セリアック病は冠動脈疾患リスクを上昇させる（Abstract 14-A-12274）

セリアック病とCVDの研究により心臓の健康に対する全身性炎症の役割に関するさらなるエビデンスが加わる

Study of celiac disease and CVD adds to mounting evidence about the role of systemic inflammation in heart health

セリアック病患者は一般集団と比べ冠動脈疾患リスクが2倍近く高い可能性があるとの研究結果が、第63回American College of Cardiology学会で発表された。研究者らは13の参加医療システムから患者の電子カルテを入手した。2,240万人近くの患者のうち、24,530人がセリアック病と診断された。セリアック病を有さない人々はコントロールとされた。2群間で喫煙や糖尿病の有無に差はなかった。セリアック病を有する者は高コレステロールを有する率がやや高かったが、血圧は低い傾向にあった。対象者は18歳以上であった。セリアック病患者はコントロール群に比べ冠動脈疾患有病率が有意に高かった（それぞれ9.5%対5.6%）。65歳未満の若年層においてもセリアック病患者と疾患を有さない者との比較において、同様の傾向が認められた（4.5%対2.4%）。セリアック病患者においては脳卒中リスクもやや高かった。今回のスタディにより、全身性炎症および自己免疫プロセスが心血管疾患発症にいかに影響するかに関してさらなる理解が深まる。

Full Text

People with celiac disease may have a near two-fold increased risk of coronary artery disease compared with the general population, according to research to be presented at the American College of Cardiology's 63rd Annual Scientific Session.

The study is the first to look at the association between celiac disease and coronary artery disease and adds to the evolving understanding of how systemic inflammation and autoimmune processes might influence cardiovascular disease development. Data also showed a slightly higher risk of stroke among people with celiac disease compared to controls.

Celiac disease is a chronic inflammatory condition of the digestive system that can damage the small intestine, eventually interfering with the absorption of key nutrients. People with celiac disease are unable to tolerate gluten – a protein found in food such as wheat, rye and barley. Gluten is thought to trigger an immune and inflammatory response in the gut.

"People with celiac disease have some persistent low-grade inflammation in the gut that can spill immune mediators into the bloodstream, which can then accelerate the process of atherosclerosis and, in turn, coronary artery disease," said R.D. Gajulapalli, M.D., clinical associate at the Cleveland Clinic and co-investigator of the study. "Our findings reinforce the idea that chronic inflammation, whether it's from an infection or a disease, can have an adverse role in coronary artery disease and heart health in general."

Researchers obtained electronic health records of patients from 13 participating health care systems between January 1999 and September 2013. Out of a total of nearly 22.4 million patients, 24,530 were diagnosed with celiac disease. Patients without celiac disease served as controls. There was no difference in smoking status or diabetes rates between the two groups. Those with celiac disease were slightly more likely to have high cholesterol, but less likely to have high blood pressure. Patients were age 18 and older. Traditional risk factors for coronary artery disease including sex, race, diabetes, high cholesterol, high blood pressure and smoking were checked between patients with celiac disease and controls to make sure they were comparable.

Researchers found a significantly higher prevalence of coronary artery disease among patients with celiac disease compared to the control population (9.5 percent compared to 5.6 percent, respectively). Data showed a similar trend among younger patients, those under age 65, with celiac disease compared to those without celiac disease (4.5 percent compared to 2.4 percent).

"This is an important study because it highlights a specific patient population who might be at higher risk for coronary artery disease, even in the absence of traditional cardiovascular risk factors," Gajulapalli said. "We were surprised by the strength of the association, especially in younger people. Patients and doctors should be aware of this association."

Experts believe upwards of 80 percent of people with celiac disease are underdiagnosed or misdiagnosed with conditions such as lactose intolerance and irritable bowel syndrome. Previous research shows celiac disease has been on the rise and is four times more common now than it was 50 years ago. The only treatment for celiac disease is adopting a gluten-free diet. Although gluten is mainly found in foods, it can also be in everyday products such as medicines, vitamins and lip balms.

Celiac disease has been linked to arrhythmias and possible heart failure.
"Whether patients with celiac disease will need more intense risk factor modification like in diabetic patients with coronary artery disease will need to be studied," Gajulapalli said. For now, he says people with this and other inflammatory diseases should maintain a healthy lifestyle and be aware of traditional cardiovascular risk factors including diabetes, high blood pressure and high cholesterol.

Larger studies are needed to confirm this association and to examine how the severity of celiac disease may play a role. Because so many people may have gluten sensitivities but do not have celiac disease, future research should investigate whether this larger population may also be at risk for coronary artery disease. Earlier studies have linked celiac disease with arrhythmias, which is what prompted researchers to conduct this study.

ACC2014特集

宇宙において宇宙飛行士の心臓はより球状になる（Abstract 14-A-11725）

無重力環境における宇宙飛行士の心臓に関するスタディは地球上の一定の心血管疾患患者にも恩恵をもたらす可能性がある

Study of astronaut's hearts in a microgravity environment may also benefit certain cardiovascular patients on Earth

12人の宇宙飛行士のスタディの結果、心臓は宇宙において無重力空間に長期間曝露されると心臓に問題を引き起こす可能性のある球状化を来すことが示された、と第63回American College of Cardiology学会で発表された。このスタディはまた、地球上の患者の一般的な心血管疾患をより理解することにも繋がると研究チームは述べている。彼らは、宇宙飛行士に国際宇宙ステーションに設置された超音波機器を用いて自分の心臓の画像を撮れるよう訓練した。12人の宇宙飛行士が参加し、飛行前、飛行中および飛行後に心臓の形のデータを提供した。その結果、宇宙において心臓は9.4%さらに球状になり、この変化は研究者らがこのプロジェクト用に開発した複雑な数式モデルを用いて予測したものに類似の変化であることが示された。宇宙で認められたこの形状変化の健康への長期影響は不明であるが、より球状の形状は心臓の運動効率が低下していることを意味する可能性がある。宇宙飛行士用に開発された運動療法は、長期臥床または心不全のような重度の活動制限を有する地球上の人々の心臓の健康維持にも役立つ可能性があると研究者らは述べている。

Full Text

New findings from a study of 12 astronauts show the heart becomes more spherical when exposed to long periods of microgravity in space, a change that could lead to cardiac problems, according to research presented at the American College of Cardiology's 63rd Annual Scientific Session.

With implications for an eventual manned mission to Mars, the findings represent an important step toward understanding how a spaceflight of 18 months or more could affect astronauts' heart health.

"The heart doesn't work as hard in space, which can cause a loss of muscle mass," said James Thomas, M.D., Moore Chair of Cardiovascular Imaging and Lead Scientist for Ultrasound at NASA, and senior author of the study. "That can have serious consequences after the return to Earth, so we're looking into whether there are measures that can be taken to prevent or counteract that loss."

The researchers say that knowing the amount and type of exercise astronauts need to perform to keep the heart healthy is going to be very important to guarantee their safety on a long flight like a mission to Mars. Thomas adds that exercise regimens developed for astronauts could also be used to help maintain heart health in people on Earth who have severe physical limitations, such as people on extended bed rest or those with heart failure regime.

The research team trained astronauts to take images of their hearts using ultrasound machines installed on the International Space Station. Twelve astronauts participated, providing data on heart shape before, during and after spaceflight.

The results show the heart in space becomes more spherical by a factor of 9.4 percent, a transformation similar to what scientists had predicted with sophisticated mathematical models developed for the project. By validating those models, the study could also lead to a better understanding of common cardiovascular conditions in patients on Earth.

"The models predicted the changes we observed in the astronauts almost exactly. It gives us confidence that we can move ahead and start using these models for more clinically important applications on Earth, such as to predict what happens to the heart under different stresses," Thomas said.

The team is now working to generalize the models to analyze such conditions as ischemic heart disease, hypertrophic cardiomyopathy and valvular heart disease.
"The models could help us simulate those pathologies to understand the impact on cardiac function," Thomas said.

The astronauts' more spherical heart shape appears to be temporary, with the heart returning to its normal elongated shape shortly after the return to Earth. The more spherical shape experienced in space may mean the heart is performing less efficiently, although the long-term health effects of the shape change are not known.

Spaceflight is known to cause a variety of cardiac effects. Upon return to Earth, astronauts commonly become lightheaded or pass out in a condition known as orthostatic hypotension, in which the body experiences a sudden drop in blood pressure when standing up. Arrhythmias have also been observed during space travel, and there is concern that the radiation astronauts are exposed to in space may accelerate atherosclerosis. The research team is continuing to examine these and other potential cardiovascular effects.

This study is funded by the National Space Biomedical Research Institute through NASA Cooperative Agreement NCC9-58.

ACC2014特集

スタチンは勃起不全の症状を改善する（Abstract 14-A-7744）

スタチンは勃起不全を有する高コレステロールの男性にさらなる有益性を提供する可能性がある

Statins may offer additional benefit for men with high cholesterol and erectile dysfunction

スタチンは勃起不全を有意に改善させるとの研究者らが期待する事実により、心臓発作のリスク軽減目的でスタチン内服を必要とする男性らが勇気付けられるだろうとの研究結果が第63回American College of Cardiology学会で発表され、同時に*Journal of Sexual Medicine*オンライン版に掲載された。勃起不全とスタチンに関する過去のスタディの初めてのメタ解析において、研究者らはInternational Inventory of Erectile Function−5つの質問を用いた自己評価で、それぞれの質問につき5点満点で合計し、点数が低いほど性機能低下を示すーを用いて、勃起機能を計測した。11のスタディ全てを組み合わせた解析の結果、勃起不全を有する高コレステロールの男性において、スタチンの勃起機能に対する統計学的に有意な効果が示された。全体で、勃起機能スコアはスタチン内服男性で3.4%高かった（14.0から17.4へ上昇、23.4%上昇）。スタチンによる勃起機能スコア上昇は、シルデナフィルやタダラフィルのような薬剤で報告されているスコア上昇のほぼ3分の1から2分の1であった。スタチンは血管の適切な拡張およびペニスへの血流改善を促すことにより勃起機能を改善するのであろうと研究者らは考えている。

Full Text

Statins are associated with a significant improvement in erectile function, a fact researchers hope will encourage men who need statins to reduce their risk of heart attack to take them, according to research presented at the American College of Cardiology's 63rd Annual Scientific Session and simultaneously published online in the *Journal of Sexual Medicine*.

Erectile dysfunction is common in older men, especially among those with cardiovascular risk factors where cholesterol-lowering statins are frequently prescribed. Previous research has suggested a negative association between statin therapy and testosterone levels, leading to questions about the effects of these widely used medications on the quality of erection.

In the first meta-analysis of previous studies on erectile dysfunction and statins, researchers identified 11 randomized, controlled trials that measured erectile function using the International Inventory of Erectile Function – a self-administered survey with five questions, each scored on a five-point scale and totaled, with lower values representing poorer sexual function. Analysis of all 11 studies combined found a statistically significant effect of statins on erectile function in men who had both high cholesterol and erectile dysfunction. Overall, erectile function scores increased by 3.4 points in men who took statins (from 14.0 to 17.4, a 24.3 percent increase).

"The increase in erectile function scores with statins was approximately one-third to one-half of what has been reported with drugs like sildenafil or tadalafil," said John B. Kostis, M.D., director of the Cardiovascular Institute and associate dean for Cardiovascular Research at Rutgers Robert Wood Johnson Medical School, and the lead investigator of the study.

"It was larger than the reported effect of lifestyle modification," Kostis said. "For men with erectile dysfunction who need statins to control cholesterol, this may be an extra benefit."

Researchers believe that statins may work to improve erectile function by helping blood vessels dilate properly and improving vascular blood flow to the penis, which is often restricted in men with erectile dysfunction. While statins are not recommended as a primary treatment for erectile dysfunction in patients with healthy cholesterol levels, the added benefit may encourage more men who need statins to take them. Millions of people are prescribed statins to prevent heart disease, but some stop taking the medication or take less than the prescribed dose, Kostis said. Rather than preventing the possibility of a heart attack in the future, the more immediate benefit of improving erectile function might improve adherence to statin therapy, he added.

Erectile dysfunction affects an estimated 18 million to 30 million men and occurs more often in men over the age of 40. Common causes include heart disease, high cholesterol, high blood pressure, diabetes, obesity, tobacco use, depression and stress.

Kostis said that larger randomized controlled trials are needed to further investigate the link between statin therapy and erectile function.

ACC2014特集

出産した子供の数は女性の将来の心血管系の健康状態に影響する（Abstract 14-A-10936）

4人以上の生児出生を有する女性は動脈硬化の早期徴候を示す確率が高い

Women who have four or more live births are more likely to show early signs of atherosclerosis

子供を4人以上出産した女性はそれより妊娠の少ない女性に比べ動脈硬化所見を有する確率が高いとの研究結果が第63回American College of Cardiology学会で発表された。スタディでは、生児出生数に関する自己申告情報および関連画像データが提供可能な多民族住民ベースコホート、Dallas Heart Studyの女性1,644人（平均年齢45歳）を対象とした。コンピュータ断層画像を用いて計測した冠動脈石灰化（CAC）スコアおよび磁気共鳴画像による大動脈壁厚（AWT）により、心臓や動脈壁に潜在性の動脈硬化所見を有するか否かを判断した。2人または3人の生児出生の女性を基準に用いたところ、4人以上生児出生の女性はCACまたはAWTが異常値であるリスクが約2倍であった。この相関は社会経済的状況、教育、人種および心血管疾患リスクを上昇させることが知られている因子で補正しても、依然として認められた。興味深いことに、出産をしていないかまたは1人しか出産していない女性もまた潜在性動脈硬化所見を示し、U型の相関を認めた。

Full Text

Women who give birth to four or more children are much more likely to have evidence of atherosclerosis compared with those having fewer pregnancies, according to research presented at the American College of Cardiology's 63rd Annual Scientific Session.

While earlier studies have shown an association between several aspects of pregnancy – physiological changes, complications, number of pregnancies – and future heart disease risk, many questions remain about how pregnancy might affect cardiovascular risk. To better understand the potential link, researchers at the University of Texas Southwestern Medical Center set out to determine whether the number of live births is associated with early signs of cardiovascular disease.

"This is not a recommendation for women to only have two or three children," said Monika Sanghavi, M.D., chief cardiology fellow, University of Texas Southwestern Medical Center, and lead investigator of the study. This is the first study to look at two markers of subclinical atherosclerosis.

"Our findings add to the growing body of evidence that the changes associated with pregnancy may provide insight into a woman's future cardiovascular risk and deserves further attention."

The study included 1,644 women from the Dallas Heart Study, a multiethnic population-based cohort, who had both self-reported information about the number of live births and relevant imaging study data available. The average age at the time of analysis was 45 years and slightly more than half of the women (55 percent) were African-American. Coronary artery calcium (CAC) scores were measured using computed tomography imaging and aortic wall thickness (AWT) by magnetic resonance imaging to determine whether or not women had evidence of subclinical atherosclerosis in the heart and artery walls. CAC was positive if it was greater than 10 and AWT was abnormal if it was greater than the 75th percentile for age and gender. These tests were done as part of standard subject participation in the Dallas Heart Study.

Using women who had two or three live births as a reference, women who had given birth to four or more children had an approximately two-fold increased risk of having abnormal CAC or AWT. This association remained even after adjusting for socioeconomic status, education, race and factors known to heighten the risk of cardiovascular disease. Women who had more babies were more likely to be older, Hispanic, have high blood pressure, higher body mass index and lower socioeconomic status.

Curiously, women who had zero or just one live birth were also more likely to show evidence of subclinical atherosclerosis – revealing a U-shaped relationship.

Authors say it is unclear why this might be the case. But Sanghavi and others speculate they may have captured some women in this group who have an underlying condition that prevents them from carrying a first or second pregnancy to term, which may also predispose them to cardiovascular disease or risk factors. For example, women with polycystic ovarian syndrome can have menstrual irregularities and trouble getting pregnant, but they may also have other health changes such as excess body weight, diabetes, high blood pressure or high cholesterol.

Pregnancy itself sparks a cascade of changes that can place more strain on a woman's cardiovascular system. For example, the volume of blood being pumped through the heart increases by 50 percent. In addition, other physiological and metabolic changes occur (e.g., increased insulin resistance and higher cholesterol levels).

"Pregnancy has been called 'nature's stress test,' and for good reason," Sanghavi said. "It may also help identify women who are at increased risk for heart disease, even though right now they may not have any risk factors."

Sanghavi said this study suggests that clinicians need to be more thorough in documenting pregnancy histories to take advantage of this window into a woman's cardiovascular system. This information can be used to better estimate future risk of heart disease and monitor certain patients more closely to try to prevent future heart disease. However, what this might mean in practice has yet to be determined.
"The benefit of pregnancy is that it occurs relatively early in a woman's life and allows for early intervention for those at higher risk," she added.

The authors stressed the need for more research to both confirm this association and explore the biological underpinnings of these findings. The survey instrument that was used did not allow the authors to differentiate those women who had chosen not to become pregnant and those who were unable to become pregnant for other reasons. This would be an important distinction to make when trying to understand the increased risk in women with zero to one live births.

ACC2014特集

腎除神経術は治療抵抗性高血圧に有益性をもたらさない

SYMPLICITY HTN-3：過去のトライアルにおいて認められた腎除神経術の強力な効果は新たな厳密なスタディにおいて消失した

SYMPLICITY HTN-3: Strong effects of renal denervation seen in earlier trials disappear with rigorous design of new study

重度の治療抵抗性高血圧患者において腎除神経術は一次および二次の有効性ゴールを満たさなかったが、一次安全性エンドポイントには合致したとの切実に待ち望まれていたSYMPLICITY HTN-3のデータが第63回American College of Cardiology学会で発表され、同時に*New England Journal of Medicine*オンライン版に掲載された。研究者らは、収縮期血圧160mmHg以上の治療抵抗性高血圧患者535人を腎除神経術群または血管造影のみの群にランダムに割り付けた。両群ともに3剤以上の降圧薬治療を継続された。両スタディ群とも6か月後にはベースラインと比較し統計学的に有意な血圧低下（腎除神経群 -14.1mmHgに対しシャム治療コントロール群-11.7mmHg）を示したが、2群間に認められた外来収縮期血圧の-2.29mmHgの差は有意ではなかった。24時間収縮期血圧の変化においても結果は同様で、2群間には有意でない-1.96mmHgの差が認められた。この極めて重要なトライアルは治療抵抗性高血圧治療として腎除神経術を行ったスタディの中で最大であり、盲検化およびコントロール群のシャム治療などは最も厳密にデザインされたものである。

Full Text

Renal denervation fell short of primary and secondary efficacy goals in patients with severe resistant hypertension but did meet the primary safety endpoints, according to keenly awaited data from SYMPLICITY HTN-3 presented at the American College of Cardiology's 63rd Annual Scientific Session and simultaneously published online in the *New England Journal of Medicine*. This pivotal trial is the largest study conducted of renal artery denervation as a treatment for resistant hypertension and the most rigorously designed, including blinding and a sham treatment in the control arm.

Hypertension increases risks for myocardial infarction and stroke for up to one billion adults worldwide. People with severe resistant hypertension – high blood pressure not controlled with three classes of medications – are a very challenging subset of patients. During the renal denervation procedure with the Symplicity device used in this trial, a catheter is threaded through arteries to deliver radiofrequency energy that inactivates kidney nerves, interrupting electrical signals to and from the kidney. Renal denervation is in clinical use for uncontrolled hypertension in more than 80 countries.

This study randomly assigned 535 patients with resistant hypertension and systolic blood pressure of 160 mmHg or higher to renal denervation or angiography alone. Both groups remained on treatment regimens of three or more antihypertensive drugs, including a diuretic, at the highest tolerated doses. Renal denervation failed to achieve the primary efficacy endpoint of a decrease in systolic blood pressure measured in the doctor's office from baseline to six months or the powered secondary efficacy endpoint of decrease in average 24-hour levels by ambulatory blood pressure monitoring, which provides more reliable readings. Although both study groups showed a statistically significant decrease at six months compared with baseline (-14.1 mmHg for renal denervation compared to -11.7 mmHg for the sham treatment control), the difference of -2.29 mmHg in office systolic blood pressure between the two arms was not significant. Results were similar for change in 24-hour systolic blood pressure, with a non-significant difference between the two arms of -1.96 mmHg.

"That is a fascinating result because it highlights the importance of a properly done, rigorous randomized trial that is both blinded and sham controlled," said Deepak L. Bhatt, M.D., M.P.H., executive director of interventional cardiovascular programs, Brigham and Women's Hospital Heart and Vascular Center, professor of medicine at Harvard Medical School, and co-principal investigator. "This is the first blinded trial or sham controlled trial in the field of renal denervation. It seems that these factors really mattered. We saw no added treatment benefit of renal denervation for patients with severe resistant hypertension who were closely monitored and optimally treated with medications."

Bhatt commented on the value of the study's cooperation between interventional and non-interventional cardiologists, which demonstrated that a "good proportion" of patients with resistant hypertension in this study responded to expert medical therapy. However, new treatment options are still needed for patients with uncontrolled hypertension, he said.

The major adverse event rate of 1.4 percent for renal denervation comfortably met the safety goal of 9.8 percent, compared with 0.3 percent in the sham treatment arm. Although a particular area of concern was potential renal stenosis, there was only one case in the renal denervation group and none in the sham group.

"The field has really exploded with several devices in clinical practice despite lack of compelling data to support their use. Now we have some definitive data with one device," Bhatt said. "However, we do think research in the field should continue, especially to see if renal denervation is useful in other areas, such as heart failure or with alternative approaches. We've shown renal artery denervation is very safe."

Medtronic, Inc. funded SYMPLICITY HTN-3 and provided research funding to Bhatt for the study.

ACC2014特集

クロニジンは相殺による有益性はもたらさずリスクを上昇させる

POISE-2：クロニジンは非心臓手術後の死亡や心筋梗塞を減少させない

POISE-2: Clonidine does not reduce deaths or myocardial infarction after non-cardiac surgery

クロニジンは非心臓手術後の臨床的に問題のある血圧低下や非致死性心停止発現率を上昇させるとのPOISE-2トライアルの結果が第63回American College of Cardiology学会で発表され、*New England Journal of Medicine*オンライン版に掲載された。心血管系リスクを有する収縮期血圧105mmHg以上および心拍数55bpm以上の患者が入院手術前にクロニジンまたはプラセボ群にランダムに割り付けられた。クロニジン群（5,009人）は0.2mgのクロニジン錠を術前に、同用量となる貼付剤を術後72時間にわたり投与された。プラセボ群（5,001人）は対応する錠剤および貼付剤を与えられた。その結果、ランダム化後30日間の死亡率および非致死性心筋梗塞（MI）からなる一次エンドポイントはクロニジン群で365件およびプラセボ群で339件であり、クロニジンはこれを改善させなかった。クロニジン群でMI数増加が認められた（クロニジン群325件対プラセボ293件）が統計学的に有意ではなかった。しかし、2つの二次エンドポイントは有意であった：臨床的に重要な血圧低下はクロニジン群患者の2,385人（48%）に認められたのに対しプラセボ群では1,854人（37%）であり、非致死性心停止はクロニジン群で16件であったのに対しプラセボ群では5件であった。

Full Text

Clonidine – a drug that reduces blood pressure and heart rate – increased rates of clinically concerning hypotension and non-fatal cardiac arrest after noncardiac surgery, according to the POISE-2 trial presented at the American College of Cardiology's 63rd Annual Scientific Session and published online in the *New England Journal of Medicine*. With more than 10,000 patients in 23 countries, this randomized clinical trial is the largest study of clonidine in surgical patients.

The study's findings caught researchers by surprise. The earlier POISE-1 study found that beta-blockers greatly reduced risk of myocardial infarction (MI) during and after non-cardiac surgery, but increased risk of devastating strokes and mortality. In POISE-2, researchers used low-dose clonidine, which smaller studies had suggested would provide the heart-protecting benefits of beta-blockers without increasing stroke risk. (POISE-2 also examined aspirin in this setting. Those results are presented separately at ACC.14.)

Patients at cardiovascular risk with a systolic blood pressure of at least 105 mm Hg and a heart rate of at least 55 beats per minute were randomly assigned to clonidine or placebo before inpatient surgery. The clonidine group (5,009 patients) was given 0.2 mg clonidine in tablet form before surgery and a skin patch that delivered the same dose daily for 72 hours after surgery. The placebo group (5,001 patients) was given matching tablets and patches.

Clonidine failed to improve the primary outcome of mortality and non-fatal MI at 30 days after randomization, with 365 events for clonidine and 339 for placebo. The clonidine group had a non-significant increase in the number of MIs (325 clonidine vs. 293 placebo), but two secondary measures were significant: clinically important hypotension was seen in 2,385 clonidine patients (48 percent) versus 1,854 placebo patients (37 percent), and 16 clonidine patients had non-fatal cardiac arrest versus five in the placebo group. Patients will be followed for one year.

"Clonidine should not be given to patients having non-cardiac surgery in an attempt to reduce perioperative mortality or MI," said Daniel I. Sessler, M.D., Michael Cudahy professor and chair of the Outcomes Research Department at the Cleveland Clinic and a study investigator. "If anything, it worsens the outcome, probably by reducing blood pressure." He speculated that clonidine didn't perform as expected because it caused hypotension out of proportion to its protective effect on heart rate.

All available information suggested that the POISE-2 drug, clonidine, would improve outcomes. "That it did not prove effective tells us that the perioperative setting presents unique challenges and will require special approaches," Sessler said.

An obvious next target for study is a drug that controls heart rate without lowering blood pressure, such as ivabradine, an If-channel blocker used to treat stable angina, he said.

The study was funded by the Canadian Institutes of Health Research. None of the investigators has a personal financial interest in the research.

ACC2014特集

非心臓手術周術期のアスピリン使用は重大な出血を増加させる

POISE-2：アスピリンを再開する必要のある患者の術後リスク期間が明らかにされる

POISE-2: Data clarify post-operative risk period for patients who should restart aspirin

非心臓手術後の循環器系の問題を予防するためにアスピリンを投与された患者は、アスピリンを投与されなかった患者と比較し重篤な出血リスクが高い。アスピリンは術後心筋梗塞（MI）発症および死亡を軽減しなかったとの研究結果が第63回American College of Cardiology学会で発表され、*New England Journal of Medicine*オンライン版に掲載された。POISE-2は10,011人の患者を組み入れアスピリン内服の有無によりグループ分けした：術前6週間のうち4週間用量にかかわらずアスピリンを内服していた群（継続層）および内服しなかった群（開始層）。継続層においてはアスピリンの内服を手術の72時間以上前に中止した。全患者がプラセボまたはアスピリン200mgを術直前まで内服した。開始層はアスピリン100mgまたはプラセボを毎日30日間継続した。継続層はアスピリン100mgまたはプラセボを7日間投与され、その後に元のアスピリン療法に戻した。一次エンドポイントである30日間の死亡および非致死性MIは両群間で差がなかった（アスピリン群7%対プラセボ群7.1%）。重大な出血はアスピリン治療群で有意に高かった（4.6%対3.7%）。一次および二次転帰は2つのアスピリン層で同等であった。

Full Text

Patients given aspirin to prevent cardiac problems after non-cardiac-related surgery had a higher risk of serious bleeding than the patients who did not receive aspirin. At the same time, aspirin did not reduce incidence of post-operative myocardial infarction (MI) and death, according to data from POISE-2 presented at the American College of Cardiology's 63rd Annual Scientific Session and published online in the *New England Journal of Medicine*. POISE-2 is the largest clinical trial focused on major cardiovascular complications in non-cardiac surgery.

Although many guidelines address prophylactic aspirin in a surgical setting, the focus is largely on cardiac surgery. Little guidance is available for patients undergoing non-cardiac surgery. This phase III trial followed earlier evidence suggesting that small doses of aspirin and clonidine can ward off heart attacks and heart-related death for such patients. Data for clonidine are to be presented separately at ACC.14.

POISE-2 enrolled 10,011 patients in 23 countries and grouped them by aspirin use: those who had been taking any dose daily for four of the six weeks before surgery, which became the continuation stratum, and those who had not, the initiation stratum. For the continuation stratum, aspirin use was stopped at least 72 hours before surgery. All patients received placebo or 200 mg aspirin just before surgery. The initiation stratum continued 100 mg aspirin or placebo daily for 30 days. The continuation stratum received 100 mg aspirin or placebo for seven days and then resumed their previous aspirin regimen. The primary endpoint of death and non-fatal MI at 30 days was no different between the two groups (7 percent in the aspirin group and 7.1 percent in the placebo group). However, major bleeding was significantly higher in aspirin-treated patients than in the placebo group (4.6 percent vs. 3.7 percent). The primary and secondary outcomes were similar in the two aspirin strata.

"POISE-2 demonstrated that adding aspirin on top of prophylactic anticoagulants in patients who are having non-cardiac surgery is not beneficial," said P.J. Devereaux, M.D., Ph.D., associate professor of clinical epidemiology and biostatistics at McMaster University, and lead investigator for the study. "An important caveat is that 65 percent of our patients were on prophylactic anticoagulants."

There is strong evidence that aspirin prevents perioperative blood clots in veins if an anticoagulant isn't given, he noted. No subgroup effects were seen for vascular versus non-vascular surgery or baseline risk according to the Revised Cardiac Risk Index.

With major bleeding known to increase the likelihood of post-surgical MI and a post-hoc POISE-2 regression analysis demonstrating this relationship, researchers considered why their study found a higher risk for bleeding but not for MI. "One possibility is that aspirin did prevent some MIs, but we were causing enough bleeding to nullify that benefit," Devereaux said. The study used clinical measurements for maximum reliability in identifying MIs, because symptoms are masked by pain-killing drugs in more than 50 percent of patients who have heart attacks after surgery.

According to data analysis, the absolute risk increase for life-threatening and major bleeding with aspirin treatment drops from about 1.2 percent on the day of surgery to 0.9 percent by day four and to 0.3 by day eight. At about the eighth day, the risk returns to normal. This information will help doctors weigh benefits versus potential risks when aspirin might be indicated post-surgically, Devereaux said.

"We're confirming a finding that bleeding itself can cause MIs," he said. "We need to find a better way to prevent bleeding so we can get back to how to prevent some of these thrombotic events." Patients will be followed for a year, and one-year data will be analyzed.

Although POISE-2 is a large trial by perioperative standards, the lower (0.86) and upper (1.15) boundary of the hazard ratio for the primary outcome identifies that the possibility of appreciable benefit or harm has not been excluded, Devereaux said.

POISE-2 was funded through grants from the Canadian Institutes of Health Research, the Commonwealth Government of Australia's National Health and Medical Research Council and the Spanish Ministry of Health and Social Policy. Bayer Pharma AG provided the aspirin study drug, and Boehringer Ingelheim provided the clonidine study drug and some funding.

ACC2014特集

糖尿病管理目的の肥満手術の持続的効果

STAMPEDE：肥満手術は肥満糖尿病患者の血糖コントロールに対する強化薬物療法に勝る

STAMPEDE: Bariatric surgery beats intensive medical therapy for glycemic control in obese diabetics

過剰体重または肥満患者のコントロール不良2型糖尿病の管理において、胃バイパス術および胃スリーブ切除術は強化薬物療法よりも有効であるとの研究結果が第63回American College of Cardiology学会で発表され、*New England Journal of Medicine*オンライン版に掲載された。STAMPEDEは、血糖コントロール達成（スタディにおいて3か月の平均HbA1cレベル6%以下と定義）の補助として、肥満手術と強化薬物療法の効果を比較した最大のランダム化コントロールトライアルである。3年間のフォローアップにおいて、この一次エンドポイントを満たしたのは薬物療法では5%に過ぎなかったが、胃バイパス術患者では37.5%であり、胃スリーブ切除術群では24.5%であった。手術群患者では薬物療法のみの患者と比較し、ボディーマスインデックス、体重コントロール、中性脂肪および高密度リポ蛋白コレステロールなどの心血管系リスクファクターにおいてもまた、有意に改善した。薬物療法群では血糖コントロールにおいて1年以内の早期の改善を認めたが、これは3年以内には元のレベルに戻った。手術群では血糖値が平均2.5%低下し（ベースライン9.3%、3年後胃バイパス術および胃スリーブ切除術群でそれぞれ6.7%および7.0%）、維持された。

Full Text

Gastric bypass and sleeve gastrectomy – two of the most commonly used bariatric surgeries – are more effective than intensive medical therapy alone when it comes to managing uncontrolled type 2 diabetes in overweight or obese patients after three years, according to research presented at the American College of Cardiology's 63rd Annual Scientific Session and published online in the *New England Journal of Medicine*.

STAMPEDE is the largest randomized controlled trial with one of the longest follow-ups to compare the effect of these two procedures to intensive medical therapy in helping patients achieve glycemic control, defined in this study as a three-month average blood glucose level of 6 percent or lower – a more aggressive target than the American Diabetes Association recommendation of 7 percent. At the three-year follow up, only 5 percent of patients in the medical therapy group met this primary endpoint compared with 37.5 percent of gastric bypass and 24.5 percent of sleeve gastrectomy patients. Surgical patients also had a significant improvement in key cardiovascular risk factors including body mass index, weight control, triglycerides and high-density lipoprotein cholesterol compared to those receiving medical therapy alone.

"Both surgical options maintain their supremacy over standard intensive medical therapy at the three-year mark," said Philip Schauer, M.D., professor of surgery, director of the Bariatric and Metabolic Institute, Cleveland Clinic, and lead investigator of the study. "There is this notion that if we keep adding medications and pushing patients to lose weight on their own, they will eventually achieve the same type of results as those undergoing surgery, but that wasn't the case here."

While the medical group showed an initial improvement in glycemic control within the first year, they were almost back to baseline by year three. "Their [blood glucose level] went from 9.5 at the start of the study and dropped as low as 7.5 and then back up to 8.4 percent," he said. In contrast, the surgical groups were able to maintain a lower glucose level with an average 2.5 percent reduction (9.3 at baseline and 6.7 and 7.0 for gastric bypass and sleeve gastrectomy at year three).

A total of 150 patients, age 41 to 57, were randomly assigned to one of three treatment groups: intensive medical therapy only, which includes a combination of counseling, lifestyle changes and medications, medical therapy plus Roux-en-Y gastric bypass, or medical therapy plus sleeve gastrectomy. Nearly all patients, 91.3 percent, completed 36 months of follow up. At the start of the trial, the average patient had an average blood glucose level of 9.2 percent, was living with uncontrolled diabetes for eight or more years and was taking three or more anti-diabetic medications and three or more cardiovascular medications. All patients had some degree of obesity. The sample was 66 percent female.

After three years, weight loss was five to six times greater for patients who underwent gastric bypass or sleeve gastrectomy on average compared with those in the intensive medical therapy group. On average the gastric bypass group lost 24 percent of their body weight, sleeve gastrectomy patients lost 21percent of their weight, and those on medical therapy alone lost 4 percent.

Quality of life measures were evaluated using a validated questionnaire and were significantly improved across multiple domains in both of the surgical groups. There was no improvement among those in the intensive medical therapy group.

Reliance on cardiovascular and glucose-lowering medications was drastically reduced in the surgery groups. At three years, 5 percent to 10 percent of these patients were using insulin compared to 55 percent of those in the medical therapy group.

New data considered kidney function as measured by the amount of albumin in the urine – a marker of kidney damage due to diabetes. Albumin was significantly lower in the gastric bypass group at year three, a trend that was not seen in either of the other groups.

Even those patients who are not severely obese, those with a body mass index of 27 to 35, appear to benefit from surgery in much the same way as those with a higher body mass index, a finding that Schauer hopes will encourage insurance companies to lower the threshold for covering such procedures.

Sleeve gastrectomy involves removing part of the stomach to reduce its volume by 75 to 80 percent; gastric bypass involves two operations, the first to reduce the stomach to 2 to 3 percent of its usual volume (going from the size of a football to a golf ball when expanded) and the second to connect the new gastric pouch directly into the intestine to bypass the stomach.

Roughly 80 percent of the 23 million American adults living with type 2 diabetes are overweight or obese, so these findings may apply to a significant percentage of patients with diabetes, according to researchers. People with uncontrolled diabetes have a much higher risk of cardiovascular complications, including myocardial infarction, stroke and the development of secondary complications like neuropathy, retinopathy and amputation.

"Three years ago, top endocrinologists were curious about these surgeries, but due to the lack of randomized controlled trials and data, were reluctant to include it as a legitimate therapy," Schauer said. "But now the evidence is mounting and we see the benefits of surgery over medical therapy for these patients."

Bariatric surgery is not without risks and can cause complications such as bleeding, infection or blood clots. However, researchers report no major late surgical complications. The most common issues were reported at 12 months and included short-term dehydration, bleeding and one leak. Four out of 100 surgical patients needed operative intervention to manage complications occurring within the first year.

Schauer and his team will conduct long-term follow-up of these patients. Multicenter studies are needed to evaluate the effect of surgery and medical therapy on clinical outcomes such as heart attack, stroke, renal failure and blindness. Several studies have been published since STAMPEDE's one-year results and show similar findings.

This study was funded by Ethicon Endo-Surgery, Inc., a subsidiary of Johnson & Johnson. Dr. Schauer is a consultant with Ethicon.

ACC2014特集

血液バイオマーカーがMI否定に有望であることが示された

高感度心筋トロポニンTは胸痛患者の心筋梗塞リスク予測に役立つ

High-sensitivity cardiac troponin T helps predict myocardial infarction risk for patients with chest pain

救急外来受診患者のうち、血液バイオマーカーである高感度心筋トロポニンT（*hs*-cTnT）が不検出レベルで心電図上虚血の所見のない者は、30日以内の心筋梗塞（MI）リスクが極小であるとの研究結果が第63回American College of Cardiology学会で発表され、*Journal of the American College of Cardiology*オンライン版に掲載された。胸痛を主訴にスウェーデンの救急外来を受診し、初回検査でこのバイオマーカーが不検出レベル（< 5ng/L）であり、ECG上虚血による心筋傷害の所見のない患者約9,000人（平均年齢47歳、女性53%）がスタディに組み入れられた。30日以内に39人がMIと診断され、うち15人はECG上心筋傷害の所見がなかった。したがって、胸痛で医療機関を受診したがECG上心筋傷害所見がなく*hs*-cTnT不検出レベルの患者のうち実際に直後のMIリスクを有するのは、594人にわずか1人である。この検査のMIに対する陰性的中率は99.8%であり、死亡に関しては100%であった。この相関関係は、患者のリスクファクターや症状の持続時間に関係なく維持された。

Full Text

Patients presenting to the emergency department with an undetectable level of the blood biomarker high-sensitivity cardiac troponin T (*hs*-cTnT), and whose ECGs show no sign of restricted blood flow, have a minimal risk of myocardial infarction (MI) within 30 days, according to research presented at the American College of Cardiology's 63rd Annual Scientific Session.

In a study of all patients (14,636 in total) reporting to a Swedish emergency department with chest pain over a two-year period from 2010 to 2012, researchers examined patients' blood levels of *hs*-cTnT, a marker that indicates damage to the heart. Nearly 9,000 patients with an undetectable level of the biomarker, or less than 5ng/L, on initial testing, and whose ECGs showed no heart damage from decreased blood flow, were included in the study to examine the primary endpoint of MI within 30 days. Researchers found that the negative predictive value of the tests – the probability that patients are not at risk – was 99.8 percent for MI and 100 percent for death. This relationship held true regardless of patients' risk factors for MI or how long patients had experienced symptoms.

"Chest pain is a potentially life-threatening symptom, as well as being a very common one," said Nadia Bandstein, M.D., Department of Medicine, Karolinska Institute, Solna, Sweden, and the lead investigator of the study. "In our hospital it's the second most common symptom reported in the emergency department. Since there are no established ways to quickly rule out MI, many patients are admitted to the hospital unnecessarily, at a large cost to the patient and to society."

According to Bandstein, this is the first large study to specifically examine the use of *hs*-cTnT to predict MI risk. The impetus for the study stemmed from the hospital clinicians' observations that patients with undetectable levels of the marker who were admitted to the hospital almost never went on to have MIs or need any further work-up, and most went home within a day of admission.

High-sensitivity cardiac troponin T is a relatively new biomarker used in the diagnosis of MI and is detectable in the blood several hours before older methods of measuring troponins. Current guidelines recommend that *hs*-cTnT be analyzed at least three hours after the onset of chest pain, which commonly means that patients need to be admitted to the hospital for a second blood test and further evaluation. Bandstein says these study findings suggest that only one measure of the biomarker needs to be taken, and may allow some patients to be discharged directly from the emergency department.

"Despite our observations before the study, we were still surprised by the strength of our findings," Bandstein said. "Using this blood test along with an ECG, we will save about 500 to 1,000 admissions per year in our hospital alone, allowing us to use the beds for sicker patients."

Authors believe this study also has tremendous implications for the millions of patients around the world who seek emergency treatment for chest pain each year.

During the 30 days of follow-up, 39 of the 8,907 patients were diagnosed with MIs, and 15 of these patients showed no signs of damage on ECG. What this means, according to researchers, is that only one in 594 patients who seek medical attention for chest pain – but have no signs of heart damage on an ECG and undetectable levels of *hs*-cTnT – are actually at immediate risk of MI. The average age of patients in the study was 47, and 53 percent were women.

Bandstein recommends that further research be done to assess the risk of heart attack among patients with slightly higher levels of *hs*-cTnT (5-14 ng/L). It will also be important to look at the prognosis for patients diagnosed with heart attack based on slight elevations of the biomarker, she said.

ACC2014特集

自己拡張型TAVRを用いた際の死亡は手術と比較し少ない

CoreValue：主要試験において大動脈弁狭窄に対する自己拡張型経カテーテル大動脈弁は手術よりも優れていた

CoreValue: Self-expanding transcatheter aortic valve better than surgery for aortic stenosis in pivotal trial

重度大動脈弁狭窄を有する高リスク患者において、自己拡張型弁置換術を用いた経カテーテル大動脈弁置換術（TAVR）は従来の手術と比較し1年間の死亡率が有意に低いことが初めて示されたとの研究結果が、第63回American College of Cardiology学会で発表され、*New England Journal of Medicine*オンライン版に掲載された。CoreValve U.S. Pivotal High Risk Trialは、リスク評価にて大動脈弁手術による死亡リスクが高い患者を組み入れた。795人の患者がカテーテルまたは手術による弁置換術を施行される群にランダムに割り付けられ、747人がどちらかの施術を受けた（TAVR群390人および外科的大動脈弁手術群357人）。両群ともに平均年齢は83歳であった。その結果、初回非劣性ゴールを超えていたため、既にデザインされていた優位性解析へと移行した。30日間の死亡率には有意差はなかった（TAVR 3.3%対手術4.5%）。有意差は一次エンドポイントである1年間の総死亡において発現した（TAVR 14.2%対手術19.1%）。予備解析では、1年間の心筋梗塞、脳卒中またはこれらの関連死はTAVRで有意に低い（20.4%対27.3% ）ことも示された。

Full Text

Transcatheter aortic valve replacement with a self-expanding valve prosthesis for the first time has demonstrated significantly lower death rates at one year compared with conventional surgical valve replacement in high-risk patients with severe aortic stenosis, according to research presented at the American College of Cardiology's 63rd Annual Scientific Session and simultaneously published online in the *New England Journal of Medicine*.

Worldwide, an estimated 300,000 people have severe aortic stenosis and roughly a third of them are deemed unable to withstand the standard treatment of open-heart surgery to replace the valve. But if the condition is left untreated, risk of death is 25 percent the first year after symptoms appear and rises to 50 percent the second year. Replacement valves delivered by a catheter have been developed as a less invasive alternative to open-heart surgery.

The CoreValve U.S. Pivotal High Risk Trial enrolled patients with an assessed increased risk of death from aortic valve surgery. Of 795 patients randomly assigned to valve replacement by catheter or surgery, 747 patients underwent one of the procedures: 390 in the transcatheter aortic valve replacement (TAVR) arm and 357 in the surgical aortic valve replacement arm. The average age was about 83 years in both groups. The results exceeded the initial non-inferiority goal and, by pre-design, then moved on to a superiority analysis. Death rates at 30 days were not significantly different, with a 3.3 percent death rate for TAVR and 4.5 percent for surgery. A significant difference emerged at the one-year primary endpoint of all-cause mortality: 14.2 percent for TAVR with CoreValve compared with 19.1 percent for surgical replacement.

"This is the first prospective study of any device that suggests TAVR is superior to [surgery] in a predefined population of patients, and that's a provocative finding," said David H. Adams, M.D., professor and chairman of the Department of Cardiothoracic Surgery at Mount Sinai Medical Center and co-principal investigator of the study. He emphasized the "outstanding outcomes" in the surgical arm: "The low mortality rates with conventional surgery far exceeded the predicted mortality according to the Society of Thoracic Surgeons predictive model. In order to pass a superiority threshold, transcatheter treatment with the CoreValve device had to exceed excellent surgical outcomes."

Exploratory analyses also showed the one-year rate for heart attack, stroke or related death was significantly lower for TAVR at 20.4 percent compared with 27.3 percent for surgical replacement.

"We also performed multiple different subgroup analyses for one-year death rates and found the survival benefit of TAVR with CoreValve was consistent across all clinical subgroups we examined, regardless of thresholds," Adams said.

The 30-day observed death rates for TAVR and surgical valve replacement were much lower than the anticipated rate of 15 percent, Adams said, suggesting that the patient population may have had lower risks than intended. In addition to the STS score, frailty and other disabilities were considered in the evaluation of risk. Randomization ensured a robust trial nonetheless, he said, adding that this study confirmed that current risk assessment models, including expert physician reviews, overestimate contemporary surgical risks.

A potential limitation of the study is the higher dropout rate for patients randomly assigned to surgery, as reported with previous TAVR trials. Forty patients assigned to surgery dropped out of the study before treatment, while only four assigned to the TAVR arm dropped out. The trial was designed with this anticipated attrition rate, and a sensitivity analysis confirmed that there were no significant differences in the risk profiles between patients who underwent the assigned surgical treatment and those who withdrew, Adams said.

"We are confident that the higher withdrawal rate in the surgical arm did not affect our findings," he said.

The study was funded by Medtronic, Inc. The Icahn School of Medicine at Mount Sinai receives royalties for intellectual property developed by Adams for mitral and tricuspid repair products now owned by Edwards Lifesciences and Medtronic.

ACC2014特集

STEMIにおいてヘパリンはbivalirudinよりも優れている

HEAT-PCCI : MI後患者治療においてヘパリンを用いた方がbivalirudinを用いるよりも心血管系イベント再発が少ない

HEAT-PCCI: Fewer repeat cardiovascular events with heparin than bivalirudin in treating patients after an MI

心筋梗塞後、直接的経皮的冠動脈インターベンションを受けた患者における抗凝固薬の比較において、ヘパリンを用いた方がbivalirudinを用いたよりも28日間の重大な心血管系イベントが少なかったとの研究結果が、第63回American College of Cardiology学会で発表された。この単施設オープンラベルトライアルは、MIが疑われ冠動脈造影を施行された患者1,829人を組み入れた。患者は未分画ヘパリンまたはbivalirudinを投与される群にランダムに割り付けられた。患者は28日間追跡され、一次エンドポイント―総死亡、脳卒中、MI再発または予定外の再血行再建の合計―について調査された。データから、bivalirudinを内服している患者はこれらのアウトカム発現率が有意に高いことが示された（bivalirudin群8.7%対ヘパリン群5.7%）。2群間で最も差が大きかったのは、ステント血栓により発症したMI再発であった（bivalirudin群3.4%対ヘパリン群0.9%）。一次安全性アウトカムである重大な出血に関しては2群間で有意差はなかった（bivalirudin群3.5%対ヘパリン群3.1%）。

Full Text

In a comparison of anticoagulants, heparin was associated with significantly fewer major cardiovascular events at 28 days than bivalirudin in patients receiving primary percutaneous coronary intervention after a myocardial infarction (MI), according to research presented at the American College of Cardiology's 63rd Annual Scientific Session.

The single-center, open label trial enrolled 1,829 patients with suspected MI who received a coronary angiography. Patients were randomized to receive unfractionated heparin or bivalirudin. Patients were followed for 28 days to examine the primary endpoint – a composite of all-cause death, stroke, repeat MI or unplanned repeat procedure. Data showed that patients taking bivalirudin had a significantly higher incidence of these outcomes at 8.7 percent compared with 5.7 percent of those in the heparin group. The largest difference between the groups was in the incidence of repeat MI caused by stent thrombosis (3.4 percent in the bivalirudin group compared to 0.9 percent receiving heparin). There was no statistically significant difference in the primary safety outcome of major bleeding between groups (3.5 percent bivalirudin compared to 3.1 percent heparin).

"Both heparin and bivalirudin are used regularly worldwide in percutaneous coronary intervention, but there is still some debate about whether one drug has any advantage over the other," said Adeel Shahzad, M.B.B.S., M.R.C.P., cardiologist at the Liverpool Heart and Chest Hospital in Liverpool, UK and one of the lead investigators of the study. "We sought to evaluate the drugs by comparing outcomes in two well-matched groups of patients, and our study suggests that heparin may be a more effective agent."

All patients who reported to the study site with a possible MI between February 2012 and November 2013 were assessed for inclusion in the study. Eligible patients were immediately randomized to one of the two study groups for emergency treatment. Percutaneous coronary intervention was performed in 82 percent of patients, with similar procedural success in both groups (97.5 percent in bivalirudin compared to 97.3 percent in heparin group). Because of the life-threatening nature of the situation at time of enrollment – and routine use of both trial medications – researchers obtained approval to get patients' delayed consent. Of 1,829 treated patients, only four later refused or withdrew consent.

Patients received dual antiplatelet therapy – a combination of aspirin and another antiplatelet agent – before their procedures as part of the routine practice at the study site. Those in the heparin group received a bolus dose of unfractionated heparin of 70 units/kg (1 kg = 2.2 lbs) pre-procedure, while bivalirudin was given as a bolus of 0.75mg/kg, followed by an infusion of 1.75 mg/kg per hour for the duration of the procedure.

According to Shahzad, the routine use of heparin has the potential to reduce costs for health care providers, as the cost of bivalirudin can be much higher than heparin.

Although previous studies have compared bivalirudin to heparin, these studies have tested bivalirudin against a combination of heparin and a glycoprotein IIb/IIIa inhibitor. These studies have often shown a higher rate of bleeding in the heparin group, but Shahzad said it is difficult to know whether this was because patients were receiving two anti-clotting agents together.

Glycoprotein IIb/IIIa inhibitors were used for this study in special circumstances under current guidelines – for example, in patients with massive blood clots. Use of this medication was comparable in both groups (13.5 percent of bivalirudin patients compared to 15.5 percent of heparin), and there were no significant differences between the two treatment groups in terms of bleeding complications.

Interpretation of the study data may be limited due to single-center recruitment, the open label study design and predominantly Caucasian population. However, according to authors, this is both the largest ever single-center trial in cardiovascular medicine, as well as the first major trial to recruit 100 percent of all eligible patients, and study findings represent a true, unselected population of angioplasty patients.

Shahzad said that further research should be done to determine the best use of glycoprotein inhibitors.

Support for the study was provided by unrestricted grants from The Medicines Company, Parsippany, N.J., and AstraZeneca, Wilmington, Del.

ACC2014特集

モノクローナル抗体阻害とスタチンの組み合わせのLDL-Cに関する評価

LAPLACE-2：Evolocumabはスタチン単独療法時よりもさらにLDL-Cを良好に低下させ、この結果から2剤併用療法の有効性が示唆される

LAPLACE-2: Evolocumab safely drops LDL cholesterol well below statin-only baseline suggesting efficacy of 2-drug approach

モノクローナル抗体evolocumabはスタチンに追加することにより低密度リポ蛋白（LDL）コレステロールを極めて有意に低下させたとの第III相LAPLACE-2試験の結果が、第63回American College of Cardiology学会で発表された。Evolocumabは、PCSK9を阻害することにより肝臓による血液からのLDL除去能を上昇させる。1,899人の患者が、evolocumabまたはプラセボ、evolocumabとプラセボ、プラセボおよびエゼチミブ、またはプラセボのみの異なる用量およびスケジュールに割り付けられた。Evolocumab治療を受けた全グループにおいてプラセボと比較し極めて有意なLDLコレステロール低下を示した：evolocumab注射を2週間毎に施行する群で66～75%、4週毎の群で63～75%。LDLコレステロール<70mg/dLを達成したのは中等度強化スタチン群で86～94%であり、高度強化群で93～95%であった。エゼチミブは、中等度強化スタチン群でLDLコレステロールを17～20%低下させ、高度強化群で51～62%低下させた。Evolocumabを追加することにより、LDLコレステロールレベルが中等度強化スタチン群で39～49mg/dLに低下し、高度強化群で33～39mg/dLに低下した。

Full Text

The monoclonal antibody evolocumab produced highly significant reductions in low-density lipoprotein (LDL) cholesterol as an add-on to statins in all treatment groups, according to data from the LAPLACE-2 study presented at the American College of Cardiology's 63rd Annual Scientific Session.

"High-risk patients – such as those with clinical cardiovascular disease, high LDL cholesterol levels or diabetes – are ideally treated with high-intensity statins that lower LDL cholesterol by at least 50 percent, but that isn't always possible," said Jennifer G. Robinson, M.D., M.P.H., director of the Prevention Intervention Center at the University of Iowa College of Public Health.

"Many patients can't tolerate high-intensity statins and cannot achieve desired LDL reductions with moderate- or low-intensity statins, and those with high cholesterol levels often need more than high-intensity statins to lower LDL levels adequately." Robinson said evolocumab may be useful for these patients. Unlike statins, which are taken in pill form, evolocumab is administered as an injection.

LAPLACE-2 is a large phase III study of evolocumab in patients randomly assigned to a high- or moderate-intensity statin to reduce LDL cholesterol. Evolocumab works by inhibiting PCSK9, which leads to an increase in the liver's ability to clear LDL cholesterol from the blood. High-intensity statins such as 80-mg atorvastatin and 40-mg rosuvastatin lower LDL by 50 percent or more; moderate-intensity statins such as 40-mg simvastatin, 10-mg atorvastatin and 5-mg rosuvastatin drop LDL levels by 30 to nearly 50 percent. Evolocumab was also compared with ezetimibe, another drug commonly used to lower LDL cholesterol. After a four-week period to stabilize lipids with one of these five statin regimens, 1,899 patients were randomly assigned to different doses and schedules of evolocumab or placebo, evolocumab and placebo, placebo and ezetimibe, or placebo only.

All evolocumab-treated groups showed highly significant reductions in LDL cholesterol versus placebo: 66 percent to 75 percent on a schedule of evolocumab injections every two weeks, or 63 percent to 75 percent on a four-week schedule. Patients achieved an LDL cholesterol level of less than 70 mg/dL in 86 percent to 94 percent in the moderate-intensity statin groups and 93 percent to 95 percent in the high-intensity groups. Ezetimibe reduced LDL cholesterol by 17 percent to 20 percent in moderate-intensity statin groups and 51 percent to 62 percent in high-intensity groups. Adding evolocumab reduced LDL cholesterol levels to 39 mg/dL to 49 mg/dL with moderate-intensity statin regimens and 33 mg/dL to 39 mg/dL with high-intensity regimens. Evolocumab also significantly reduced non-HDL cholesterol, apolipoprotein B and lipoprotein (a) levels.

Efficacy and safety endpoints were met. Evolocumab was well tolerated, with adverse event rates similar to those in placebo and ezetimibe-treated groups and no sign of liver damage or muscle problems.

"Heart attack and stroke remain the leading cause of death in the United States and around the world," Robinson said. "People are excited about PCSK9 inhibitors because they'll let us test whether a whole lot more LDL lowering will result in large additional reductions in cardiovascular events in statin-treated patients."

The ongoing FOURIER trial will assess whether additional lowering of LDL cholesterol with evolocumab, on top of high- and moderate-intensity statin therapy, reduces the number of cardiovascular events over a period of years.

Robinson was an investigator for LAPLACE-2 and consults for Amgen, which funded the study.

ACC2014特集

抗PCSK9抗体薬はLDLコレステロール低下に有効である

GAUSS-2 : スタチン不耐性の難治性患者に対しevolocumabはエゼチミブよりも有効である

GAUSS-2: Evolocumab superior to ezetimibe for clinically challenging statin-intolerant patients

低密度リポ蛋白コレステロール（LDL-C）を低下させるPCSK9阻害薬と呼ばれるある種の注射剤evolocumabは、スタチン内服不能患者において副作用がほとんどなくエゼチミブよりも有効であるとのGAUSS-2の結果が第63回American College of Cardiology学会で発表され、*Journal of the American College of Cardiology*オンライン版に掲載された。GAUSS-2スタディでは、307人の患者（平均年齢62歳、女性46%）が2つのevolocumab療法群（140mgを2週間毎または420mgを月1回に加えプラセボを毎日内服）または2つのエゼチミブ療法群（プラセボ注射を2週間毎または月1回に加えエゼチミブ10mgを毎日内服）のいずれかにランダムに割り付けられた。LDL-Cのベースラインからの低下である一次エンドポイントは合致した：evolocumab治療群において第12週のLDL-Cのベースラインからの低下が53～56%であったのに対し、エゼチミブ治療群では37～39%。筋骨格系の副作用はevolocumab使用患者の12%において報告されたのに対し、エゼチミブでは23%であった。治療関連副作用がevolocumab群の8%、およびエゼチミブ群の13%に認められたため、治験薬は中止された。

Full Text

Evolocumab, an injected form of a class of drugs called PCSK9 inhibitors that lower low-density lipoprotein cholesterol (LDL-C) outperformed ezetimibe with few side effects in patients unable to take statins, according to research from GAUSS-2 presented at the American College of Cardiology's 63rd Annual Scientific Session and published online in the *Journal of the American College of Cardiology*.

High LDL cholesterol is considered a major risk factor for cardiovascular disease. Statins are commonly prescribed to reduce that risk. Currently ezetimibe is one of the few options to lower LDL-C for patients who cannot tolerate statins, but it is less effective than statins in decreasing LDL-C.

GAUSS-2 is a 14-country, 12-week double-blind comparison of subcutaneously administered evolocumab versus oral ezetimibe in patients with high cholesterol who were unable to tolerate effective doses of at least two different statins. In this phase III study, half of patients tried three statins unsuccessfully, and 22 percent couldn't tolerate any of at least four different statin drugs. The patients had a minimum LDL-C level of 193 mg/dL.

A total of 307 patients were randomly assigned to one of two evolocumab regimens (140 mg every two weeks or 420 mg per month, plus daily placebo) or one of two ezetimibe groups (a placebo injection every two weeks or monthly, plus 10 mg oral ezetimibe daily). Mean age was 62 years, and 46 percent of patients were women.

The primary endpoints of LDL-C reductions from baseline were met: 53 percent to 56 percent decrease of LDL-C from baseline at week 12 in evolocumab-treated patients, corresponding to a 37 percent to 39 percent LDL-C decrease with ezetimibe. Musculoskeletal side effects were reported in 12 percent of patients on evolocumab compared to 23 percent on ezetimibe. More than 94 percent of all enrolled patients completed the study. The study drug was stopped because of treatment-related side effects in 8 percent of evolocumab patients and 13 percent of ezetimibe patients. Safety data for evolcumab versus ezetimibe include the following side effects: headache (8 percent vs. 9 percent), muscle pain (8 percent vs. 18 percent), pain in extremities (7 percent vs. 1 percent), muscle spasms (6 percent vs. 4 percent), fatigue (4 percent vs. 10 percent), nausea (4 percent vs. 7 percent), diarrhea (2 percent vs. 7 percent), sensation of tingling, prickling or burning known as paresthesia (1 percent vs. 5 percent). Patients who were taking low-dose statins were more likely to develop muscle pain in both study arms than those who took no statins (evolocumab, 17 percent vs. 6 percent; ezetimibe, 21 percent vs. 17 percent).

"We have a growing population of patients treated with at least two different types of statins who still experience side effects so much they want to discontinue the drug," said Erik S.G. Stroes, M.D., chair and professor at the Department of Vascular Medicine in Amsterdam's Medical Center and the study's principal investigator. "The one big difference between our study and others in patients at increased cardiovascular risk is that for these patients, we don't have a good alternative treatment – no drug with robust LDL-lowering potency and good tolerability. For clinicians trained to solve problems, an unmet clinical need is a big issue."

Earlier studies indicate that more than 75 percent of patients who failed one statin can still do well on a second statin drug. This finding makes patients who have been unable to tolerate two or more statins a particularly challenging group.

Stroes noted that clinicians have debated whether cardiovascular patients would accept a drug administered by injection, but the study's cardiovascular physicians and internists found few problems with the subcutaneous regimen. Evolocumab must be delivered by this route because it's a fully human monoclonal antibody, a protein that will be broken down in the stomach and bowel if taken orally.

"What's innovative here is that if you give a drug, it's hardly ever specific; statins, for example, can work on a lot of organs," Stroes said. "An antibody is, in and of itself, inert. It binds selectively to a particular sequence on a protein or bacteria and can have a predictable effect on a particular system. That's most likely why evolocumab has a good safety profile with very high efficacy. This study suggests that statin-induced myopathy may be due to another molecular pathway and is not related to LDL-C lowering per se."

There is no generally accepted definition of statin intolerance yet, Stroes said. The GAUSS-3 study, planned to start in the second half of 2014, will include a separate placebo-controlled re-exposure to statin before evolocumab therapy.

"It will help in further delineating statin intolerance and how that should be defined in clinical practice," he said.

Stroes noted two limitations to the study. Reducing LDL-C levels has been demonstrated to translate into a reduced risk of cardiovascular events primarily with statin treatment. The benefit of evolocumab on cardiovascular endpoints awaits the results of the ongoing FOURIER trial. Additionally, the 12-week duration of this study was rather short considering that the majority of patients require life-long treatment to manage LDL-C. The good tolerability observed in this study also needs confirmation in the ongoing long-term trials, Stroes said.

The GAUSS-2 trial was funded by Amgen, Inc.

ACC2014特集

ステント留置後抗凝固療法の個別化によりMIおよび死亡リスクが低下した

高リスク患者において薬剤溶出ステントはベアメタルステントよりも1年後の予後が良好であることが示された

Drug-eluting stents demonstrate better outcomes after one year than bare metal stents in at-risk patients

出血または血栓リスクが高いため薬剤溶出ステントの適応が不確かであると以前は思われた患者に、薬剤溶出ステント留置後に個別化した抗凝固療法を行った場合、薬剤溶出ステントを使用した方がベアメタルステントを使用した場合よりも1年後の心血管イベントリスクが低いとの研究結果が第63回American College of Cardiology学会で発表された。薬剤溶出ステントを使用された患者のうち計140人、つまり17.5%が1年以内に重大な心血管イベントを発現したのに対し、ベアメタルステントを留置された患者におけるその割合は178人、22.1%であった。薬剤溶出ステントを使用された患者はまた、心筋梗塞（2.9%対8.1%）および再血行再建施行（5.9%対10.7%）が少なかった。薬剤溶出ステント群患者においては、ステント周囲血栓発現率もまた低かった（2.0%対4.1%）。出血率は両群間に差は認めなかった。抗血栓療法施行期間が現在推奨されているよりも短かった患者において良好な結果が認められたことから、現在のガイドラインにおける薬剤溶出ステント留置後のより長期の抗血小板薬療法に対し疑問が投げかけられる可能性があり、より個別化した方策の必要性が示されていると筆者らは述べている。

Full Text

Use of drug-eluting stents is associated with a lower risk of major cardiovascular events at one year compared to bare metal stents when followed by an individualized course of anticoagulants among patients previously thought to be uncertain candidates for drug-eluting stents due to their heightened risk of bleeding or blood clots, according to research presented at the American College of Cardiology's 63rd Annual Scientific Session.

Positive study findings for patients receiving a shorter than currently recommended course of blood thinners may call into question existing guidelines for a more prolonged anti-platelet therapy following placement of drug-eluting stents, which points to the need for a more personalized approach, according to authors.

This multinational, single-blinded trial involved 1,606 patients who were randomly assigned to receive a specific type of drug-eluting stent (Zotarolimus-eluting stent) or a bare metal stent. The purpose of the study was to assess whether implantation of the drug-eluting stent followed by an individualized course of dual anti-platelet therapy would decrease the incidence of 12-month major adverse cardiovascular events compared to implantation with a bare metal stent among patients classified as uncertain candidates for drug-eluting stents. A significantly higher number of patients in the bare metal stent group had major adverse cardiovascular events at one year, including all-cause death, non-fatal heart attacks or any procedures to re-open the artery.

"Given the assumed risks, we were surprised by the lower rate of myocardial infarction (MI) and restenosis among our drug-eluting stent patients," said Marco Valgimigli, M.D., Ph.D., cardiologist and associate professor, Erasmus University Medical Center in the Netherlands, and lead investigator of the study. "For the first time, we have handled a drug-eluting stent as we would a bare metal stent in terms of the duration and intensity of anti-platelet therapy and have still shown the superior safety and efficacy of the drug-eluting stent."

A total of 140 or 17.5 percent of patients with the drug-eluting stent had a major cardiovascular event in the first year compared with 178 or 22.1 percent of patients implanted with the bare metal stent. Patients with the drug-eluting stent also had lower rates of MI (2.9 compared to 8.1 percent) and revascularization procedures (5.9 compared to 10.7 percent). This group also had lower rates of blood clots around the stent (2.0 compared to 4.1 percent). The rate of bleeding did not differ between groups.

Patients were enrolled at 20 sites in Italy, Switzerland, Portugal and Hungary. All were undergoing percutaneous coronary intervention with stent implantation. Adult patients who met any one of the three criteria to be uncertain candidates for drug-eluting stents were randomly assigned to receive bare metal or drug-eluting stents. To qualify as "uncertain" candidates for drug-eluting stents, patients in the study had to either have a high risk of blood clots, high risk of bleeding and/or low risk of. Patients at a low risk of restenosis were included because the risk of blood clots associated with drug-eluting stents – along with the assumed risk of bleeding from the prolonged course of blood thinners taken afterward – may, in fact, outweigh benefits of this type of stent for these patients.

The majority of patients (95.4 percent) took some course of dual anti-platelet therapy after stent placement, 96.7 percent with aspirin and clopidogrel and the remaining 3.3 percent with aspirin and either prasugrel or ticagrelor. Duration of therapy was dictated by patients' individual risk factors and spanned from no treatment to six to 12 months, with a median of 32 days. Patients who were not eligible for dual anti-platelet therapy were treated with either aspirin or an anti-platelet alone. This protocol represents a departure from current guidelines that recommend the use of dual anti-platelet therapy for six to 12 months after the placement of a drug-eluting stent.

Authors caution that the results of this study pertain to the Zotarolimus-eluting stent and may not apply to other types of drug-eluting stents. According to Valgimigli, additional research is needed to determine whether the personalized dual anti-platelet therapy tested in this study can be safely implemented in patients using other types of drug-eluting stents. He also suggests that a longer follow-up study be conducted to confirm results of this study over time.

Support for the study was provided by Medtronic, Minneapolis.

ACC2014特集

ビタミンD欠乏はより重篤な心疾患と関連する

ビタミンDレベル低下は冠動脈疾患の範囲および重症度の予測因子となる

Lower levels of vitamin D predict extent and severity of coronary artery disease

ビタミンDレベルが低いことと冠動脈疾患を有する確率および重症度が高いこととに関連があることから、ビタミンD欠乏は心疾患の独立した危険因子であるとの研究結果が第63回American College of Cardiology学会で発表された。ビタミンDレベルと冠動脈疾患との関連を評価したこの種で最大のこのスタディにおいて、研究者らは1,484人の患者においてビタミンDレベルを評価した。冠動脈造影を施行される患者の70.4%においてビタミンD欠乏（20ng/mL）が認められた。ビタミンDレベルが最低の患者群では冠動脈疾患有病率が32%高く、多枝病変を有する重症冠動脈疾患の頻度が20%近く高く、ビタミンD欠乏と冠動脈疾患有病率が高いことに関連が認められた。ビタミンD欠乏が重症なほどより心疾患が進行していた。ビタミンDレベルが10ng/mL未満の患者はこれが正常範囲内の者と比較し、冠動脈硬化が2倍近く多く認められた。これらの結果からビタミンD欠乏は動脈硬化の結果というよりも原因であることを示唆している、と筆者らは述べている。

Full Text

Vitamin D deficiency is an independent risk factor for heart disease with lower levels of vitamin D being associated with a higher presence and severity of coronary artery disease, according to research to be presented at the American College of Cardiology's 63rd Annual Scientific Session.

A growing body of research shows that vitamin D may be beneficial in preventing heart disease. Several recent studies also support the idea that low levels of vitamin D are linked to an increased risk of heart disease; however, it is still not clear whether adding vitamin D supplements may help reduce that risk.

In the largest study of its kind to evaluate the relationship between vitamin D levels and coronary artery disease, vitamin D deficiency (20ng/mL) was observed in 70.4 percent of patients undergoing coronary angiography. Vitamin D deficiency was associated with higher prevalence of coronary artery disease, with a 32 percent higher occurrence in patients with the lowest vitamin D levels and a near 20 percent higher frequency of severe disease affecting multiple vessels. A progressive increase in heart disease was found according to the severity of vitamin D deficiency. Patients with values lower than 10 mg/dl had a near two-fold increased rate of coronary atherosclerosis as compared with those showing normal levels.

Researchers evaluated vitamin D levels in 1,484 patients. Vitamin D deficiency was defined as levels lower than 20ng/mL, and severe vitamin D deficiency was defined as levels under 10ng/mL. Patients were considered to have coronary artery disease if they had a diameter reduction of greater than 50 percent in at least one coronary artery. The extent and severity of heart disease were measured by quantitative coronary angiography.

"Present results suggest vitamin D deficiency to be the cause rather than the consequence of atherosclerosis," said Monica Verdoia, M.D., specializing cardiologist at the Department of Cardiology, Ospedale Maggiore della Carità, Eastern Piedmont University in Novara, Italy, and investigator on the study on behalf of the Novara Atherosclerosis study group by Prof. Giuseppe De Luca. "Although evidence of benefits with vitamin D supplementation in cardiovascular outcomes are still lacking, strategies to raise endogenous vitamin D should probably be advised in the prevention of cardiovascular disease."

A diet rich in vitamin D and moderate exercise outdoors should be advised in both patients with and without cardiovascular disease, Verdoia said. Vitamin D acts as a regulator on the function of the immune system as well as inflammatory processes that contribute to risk factors for heart disease, she said.

Verdoia said the importance of the study is to provide deeper insight into stratification tools for assessing the risk of coronary artery disease in a real world population, where vitamin D deficiency has a dramatic prevalence. She stresses the need to make funding a priority in the research on vitamin D in cardiovascular prevention. The research team plans to proceed with clinical trials evaluating the treatment of vitamin D deficiency and to investigate the mechanisms by which vitamin D can influence the development of atherosclerosis.

Vitamin D is being studied for its possible connection to several diseases and health problems, including diabetes, high blood pressure, multiple sclerosis, autoimmune conditions, bone disorders and some types of cancer.

A limitation of the study is that researchers did not evaluate the long-term outcomes for study patients, so it is unknown whether those with lower vitamin D levels experienced a higher rate of recurrent events or a quicker progression of the coronary disease, although other studies have suggested this is the case.

ACC2014特集

心臓再同期療法は心不全の生存率を改善する

2つのタイプのペースメーカーを比較したスタディの結果、軽度心不全患者における明らかな有益性が認められた

Study comparing two types of pacemakers finds clear benefits for patients in mild heart failure

両室ペーシング機能付き植込み型除細動器（CRT-D）として知られる特別なペースメーカーを植え込まれた軽度心不全患者は、従来の植込み型除細動器（ICD）を植え込まれた患者よりも生存期間が長い可能性があるとの研究結果が第63回American College of Cardiology学会で発表された。Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapyトライアルでは、軽症心不全症状を有する患者および心不全症状を有さない患者1,820人（左脚ブロックを有する1,281人を含む）を組み入れ、彼らをCRT-D療法またはICDを施行される群にランダムに割り付けた。患者はクラス1または2の心不全と診断され、左室機能障害を有し左室駆出率は30%以下であった。オリジナルのトライアルは患者を平均2.4年間追跡したが、今回のスタディではこの追跡期間を組み入れから最長7年間に延長した。CRT-Dを植え込まれた左脚ブロック患者は従来のICDを埋め込まれた患者よりも死亡リスクが41%低下した。このサブセットにおいて、CRT-D患者の7年間後の総死亡率は18%であったのに対し、ICD群では29%であった。CRT-D群患者の5年生存率は90%近かった。

Full Text

Patients in mild heart failure who receive a specialized pacemaker known as cardiac resynchronization therapy with a defibrillator (CRT-D) may live longer than those implanted with a traditional implantable cardioverter defibrillator (ICD), according to research presented at the American College of Cardiology's 63rd Annual Scientific Session.

In the first study to look at CRT-D in mildly symptomatic patients, researchers found that patients with left bundle branch block implanted with a CRT-D had a 41 percent reduced risk of death compared to patients who had a conventional ICD. The probability of all-cause mortality at seven years was 18 percent among the CRT-D patients, compared to 29 percent in the ICD group in this subset of patients. The five-year survival rate for patients with CRT-D was close to 90 percent.

"Based on our findings, we now have an intervention that can potentially change the outcomes for certain heart failure patients," said Ilan Goldenberg, M.D., director of the department of cardiology, Israel's Leviev Heart Center, and one of the lead investigators of the study. "We can intervene early in the course of the disease to reduce the risk of long-term mortality in these patients."

The Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy trial enrolled 1,820 patients with mild or no heart failure symptoms – including 1,281with left bundle branch block in this analysis – and randomized them to receive CRT-D therapy or ICD. A CRT-D differs from an ICD in that it has a second electrode over the left ventricle of the heart to help synchronize a patient's heartbeat and improve cardiac function.

Patients enrolled in the study were diagnosed with New York Heart Association Class 1 or 2 heart failure, left ventricular dysfunction and an ejection fraction of 30 percent or lower. The original trial followed patients for an average of 2.4 years, and the current study extended this follow-up for up to seven years from enrollment.

According to Goldenberg, previous studies have shown survival benefits from CRT-D in patients with moderate-to-severe symptoms, where intervention took place relatively late in the course of the disease when mortality rates are high. This study is the first to show the significant survival benefit when CRT-D is used with mildly symptomatic patients or asymptomatic patients with cardiac dysfunction.

Approximately half of patients who develop moderate or severe heart failure die within five years of diagnosis, making it important to intervene early in the clinical course of the disease.

The significant long-term survival benefit of CRT-D in the trial was observed only among patients with left bundle branch block, Goldenberg said. The study does not support early intervention with CRT-D in patients without left bundle branch block.

While researchers expected to find mortality reduction in patients with left bundle branch block during long-term follow-up, Goldenberg said, "we were surprised by the consistency of results in each subgroup of these patients, regardless of age, gender or the cause or duration of heart failure."

Goldenberg recommends additional research to see if similar benefits are found in patients with higher ejection fractions and among those without any symptoms of heart failure. The study was supported by an unrestricted grant from Boston Scientific, St. Paul, Minn.

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

ACC2014特集