的解析において、この薬剤が重大な有害心血管イベントを軽減させないことが示された後に早期中断された、と第65回American College of Cardiology年次集会で発表された。第3相ACCELERATEトライアルにおいて、コレステロールに対する好ましい効果はスタディの主要エンドポイント（心血管死までの時間、心筋梗塞、脳卒中、冠動脈バイパス手術または不安定狭心症による胸痛のための入院）を低下させることには少しもつながらなかった。

Full Text

Despite lowering low-density lipoprotein (LDL) while markedly increasing levels of high-density lipoprotein (HDL) a large clinical trial to investigate the cholesterol drug evacetrapib was discontinued early after a preliminary analysis showed it did not reduce rates of major adverse cardiovascular events, according to research presented at the American College of Cardiology's 65th Annual Scientific Session.

The favorable effects on cholesterol did not translate into any reduction in the study's primary endpoint: the amount of time until cardiovascular death, myocardial infarction, stroke, coronary artery bypass surgery or hospitalization for chest pain due to unstable angina.

"Here we've got an agent that more than doubles the levels of good cholesterol and lowers bad cholesterol and yet has no effect on clinical events," said Stephen Nicholls, M.B.B.S, Ph.D., a professor at Australia's University of Adelaide, cardiologist at Royal Adelaide Hospital and the study's lead author. "We were disappointed and surprised by the results."

The ACCELERATE trial was a phase 3, randomized, double-blind trial conducted in approximately 540 global health centers involving more than 12,000 patients at high risk for serious cardiovascular problems. Participants were randomized to receive either 130 milligrams of evacetrapib or a placebo daily for at least 18 months. All patients also received standard medical therapy throughout the trial, which in a vast majority of cases included treatment with statins or other cholesterol-lowering drugs.

On average, patients taking evacetrapib lowered their LDL cholesterol by 37 percent and increased their HDL cholesterol by 130 percent compared with patients taking a placebo. However, there was no difference between the two groups in terms of the study's primary endpoint.

The findings make evacetrapib the third failure in a class of drugs known as cholesteryl ester transfer protein (CETP) inhibitors, which are designed to disrupt the natural process by which HDL cholesterol is converted into LDL cholesterol in the body. The first such drug, torcetrapib, was abandoned after a phase 3 clinical trial revealed it increased the risk of cardiovascular events and death. Development of a second CETP inhibitor, dalcetrapib, was stopped when a phase 2 clinical trial found the drug to be ineffective.

"There has been, and continues to be, a lot of confusion about what's going on with this class of drugs, since we don't yet have one that can be brought to the clinic to prevent heart attack and stroke in our patients," Nicholls said. "As we close out the trial, we're trying to understand how a drug that seems to do all the right things in terms of blood cholesterol levels doesn't then translate into reducing clinical events."

The results raised no safety concerns for evacetrapib and did not reveal any major side effects. Nicholls said the findings could offer evidence challenging conventional thinking regarding the benefits of HDL cholesterol in protecting against cardiovascular problems. Another possible explanation is that existing treatments, such as statins, are already so effective at improving cardiovascular outcomes that it has become more difficult to further improve outcomes in high-risk patients. Alternatively, the results could indicate that evacetrapib's active ingredient or the biological pathway it is designed to affect simply has no effect on cardiovascular risk.

All study participants either had an acute coronary syndrome such as an MI or unstable angina 30 days to one year before enrolling; had cerebrovascular atherosclerotic disease; had peripheral vascular disease; or had both diabetes and coronary artery disease.

"We tested the drug in high-risk patients because they are the patients with the greatest need for new drugs above and beyond what we already use in our clinics," Nicholls said. "Low risk patients could be another group of patients that could potentially benefit from this drug, but we didn't test that and to do so would require an extraordinarily large study that asks a different question from the one our study was designed to address."

The study was funded by Eli Lilly, a company for which Nicholls has served as a consultant. Nicholls has received research support or consulting fees from other pharmaceutical companies including AstraZeneca, Amgen, Novartis, Cerenis and others.

ACC2016特集

肥満手術の血糖値に対する効果は時間が経過しても持続する(LBCT 416-12)

STAMPEDE：肥満手術施行患者は術後5年間インスリンを使用することなく健康的な血糖値を維持している

STAMPEDE: Patients maintain healthy blood glucose levels without the use of insulin five years after bariatric surgery

第65回American College of Cardiology年次集会で発表されたSTAMPEDEトライアルの追跡結果から、軽度から中等度の2型糖尿病患者において肥満手術の血糖コントロールに対する有益な効果は最長5年間持続し、糖尿病治療薬のみの治療法に対する優越性は時間とともに拡大する可能性があることが示された。胃バイパス手術患者の29%およびスリーブ状胃切除術患者の23%が正常血糖値を達成し維持したのに対し、薬物療法のみの患者におけるその割合は5%であった。減量は胃バイパス術およびスリーブ状胃切除術において薬物療法よりも有意に大であり、血糖コントロールの主要な促進因子であった。

Full Text

In the final, five-year follow-up report from the influential STAMPEDE trial, Cleveland Clinic research shows that bariatric surgery's beneficial effects on blood glucose control in mild and moderately obese patients with type 2 diabetes may persist for up to five years, with the advantage over diabetes medications-only approach widening over time.

The five-year follow-up also reported that:

- Over 88 percent of gastric bypass and sleeve gastrectomy patients maintained healthy blood glucose levels without the use of insulin.
- 29 percent of gastric bypass patients and 23 percent of sleeve gastrectomy patients achieved and maintained normal blood glucose levels, compared to just 5 percent of those on medication alone.
- Weight loss was significantly greater with gastric bypass and sleeve gastrectomy than with medications and was the primary driver for glucose control.
- The effects of both surgical procedures to normalize glucose levels did however diminish overtime and some late complications were noted with surgery.

"Our findings show continued durability of glycemic control after metabolic surgery, as well as persistent weight loss, reduction in diabetes and cardiovascular medications at five years," said Philip Schauer, M.D., lead author and Cleveland Clinic bariatric surgeon, who presented the results at ACC.16, the American College of Cardiology's 65th Annual Scientific Session.

"The superior benefits of surgery to attain diabetes treatment goals must be carefully balanced with the long-term risks associated with surgery for individual patients," said Sangeeta Kashyap, M.D., co-investigator involved with the trial and an endocrinologist at Cleveland Clinic's Endocrinology & Metabolism Institute.

"Left unchecked, diabetes can lead to kidney failure, blindness, and limb amputation," said Dr. Kashyap. "At the five-year mark, bariatric surgery's metabolic effect persists and is more effective at treating type 2 diabetes in moderate and severely obese patients when compared to medical therapy."

The STAMPEDE (Surgical Therapy And Medications Potentially Eradicate Diabetes Efficiently) trial is the largest randomized trial with one of the longest follow-ups comparing medical therapy with bariatric surgery.

The trial initially involved 150 overweight patients with poorly controlled diabetes. The patients were divided into three groups: 1) Fifty patients received intensive medical therapy only, including counseling and medications; 2) Fifty patients underwent Roux-en-Y gastric bypass surgery and received medical therapy; 3) Fifty patients underwent sleeve gastrectomy and received medical therapy.

Effectiveness was gauged by the percentage of patients who achieved blood sugar control, defined in this study as hemoglobin HbA1c level of less than or equal to 6.0 percent – a more aggressive target than the American Diabetes Association's guidelines. HbA1c is a standard laboratory test that reflects average blood sugar over three months.

Findings from the five-year follow-up confirm those from the one-year and three-year reports and include the following:

- Rates of achieving and maintaining an HbA1c level of 6.0 percent or less at five years were significantly higher with gastric bypass (29 percent) and sleeve gastrectomy (23 percent) than with intensive medical therapy alone (5 percent).
- Weight loss was significantly greater with gastric bypass and sleeve gastrectomy than with medical therapy.
- Use of cardiovascular and glucose-lowering medications, including insulin, at five years was significantly reduced from baseline in both surgical groups, and was significantly lower in the surgical groups than in the medical therapy group. Over 88 percent of surgically treated patients maintained glycemic control without use of insulin.

The five-year analysis also yielded several new insights, including the following:

- In the two surgical groups, achieving the primary end point of an HBA1c less than or equal to ≤ 6.0 percent was predicted both by a reduction in body mass index (BMI) and a duration of diabetes of less than eight years.
- There were no late major complications of surgery except for one reoperation (a successful laparoscopic conversion of sleeve gastrectomy to gastric bypass for recurrent gastric fistula) four years after randomization.
- Significant and durable improvements in bodily pain and general health were demonstrated using a validated quality-of-life instrument in both surgical groups relative to the medical group.
- Several biomarkers associated with heightened cardiovascular risk were reduced in the surgical arms, but there were no beneficial effects on retinopathy or nephropathy seen at 5 years.

"Some advantages of gastric bypass over sleeve gastrectomy have emerged during follow-up," Dr. Schauer said. "At five years, gastric bypass maintained greater weight loss than sleeve gastrectomy while requiring fewer medications."

He also notes that the final STAMPEDE results might help expand the population of patients in whom bariatric surgery may be considered for improving glycemic control.

"Most clinical guidelines and insurance policies for bariatric surgery limit access to patients with a BMI of 35 or above," Dr. Schauer added. "Our five-year results demonstrate that glycemic improvement in patients with a BMI of 27 to 34 is durable at least up to five years."

The STAMPEDE study was funded by Ethicon, part of the Johnson & Johnson family of companies, through its Metabolic Applied Research Strategy (MARS) program. The NIH grant number is R01 DK089547.

Dr. Schauer is a paid consultant for Ethicon.

ACC2016特集

幹細胞治療は心不全の転帰を改善する (LBCT 1172-079)

ixCELL-DCM：試験的幹細胞治療後に心不全患者の転帰が改善した

ixCELL-DCM: Heart failure patients experience improved outcomes following investigational stem cell treatment

患者自身の骨髄から得た幹細胞による試験的幹細胞治療は重症心不全患者の転帰を有意に改善した、とAmerican College of Cardiology年次集会で発表され、同時に*Lancet*に掲載された。この第II相試験において、医師は虚血性拡張型心筋症と診断された患者109人を12か月間追跡した。幹細胞治療を受けた患者58人においては、プラセボを投与された患者51人よりも死亡、入院および症状増悪率が37%低かった。幹細胞治療を受けた患者のうち死亡したのは3.4%であったのに対し、プラセボ投与群では13.7%であった。

Full Text

An investigational stem cell therapy derived from patients' own blood marrow significantly improved outcomes in patients with severe heart failure, according to a study from the Cedars-Sinai Heart Institute.

The research was presented as a late-breaking clinical trial at the American College of Cardiology Scientific Sessions and simultaneously published in *The Lancet*.

"This is an important step forward for heart patients in particular and for stem cell medicine in general," said Timothy D. Henry, M.D., director of the Cardiology Division at the Cedars-Sinai Heart Institute and one of the study's lead authors. "The results indicate that stem cells could be ushering in a bright new era in heart failure treatments."

Called ixmyelocel-T, the stem cell treatment developed by pharmaceutical company Vericel is made from a patient's own bone marrow. A sample of marrow is extracted from the patient and sent to a laboratory, where it undergoes a two-week process to rapidly multiply the number of stem cells and enhance their quality. The stem cell-rich marrow is then infused into the patient's heart muscle during a minimally invasive, catheter-based procedure.

"Our intent is to increase the number of functioning cells in the heart muscle, which, in turn, strengthen the heart and result in alleviating or slowing the advance of severe heart failure," Henry said.

In the Phase II study, physicians followed 109 patients over a 12-month period. All were diagnosed with ischemic cardiomyopathy, a type of heart failure that usually results from a heart attack or coronary artery disease. The 58 patients who received the stem cell therapy showed a 37 percent lower rate of deaths, hospitalizations and worsening symptoms compared to 51 patients who received a placebo.

Of patients who received stem cells, 3.4 percent died compared to 13.7 percent of placebo patients who died. In addition, 37.9 percent of those who received stem cells were hospitalized with cardiovascular issues during the study vs. 49 percent of patients who received the placebo.

"Our focus is on finding each of our patients the most advanced treatment for their disease," said Eduardo Marbán, M.D., Ph.D., director of the Cedars-Sinai Heart Institute. "Stem cells offer us an opportunity to improve cardiac care, expand treatment options and transform the future of heart medicine."

Henry is a lead author along with Amit N. Patel, M.D., M.S., of the University of Utah. Cedars-Sinai also was one of the lead enrollers in the study.

ACC2016特集

院外心停止に対する抗不整脈薬投与が疑問視される(LBCT 410-08)

ALPS：院外心停止に対する抗不整脈薬投与の有益性に関する結果は様々である

ALPS: Mixed results on benefits of antiarrhythmic drugs for out of hospital cardiac arrest

院外心停止を来した患者において、2つの抗不整脈薬-アミオダロンおよびリドカイン-の使用はいずれも退院までの生存率または神経学的転帰を有意に改善しない、とのALPSスタディの結果が第65回American College of Cardiology年次集会で発表された。しかし、バイスタンダーに目撃されていた心停止患者のうち、蘇生中にアミオダロンまたはリドカインを投与された患者は、プラセボを投与された患者に比べ、退院までの生存確率が5%大であり、統計学的に有意な差であった。この結果は*New England Journal of Medicine*に掲載された。

Full Text

Paramedics often give heart rhythm stabilizing drugs to patients who are suffering out-of-hospital cardiac arrest when they fail to regain a stable heart rhythm after electrical shock treatment. In a study presented at the American College of Cardiology's 65th Annual Scientific Session, these drugs, specifically amiodarone and lidocaine, did not significantly improve such patients' likelihood of surviving to hospital discharge overall. However, among patients whose cardiac arrest was witnessed by a bystander, those who received either amiodarone or lidocaine during resuscitation had a 5 percent greater chance of survival to hospital discharge compared with those who received a placebo, which was a statistically significant difference. Witnessed cardiac arrests represented more than half of the study's population.

This trial is the first and largest randomized, double-blind, placebo-controlled study to assess the impact of amiodarone and lidocaine on survival to hospital discharge after out-of-hospital cardiac arrest triggered by two types of dangerous heart rhythms: ventricular fibrillation and pulseless ventricular tachycardia. Many cardiac arrest cases per year are specifically caused by these heart rhythms, and in more than half of these cases, paramedics are unable to restore a stable heart rhythm using defibrillator shocks alone. Amiodarone and lidocaine are thought to work by stabilizing the electrical signaling within the heart.

Among all study participants, patients receiving amiodarone fared slightly better in terms of survival to hospital discharge, the study's primary endpoint, but did not achieve statistical significance. The finding that both these drugs significantly improved rates of survival to hospital discharge when the cardiac arrest was witnessed by a bystander suggests their benefit may be linked to how quickly such events are recognized and drug treatment is started.

"You can see these results as a cup half empty or a cup half full," said Peter Kudenchuk, M.D., a cardiac electrophysiologist and professor of medicine at the University of Washington and the study's lead author. "From a statistical perspective, neither drug significantly improved survival to hospital discharge in the overall group of treated patients. Still, a beneficial clinical effect from these medications is undeniable. Both drugs significantly improved the chances of survival to hospital admission, so they clearly did their job in stabilizing dangerous heart rhythms and getting patients to the hospital alive.

Surviving cardiac arrest requires cardiopulmonary resuscitation (CPR) and immediate medical attention. Patients whose cardiac arrest is witnessed by a bystander are believed to have a better chance of survival because they are recognized sooner after their collapse and less likely to have already sustained fatal organ damage upon receiving medical attention.

"If you look at patients who had a witnessed cardiac arrest, a group with the best hope of being saved by effective treatments, the drugs significantly improved survival," Kudenchuk said. "By comparison, in persons whose cardiac arrest was not witnessed, many of whom may not have been discovered until long after their collapse, antiarrhythmic drugs had no significant effect, probably because there was so little chance of survival by that point anyway. When outcomes from these two groups were added together, the absence of any benefit from drug therapy in patients with an unwitnessed arrest may have muted the significant benefit seen in those with a witnessed cardiac arrest, resulting in the marginal overall outcome of the study."

Paramedics across 10 communities in the United States and Canada were trained on the study's protocols and screened nearly 38,000 out-of-hospital cardiac arrest patients for possible inclusion in the trial. Study participation was restricted to patients with either ventricular fibrillation or ventricular tachycardia who did not achieve a stable heart rhythm after at least one defibrillator shock and, therefore, represent the typical group of those who receive such medications for cardiac arrest in clinical practice. Children, persons with advance (do-not-resuscitate) directives, and patients in protected groups such as prisoners and pregnant women were excluded.

After screening, the trial randomized 3,026 study participants to receive up to 450 milligrams of amiodarone, up to 180 milligrams of lidocaine or a saline placebo. The drugs and placebo were provided to paramedics in indistinguishable boxes containing three syringes, each containing a third of the maximum total dose, to ensure that neither patients nor care providers knew which treatment was used for a given patient. In total, 974 patients received amiodarone, 993 received lidocaine and 1,059 received a placebo. Paramedics used a standard monitoring device to objectively track and record heart rhythms and other parameters during resuscitation.

Survival to hospital discharge among the 1,934 study participants whose cardiac arrest was witnessed by a bystander was improved from about 23 percent for those taking placebo to 28 percent for patients taking either drug, results that were statistically significant.

"If you assume these drugs might improve survival rates by just 3 percent overall or by 5 percent in witnessed cardiac arrest events, this means they could save 1,800 additional patients every year in the United States alone from out-of-hospital cardiac arrest. That's a huge potential impact on the single greatest killer of men and women with heart disease," Kudenchuk said.

The antiarrhythmic drugs also showed some benefits for other outcomes. Among all patients, those receiving either amiodarone or lidocaine required significantly fewer shocks to achieve a stable heart rhythm and were significantly more likely to survive to hospital admission. There was a low frequency of adverse side effects for both amiodarone and lidocaine. Favorable neurological outcome did not differ between the drug and placebo treatment groups. Overall, patients who survived to hospital discharge left with at most only a slight disability.

The patients randomized in the trial across the three patient groups were similar in terms of their demographic characteristics, the quality of CPR that was administered and the treatments they received after being admitted to the hospital.
Kudenchuk noted that one limitation of the study is that drug treatment was relatively late, which may have lessened its effectiveness. The trial also did not compare the effects of different doses or drug protocols and did not assess amiodarone and lidocaine when used in combination. Kudenchuk said the study is an important step toward elucidating potential benefits of antiarrhythmic drugs for out-of-hospital cardiac arrest, but the size of the study may have been insufficient to establish these benefits with greater statistical certainty. Additional study could shed light on how different approaches could further improve outcomes.

The study was funded by the National Heart, Lung, and Blood Institute, American Heart Association, U.S. Army, Canadian Institutes of Health Research and Defense Research and Development Canada. Baxter International provided the placebo and medications used in the trial at no cost, but the company was not involved in the study design or analysis.

The results of the study were published in three reports online in *the New England Journal of Medicine* at the time of presentation.

ACC2016特集

ステント留置を遅らせても臨床的有益性は示さなかった (LBCT 405-08)

DANAMI-3-DEFER：ステント留置の遅延または延期に関する最大規模のトライアルは有望な予備試験の結果を否定する

DANAMI-3-DEFER: Largest trial of delayed or deferred stent implantations contradicts findings of promising preliminary studies

ST上昇型心筋梗塞（STEMI）を来した患者に対するステント留置の遅延または延期は臨床的な有益性を示さなかった、とのDANAMI-3-DEFERトライアルの研究結果が第65回American College of Cardiology年次集会で発表され、*Lancet*に掲載された。平均追跡期間43か月後に、DEFER群のうち105人（17%）および標準治療群のうち109人（18%）が主要評価項目（総死亡、心不全による入院、2回目のMI、および予定外の再血行再建術の複合評価項目）に合致し、有意差はなかった。これらの結果は、ステント留置の延期は臨床的に有益であるとの予備試験の結果に反論するものである。

Full Text

Delayed or deferred stent implantation in patients experiencing the deadliest form of heart attack—ST-segment elevation myocardial infarction (STEMI)—failed to reduce death from any cause, hospitalization for heart failure, subsequent heart attacks or the need for a repeat revascularization, researchers reported at the American College of Cardiology's 65th Annual Scientific Session.

"The take-home message from this study is that deferred stent implantation cannot be recommended as a routine procedure for STEMI patients treated with primary percutaneous coronary intervention," said Henning Kelbaek, M.D., of Roskilde Hospital, University of Copenhagen, Denmark, and lead author of the study. "Our results completely rebut the promising findings of preliminary studies that suggested deferred stenting should translate to clinical benefit."

After the blocked artery is opened, the blockage site often contains residual blood clots that may, when the stent is implanted, be displaced downstream into the small branches of the artery. If this happens, it can damage heart muscle and block small blood vessels. Previous small studies suggested that delaying stent implantation for a period of time ranging from several hours to several days after reopening the artery might reduce the risk of blood-flow disturbance. The thinking was that medication given during the delay might allow the residual blood clots to diminish, reducing the risk of a displaced clot damaging the small branches of the artery. The DANAMI-3-DEFER trial was the largest trial yet conducted to evaluate whether delaying stent implantation would improve patients' survival and reduce their risk of heart failure or another heart attack.

In the trial, which took place in Denmark, 1,234 patients (average age 61; 75 percent male) with acute STEMI symptoms of less than 12 hours' duration were randomly assigned to receive standard angioplasty with immediate stent implantation or angioplasty followed by stent implantation after a re-examination 24 to 48 hours later. After an average follow-up time of 43 months, 105 patients or 17 percent in the DEFER group and 109 or 18 percent in the standard treatment group met the primary endpoint, a composite of death from any cause, hospitalization for heart failure, a second heart attack, and unplanned repeat angioplasty, a nonsignificant difference.

Although the trial was the largest so far to address the issue of delayed stent implantation, it may not have been large enough to detect a difference between the two treatment groups, Kelbaek said. Another limitation is that the trial did not select patients who were at the highest risk for developing another arterial blockage, such as those over age 65, those who have had more than one heart attack or those known to have a large number of blood clots.

"We cannot rule out that a fraction of our patients who met these criteria might have benefitted from delayed stent placement, especially because we found a small improvement in heart-muscle function 18 months after treatment among patients who underwent deferred stenting," Kelbaek said.

The study was not powered to detect this improvement, but Kelbaek said he and his team would now look carefully for possible "hypothesis-generating" findings in subsets of patients—both those who might have benefitted from the deferred-treatment strategy and, equally important, those in whom this strategy might have worsened their condition.

The DANAMI-3-DEFER trial was funded by the Danish Agency for Science, Technology and Innovation and Danish Council for Strategic Research.

This study was published online in *The Lancet* at the time of presentation.

ACC2016特集

心筋梗塞後のlosmapimod投与により改善は認めなかった (LBCT 410-14)

LATITUDE-TIMI 60：抗炎症薬は心筋梗塞後の重大な心血管イベントリスクを低下させない

LATITUDE-TIMI 60: Anti-inflammatory drug does not reduce risk of major cardiovascular events following myocardial infarction

急性心筋梗塞（MI）で入院した患者において、抗炎症薬losmapimodは12週間の治療期間中の重大な心血管イベントの再発リスクを減少させなかった、と第65回American College of Cardiology年次集会で発表され、同時に*JAMA*に掲載された。第3相LATITUDE-TIMI 60トライアルにおいて、主要評価項目（心血管死、MI、または緊急冠動脈血行再建術を要する重症再発性心筋虚血の複合評価項目）が12週までに発現したのは、プラセボ群で7%であったのに対し、losmapimod群では8.1%であった。重篤な有害事象の発現率は、losmapimod群で16%であり、プラセボ群では14.2%であった。

Full Text

Michelle L. O'Donoghue, M.D., M.P.H., of Brigham and Women's Hospital, Boston, and colleagues evaluated the efficacy and safety of the anti-inflammatory drug losmapimod on cardiovascular outcomes in patients hospitalized after a heart attack. The study was published online by *JAMA* to coincide with its presentation at the American College of Cardiology's 65th Annual Scientific Session.

Inflammation stimulated by the enzyme p38 mitogen-activated protein kinase (MAPK) is implicated in atherogenesis and plaque destabilization. Pilot data in a phase 2 trial in patients with non-ST elevation myocardial infarction (NSTEMI) indicated that the p38 MAPK inhibitor losmapimod lessens inflammation and may improve outcomes.

In this phase 3 trial (LATITUDE-TIMI 60 trial), Dr. O'Donoghue and colleagues randomly assigned patients who had been hospitalized with an acute MI and had at least 1 additional predictor of cardiovascular risk to either twice-daily losmapimod (n = 1,738) or matching placebo (n = 1,765) on a background of guideline-recommended therapy. Patients were treated for 12 weeks and followed up for an additional 12 weeks. The study was conducted at 322 sites in 34 countries. Part A of the trial consisted of a group (n = 3,503) to provide an initial assessment of safety and exploratory efficacy before considering progression to part B (approximately 22,000 patients).

Among the 3,503 patients in part A, the primary end point (a composite of cardiovascular death, MI, or severe recurrent ischemia requiring urgent coronary revascularization with the principal analysis specified at week 12) occurred by 12 weeks in 123 patients treated with placebo (7 percent) and 139 patients treated with losmapimod (8.1 percent). The on-treatment rates of serious adverse events were 16 percent with losmapimod and 14.2 percent with placebo.

The authors write that the results of this exploratory efficacy study did not justify proceeding to a larger efficacy trial in the existing patient population.

"In this trial, losmapimod did not reduce the risk of recurrent major adverse cardiovascular events through 12 weeks of treatment in patients hospitalized with acute MI. Furthermore, there was no evidence that losmapimod reduced the incidence of any secondary outcomes including all-cause mortality. Therefore, our findings do not support a strategy of p38 MAPK inhibition with losmapimod in patients hospitalized with MI."

"Because inflammation is believed to play a key role in atherogenesis, there remains intense interest to identify an anti-inflammatory therapeutic that will reduce the risk of cardiovascular events. However, because inflammation acts along multiple redundant and interconnected pathways, the identification of an appropriate target may be difficult, and it is challenging to predict clinical efficacy prior to phase 3 testing."

This trial was funded by GlaxoSmithKline.

ACC2016特集

クライオアブレーションは高周波アブレーションに匹敵する (LBCT 410-10)

FIRE and ICE：発作性心房細動におけるクライオアブレーションの安全性および有効性は高周波アブレーションと同等である

FIRE and ICE: Cryoablation comparable in safety and efficacy as RF ablation in paroxysmal atrial fibrillation

発作性心房細動（PAF）の治療において、クライオバルーンアブレーションの有効性および安全性は高周波カテーテル（RFC）アブレーションと同等である、とのFIRE and ICEトライアルの結果が示された。クライオバルーンはRFアブレーション治療群に比べ施術時間が短く（平均=124分対141分；p=0.0001）、透視時間はRFカテーテルの方が短かった（RFで平均17分；クライオバルーンで平均22分；p=0.0001）。このスタディ結果は第65回American College of Cardiology年次集会Late Breaking Clinical Sessionで発表され、同時に*New England Journal of Medicine*に掲載された。

Full Text

Cryoballoon ablation efficacy and safety was equivalent to radiofrequency catheter (RFC) ablation for the treatment of paroxysmal atrial fibrillation (PAF), results of the FIRE and ICE trial show.

The positive results from the landmark FIRE AND ICE clinical trial, demonstrated comparable safety and effectiveness for the Arctic Front® Cryoballoon Catheter Family compared to the ThermoCool® line of radiofrequency (RF) ablation catheters for the treatment of symptomatic paroxysmal atrial fibrillation (AF). The study, presented in a late-breaking session at the American College of Cardiology's 65th Annual Scientific Sessions and published simultaneously in *The New England Journal of Medicine*, provides further clinical validation that Cryoballoon ablation is a safe and effective option for ablation treatment, with shorter and more consistent procedure times.

"Through this rigorously designed trial, we found that Cryoballoon catheter technology is not only comparable to RF ablation - the current standard of care - but also delivered key procedural efficiencies," said Prof. Karl-Heinz Kuck, M.D., director of cardiology at Asklepios Klinik St. Georg, Hamburg, Germany, and principal investigator of the trial. "The simple, straightforward cryoablation procedure may allow us to treat more patients with AF."

The trial met its primary efficacy endpoint of showing non-inferiority for the Arctic Front Cryoballoon catheters without 3D mapping compared to ThermoCool® RF ablation catheters using 3D mapping (p=0.0004) in reducing arrhythmia recurrence and the need for antiarrhythmic drug therapy and/or re-ablation. It also met its primary safety endpoint of time to first all-cause death, all-cause stroke/TIA, or treatment-related serious adverse events (p=0.24); both technologies had similarly low complication rates. The Cryoballoon demonstrated shorter procedure times (mean=124 minutes) compared to the RF ablation treatment arm (mean=141 minutes; p=0.0001), and fluoroscopy times were shorter with the RF catheter (mean=17 minutes with RF; mean=22 minutes with cryoballoon; p=0.0001).

Isolating the pulmonary veins (pulmonary vein isolation, or PVI), which are a source of erratic electrical signals that cause AF, is a standard approach for treating AF patients: the Cryoballoon uses coolant to create contiguous, circumferential lesions to achieve PVI; RF ablation uses heat (RF energy) and requires 3D mapping as well as point-by-point application to achieve PVI.

A total of 769 patients from 16 medical centers throughout Europe were enrolled in the trial. All subjects were diagnosed with paroxysmal AF, had failed at least one antiarrhythimic drug and were followed for up to 33 months (mean = 1.54 years) following initial ablation. A non-inferiority design is often used to demonstrate that a newer technology is comparable to the currently accepted and existing technology.

"As the largest head-to-head study comparing these two technologies to treat AF, the FIRE AND ICE results provide important clinical insights on safety and effectiveness, and also show Cryoablation with more consistent procedure times, which benefits both patients and physicians," said Colleen Fowler, vice president and general manager of the AF Solutions business, part of the Cardiac and Vascular Group at Medtronic. "As the world's population continues to age, the demand for safe, clinically effective and efficient advanced treatment options will only increase. Today's findings further support the rapid global adoption of Cryoablation and serve as a significant milestone in helping guide optimal patient care."

Medtronic funded the trial. Dr. Kuck reports consultant fees/honoraria from Biosense Webster, Edwards Lifesciences, and St Jude, and serving as a speaker for Medtronic.

ACC2016特集

CABGは心不全患者の寿命を延長させる(LBCT 406-12)

STICHES：重症LV機能不全患者においてバイパス手術は10年生存率を改善する

STICHES: Bypass surgery improves 10-year survival in patients with severe LV dysfunction

これまで考えられていたより多くの冠動脈疾患患者が、冠動脈バイパス（CABG）手術により恩恵をこうむる可能性がある、と第65回American College of Cardiology年次集会で発表され、*New England Journal of Medicine*に掲載された。薬物療法にCABGを追加することにより、冠動脈疾患、左室機能不全、および心不全の患者の死亡および入院が有意に低下することが示された。10年間の総死亡リスクは16%減少し、生存期間中央値は約1年半延長した。

Full Text

fluoroscopy: Scientists funded by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health have found that a greater number of patients with coronary artery disease may benefit from coronary artery bypass graft (CABG) surgery than previously thought.

CABG was thought to be too risky for patients with the long-term effects of coronary artery disease: left ventricular dysfunction and heart failure. Studies of the safety and effectiveness of CABG in the 1970s excluded most patients with these two conditions. The procedure was typically used to relieve angina, or chest pain.

"With limited data showing any benefit for patients with left ventricular dysfunction and heart failure, physicians and patients were less likely to engage in such an invasive, and thus risky, procedure as CABG for diagnosis and treatment," said lead author Eric J. Velazquez, MD, FACP, FACC, FASE, FAHA, of Duke University Medical Center. "Patients with these conditions largely received medical therapy alone and had poor outcomes."

Dr. Velazquez and his team conducted a five-year global, randomized controlled clinical trial, called the Surgical Treatment for Ischemic Heart Failure (STICH) study, and a five-year extension study to evaluate whether CABG plus guideline-directed medical therapy had a durable benefit over medical therapy alone for patients with coronary artery disease and left ventricular dysfunction. The researchers found that CABG added to medical therapy led to significantly lower rates of death and hospitalization among patients with coronary artery disease, left ventricular dysfunction, and heart failure.

"Our results usher in a new era in the treatment of coronary artery disease because we now have evidence that with CABG and medical therapy, there is a 16 percent reduction in the risk of death from any cause over 10 years," Dr. Velazquez said.

He added that there is also a median survival benefit of nearly a year and a half, and that he and his team saw that the addition of CABG to medical therapy prevented a death from any cause for every 14 patients they treated. Their data further suggest that the reduction in the risk of death could be even greater in real-world practice.

"Conducting this trial was critically important to determine in a scientifically rigorous study that CABG improves survival for individuals with coronary artery disease and compromised left ventricular function," said NHLBI Director Gary H. Gibbons, MD. "The current 10-year follow-up provides new important insights about patient subgroups that are more likely to benefit from CABG as compared to medical therapy alone. As such, we now have a solid evidence base to inform patient care and the future development of clinical practice recommendations."

Dr. Velazquez noted that the results are particularly important because the prevalence of left ventricular dysfunction and heart failure is expected to increase to approximately 8 million individuals by 2030 in the U.S. alone. The increase in the projected prevalence is a result of advances in the management of cardiovascular disease and its risk factors, increasingly transforming coronary artery disease into a chronic disease with long-term effects such as left ventricular dysfunction and heart failure.

George Sopko, MD, MPH, the program director in NHLBI's Division of Cardiovascular Sciences who administered the study grant, added that this investigation, published in *The New England Journal of Medicine*, is one of only a few cardiovascular trials with 10 years of follow-up and with approximately 98 percent of the patients followed throughout the study period.

"It is unusual to have this quality of follow-up for so long," said Dr. Sopko. "It speaks to the rigor of the results." He added that the results are very generalizable, as the study included a diverse patient population spread across 22 countries and various health systems.

Research may lead to improved outcomes for large number of patients who previously had limited therapeutic options.

ACC2016特集