高用量EPAによる心血管疾患予防 (LBS.01 Abstract 19515)

REDUCE-IT：高用量の高純度EPAを含むオメガ3脂肪酸製剤は心血管イベントのリスクを軽減する

REDUCE-IT: High dose of pure EPA in omega-3 drug cuts risk of cardiovascular events

EPAとして知られ高純度かつ安定した形のオメガ３脂肪酸は、スタチンを内服しても依然として心血管疾患リスクが高い患者における心血管疾患、心筋梗塞、および脳卒中による死亡リスクを軽減した、とAmerican Heart Association Scientific Sessions 2018で発表され、同時に*New England Journal of Medicine*に掲載された。REDUCE-ITトライアルの結果、イコサペント酸エチルが重大な心血管イベントを25%減少させ、うち20%は心血管疾患死の減少、31%はMIの減少であり、28%は脳卒中の減少であった。

Full Text

Results released from a major clinical trial may have direct implications for patients who remain at increased cardiovascular risk despite taking statin therapy. The trial, led by investigators at Brigham and Women's Hospital, has found that a drug developed by Amarin Corporation plc, icosapent ethyl – a pure and stable form of the omega-3 acid known as EPA – reduced the risk of death due to cardiovascular causes, myocardial infarction (MI), and stroke in this population.

The main results of the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) were presented by Deepak L. Bhatt, MD, MPH, executive director of Interventional Cardiovascular Programs at the Brigham and professor of medicine at Harvard Medical School, at the American Heart Association Scientific Sessions 2018 and published simultaneously in the *New England Journal of Medicine*.

"We are reporting a remarkable degree of risk reduction," said Bhatt. "We've found that icosapent ethyl reduced the risk of important cardiovascular events by 25 percent, including a 20 percent reduction in death due to cardiovascular causes, a 31 percent reduction in MI, and a 28 percent reduction in stroke. The REDUCE-IT trial sets a new standard of care for patients who have elevated triglycerides and are at increased cardiovascular risk despite statin therapy. This may be the biggest development in cardiovascular prevention since statins."

Icosapent ethyl is a prescription medication approved to reduce triglyceride levels in patients with very high triglycerides. Studies have suggested that icosapent ethyl may have additional attributes such as anti-inflammatory and cell membrane-stabilizing properties that may also contribute to reducing cardiovascular risk.

REDUCE-IT included more than 8,000 patients with well-controlled LDL-cholesterol who were taking statins to prevent a first or subsequent cardiovascular event. Approximately 70 percent of patients in the study had established atherosclerosis and the rest had diabetes plus at least one other cardiovascular risk factor. Patients had triglyceride levels that ranged from borderline high (135 mg/dL) to near very high (499 mg/dL). Patients were randomized to receive either 2 grams icosapent ethyl twice daily or a placebo and were followed for an average of approximately five years.

Hospitalization for chest pain, MI, procedures for coronary artery disease such as stenting, stroke, and cardiovascular death occurred in 17.2 percent of patients taking icosapent ethyl versus 22 percent of patients taking the placebo – an absolute risk reduction of 4.8 percent. The team also reported a significant 26 percent reduction in the trial's key secondary endpoint, which included cardiovascular death, nonfatal heart attack, or nonfatal stroke (11.2 percent for the icosapent ethyl group vs. 14.8 percent for the placebo group).

The researchers note that cardiovascular benefits appeared similar irrespective of patients' baseline levels of triglycerides or levels achieved after one year, suggesting that the cardiovascular risk reduction was not solely tied to achieving a more normal triglyceride level.

"The exact mechanisms responsible for the impressive benefits seen in the REDUCE-IT trial are not currently known," said Bhatt. "The significant effects on very different endpoints, such as cardiac arrest and stroke, suggest that this drug may have multiple biological mechanisms of action that have not been shown for any other therapy and cannot be generalized to other omega-3 products."

REDUCE-IT was sponsored by Amarin. Brigham and Women's Hospital receives research funding from Amarin for the work Bhatt did as the trial chair and as the international principal investigator.

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トピックス一覧

魚油およびビタミンDの経年による予防効果 (LBS.01 Abstract 19539)

VITAL：オメガ3脂肪酸およびビタミンDの心血管疾患およびがんのリスクに対する効果

VITAL: Effect of Omega-3 fatty acids and Vitamin D on risk of cardiovascular disease and cancer

オメガ３魚油は５年間の治療後に心筋梗塞（MI）リスクを28% 低下させたが脳卒中またはがんのリスクには効果がなかった、とAmerican Heart Association Scientific Sessions 2018で発表され、同時に*New England Journal of Medicine*に掲載された。この効果は魚の摂取量の少ない者において大（40% 減少）であった。さらに、ビタミンDはがん死を減少させ、それは治療開始1～2年後から認められた。VITALは、オメガ３脂肪酸の一次予防に関する初めての大規模試験である。

Full Text

For years, it's remained an open question: What effects do dietary supplements such as high doses of vitamin D or omega-3 fatty acids derived from fish oil have on the risk of diseases such as a myocardial infarction (MI), stroke and cancer? While there have been hints along the way, until now, no randomized clinical trial of a general population has been large enough to adequately address these questions.

Brigham and Women's Hospital investigators leading the VITamin D and OmegA-3 TriaL (VITAL) conducted a rigorous placebo-controlled trial over the course of 5.3 years, gleaning a treasure trove of information on the effects of both supplements. The team found that omega-3 fish oil reduced myocardial infarction (MI) rates but did not affect risk of stroke or cancer. In addition, vitamin D did not significantly affect MI, stroke or cancer incidence but was associated with a decrease in cancer deaths that started one to two years after participants began treatment.

Results from VITAL were presented by JoAnn Manson, MD, DrPH, chief of the Division of Preventive Medicine at the Brigham, at the American Heart Association Scientific Sessions 2018, and published simultaneously in the *New England Journal of Medicine*.

The VITAL study population was racially and ethnically diverse, and 20 percent of the participants were African American. The team found that the reduction of MI risk among those taking omega-3s was especially pronounced among African American participants, with a 77 percent reduction observed.

"VITAL is one of only a few randomized trials that has had a diverse study population" said Manson. "We found that omega-3s were associated with a reduction in risk of heart attacks across our study population, especially among participants who had lower than average fish intake (less than 1 1/2 servings per week). In addition, VITAL results showed that with time, vitamin D supplements may lower risk of cancer death. We plan to follow these participants for the next several years to see if this signal becomes stronger."

VITAL, a randomized, double-blind, placebo-controlled trial, enrolled 25,871 men and women age 50 and older from across the U.S. Eligible participants had no history of cancer, MI, stroke, or other forms of cardiovascular disease at the time of enrollment.

While earlier trials have examined whether fish oil or other supplements may prevent MI or stroke in patients with a history of heart disease or at very high risk of such disease, VITAL is the first large trial of omega-3 fatty acids for primary prevention of heart disease in a general population.

VITAL was designed to test the independent effects of vitamin D and omega-3 supplements, as well as to test for synergy between the two. Participants were divided into four groups: vitamin D (2000 IU/day of vitamin D [cholecalciferol]) plus omega-3s (1g/day of Omacor); vitamin D plus placebo omega-3s; omega-3s plus placebo vitamin D; and placebos for both.

Researchers compared those who received active omega-3s with those who received placebo. After a median of five years of treatment, 805 participants had suffered a major adverse cardiovascular event, such as an MI or stroke (386 in the omega-3 group and 419 in the placebo group). While these rates did not statistically differ, VITAL found a significant 28 percent reduction in risk of MI among participants taking the omega-3 fatty acid supplements (145 cases in the omega-3 group and 200 in the placebo group). This effect was greater among people who had lower fish intake (a 40 percent reduction). No significant differences were seen for cancer outcomes.

The research team also examined the effect of vitamin D on cancer rates. A total of 1,617 participants were diagnosed with cancer by the end of the study; 793 had been taking vitamin D and 824 had been taking the placebo, a non-significant difference. Rates of specific forms of cancer, including breast, prostate and colorectal cancer, did not differ significantly between groups. However, when the team examined rates after participants had been taking supplements for at least two years, they found that cancer deaths were significantly reduced by 25 percent among those taking vitamin D. No differences were seen for cardiovascular outcomes with vitamin D.

No serious side effects, such as bleeding, high blood calcium levels, or gastrointestinal symptoms were found with either supplement. The two supplements did not appear to interact with each other or have synergistic effects. In addition to cardiovascular disease and cancer outcomes, VITAL will report on the effects of vitamin D and omega-3s on rates of diabetes, cognitive function, autoimmune disease, respiratory infections, depression and more in the months ahead.

"Over the next six months, we will have even more results to share that may help clinicians and patients understand the benefits and risks of taking omega-3 and vitamin D supplements," said Manson. "Medical and public health authorities may look at the study results and decide if clinical guidelines should be updated. In the meantime, if you're already taking one or both of these supplements, there's no clear reason to stop. If you want to consider starting, our recommendation is to talk with your health care provider, but this does not need to be done on an urgent basis."

VITAL was supported by grants from the National Institutes of Health including support from the National Cancer Institute, National Heart, Lung and Blood Institute, Office of Dietary Supplements, National Institute of Neurological Disorders and Stroke, and the National Center for Complementary and Integrative Health. The ancillary studies are supported by grants from multiple Institutes. Pharmavite LLC of Northridge, California (vitamin D) and Pronova BioPharma of Norway and BASF (Omacor fish oil) donated the study agents, matching placebos, and packaging in the form of calendar packs. Quest Diagnostics (San Juan Capistrano, CA) measured several biomarkers at no cost to the study.

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糖尿病治療薬は心不全を予防する(LBS.02 Abstract 19485)

DECLARE-TIMI 58：SGLT-2阻害薬は心不全による入院を予防し腎疾患の進行を軽減する

DECLARE-TIMI 58: SGLT-2 inhibition prevents hospitalization for heart failure and reduces renal disease progression

選択的ナトリウム・グルコース共輸送体2 (SGLT-2) 阻害薬に対して、心血管アウトカムを評価したこれまでで最大のトライアルにおいて、多くの糖尿病患者においてダパグリフロジンが心不全による入院リスクを著明に低下させたことを明らかにした。この薬剤は血糖値を低下させ、心血管死および心不全による入院リスクを17% 低下させたが、これは心不全入院を27% 減少させたことによる。ダパグリフロジンはまた、腎アウトカムも改善した。この DECLARE-TIMI 58 の結果は、American Heart Association Scientific Sessions 2018 で発表され、同時に*New England Journal of Medicine* に掲載された。

Full Text

In the largest trial to date to assess cardiovascular outcomes for an important class of diabetes medications, researchers have found that dapagliflozin markedly reduced the risk of hospitalization for heart failure in a broad population of patients with diabetes. This benefit was seen across the study population, including in patients who did not have a history of myocardial infarction or heart failure.

Results of the Dapagliflozin Effect on CardiovascuLAR Events - Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial, sponsored by AstraZeneca, were presented by Stephen Wiviott, MD, a senior investigator in the TIMI Study Group and a cardiovascular medicine specialist at Brigham and Women's Hospital, during the American Heart Association Scientific Sessions 2018, and published simultaneously in the *New England Journal of Medicine*.

"When it comes to helping our patients control and manage blood glucose, the 'how' appears to be as important than the 'how much.' When choosing a therapy, trial results like these can help us make an informed decision about what treatments are not only safe and effective for lowering blood glucose but can also reduce risk of heart and kidney complications," said Wiviott. "DECLARE-TIMI 58 builds upon two other recent trials of SGLT2 inhibitors and shows that these drugs robustly and consistently improve heart and renal outcomes in a broad population of patients with diabetes."

Dapagliflozin, manufactured by the trial's sponsor AstraZeneca, is a selective sodium-glucose-co-transporter-2 (SGLT-2) inhibitor that blocks glucose resorption in the kidneys and promotes the elimination of excess glucose through the urine. Other SGLT-2 inhibitors have shown favorable cardiovascular effects, including a reduction in heart failure hospitalization, in patients with type 2 diabetes and established heart disease. The effectiveness of SGLT-2 inhibitors among a broader population of patients, including those not previously diagnosed with heart disease, was unclear before the current trial.

To evaluate the effects of dapagliflozin in patients with established heart disease as well as those with risk factors for heart disease, the Brigham's TIMI Study Group, in collaboration with the Hadassah Medical Organization, AstraZeneca, and others, conducted a randomized, double-blind, multi-national, placebo-controlled, phase 3b trial. Eligible participants were at least 40 years old and had type 2 diabetes. Researchers studied 17,160 participants, including 6,974 with established heart disease and 10,186 with multiple risk factors for heart disease. Participants received 10 mg of dapagliflozin daily or matched placebo.

The primary safety outcome was a composite of cardiovascular death, myocardial infarction or stroke (MACE). While dapagliflozin did not increase these events, it did not reduce the incidence in either patients with heart disease or with risk factors for heart disease. However, the drug did lower blood glucose levels throughout the trial and the composite of cardiovascular death and hospitalization for heart failure was reduced by 17 percent, driven by a 27 percent reduction in hospitalization for heart failure. The drug also improved renal outcomes, reducing a composite of several factors including end-stage renal disease and death due to renal failure.

The team saw no evidence of an increase in stroke, amputations or fracture, concerns raised from previous trials of this class of drugs. As is known for this class of medications, there was an increase in genital infection and in diabetic ketoacidosis, but the latter was a rare event and the excess was less than 1 in 1,000 individuals per year.

The TIMI Study Group Investigators also performed a meta-analysis combining the data from DECLARE-TIMI 58 and 2 other large trials of SGLT2 inhibitors. Several important patterns emerged: SGLT2 inhibitors reduce the risk of MACE by about 14 percent, but only in patients with existing atherosclerotic cardiovascular disease. In contrast, they robustly reduce the risk of hospitalization for heart failure by 31 percent and progression of renal disease by 45 percent, and these benefits were consistent regardless of a history of atherosclerotic cardiovascular disease or heart failure. These results are published simultaneously in the *Lancet*.

Marc S. Sabatine, MD, MPH, chair of the TIMI Study Group and a cardiovascular medicine specialist at the Brigham, said: "The cardiovascular outcomes trials to test the safety and efficacy of drugs for patients with diabetes have revolutionized our approach to this disease. Rather than simply focusing on changes in HbA1c, we can now use these data to select drugs that reduce the risk of important clinical events for our patients."

The TIMI study group of Brigham and Women's Hospital received a grant from AstraZeneca for the conduct of the DECLARE - TIMI 58 Trial. In addition, Drs. Wiviott and Sabatine report receiving consulting fees from AstraZeneca for participation in scientific advisory boards.

心疾患を有する糖尿病患者においてバイパス手術は血管形成術よりも優れている (LBS.06 Abstract 18609)

FREEDOM試験追跡結果:糖尿病および進行した心疾患を有する患者はバイパス手術を施行された方が血管形成術を施行されるよりも生存期間が長い

FREEDOM Follow-On: Patient with diabetes and advanced heart disease live longer after bypass surgery than angioplasty

糖尿病および多枝冠動脈疾患を有し、冠動脈バイパス術(CABG)で治療された患者は薬剤溶出性ステントを用いた血管形成術(PCI)で治療された同様の患者に比べ生存期間が3年長かった。8年間追跡された患者において、総死亡率はPCI群においてCABG群よりも有意に高かった(24.3% vs. 18.3%、P=0.01)。65歳未満のCABG群患者が、8年後もより多く生存していた。このFREEDOM試験の結果は、American Heart Association Scientific Sessions 2018で発表され、同時に*Journal of the American College of Cardiology*に掲載された。

Full Text

Patients who have diabetes and multivessel coronary artery disease that is treated with coronary-artery bypass grafting (CABG) survived about three years longer than similar patients who were treated with percutaneous coronary intervention with drug-eluting stents (PCI), researchers from the Icahn School of Medicine at Mount Sinai have found.

The mortality rate from all causes was significantly higher in the PCI group (24.31 percent) compared with the CABG group (18.3 percent) among 943 patients who were followed for eight years. More patients under 65 from the CABG group remained alive after eight years. This is the first study to demonstrate the long-term mortality benefit of CABG compared with PCI, a minimally invasive procedure commonly known as angioplasty, and to show that the greatest benefit is in patients under 65 years old.

Results of the FREEDOM Follow-on Study were presented as a late breaker at the American Heart Association Annual Scientific Sessions on Sunday, November 11, in Chicago and published simultaneously in the *Journal of the American College of Cardiology*.

The FREEDOM Follow-on Study is the final long-term follow-up report of the landmark FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial. After completion of the original FREEDOM trial in 2012, 25 international centers participated in the follow-on study.

Heart disease is the leading cause of morbidity and mortality in individuals with Type 2 diabetes.

"Treating people with diabetes and heart disease presents unique challenges due to increased risk for death, heart attack, and stroke," said the study's principal investigator, Valentin Fuster, MD, PhD, Director, Mount Sinai Heart, and Physician-in-Chief of The Mount Sinai Hospital. "The FREEDOM trial and Follow-on Study firmly establishes a standard of care for this high-risk population."

Although further advances in PCI have been made since the original FREEDOM trial, the data support CABG over PCI in patients with stable coronary artery disease and diabetes.

"These findings provide clear evidence that CABG plus standard medical therapy is the optimal treatment path for patients with diabetes and extensive coronary disease," said Michael Farkouh, MD, the Peter Munk Chair in Multinational Clinical Trials at the University of Toronto, adjunct scientist at the Icahn School of Medicine at Mount Sinai, and the co-principal investigator of the FREEDOM trial and FREEDOM Follow-on Study.

This study was funded by the Joseph and Vickey Safra Foundation.

Other Mount Sinai researchers who participated in the study included George Dangas, MD, PhD, Professor of Medicine (Cardiology) and Surgery at the Icahn School of Medicine and Director of Cardiovascular Innovation at the Zena and Michael A. Wiener Cardiovascular Institute, and Samin Sharma, MD, Director of Clinical and Interventional Cardiology, The Mount Sinai Hospital. Other institutions involved in this research include the University of Toronto.

意思決定支援ツールが心房細動の管理を改善する(LBS.03 Abstract 17685)

AF-ALERT：オンラインの臨床方針決定支援システムは心房細動患者の心血管イベント予防に対し強力なツールである

AF-ALERT: Online clinical decision support system is powerful tool for prevention of cardiovascular events in patients with atrial fibrillation

入院中の高リスク心房細動患者において、脳卒中予防のために抗凝固療法を増加させるようにデザインされた警告ベースのコンピュータ意思決定支援システム(CDS)により、重大な心血管有害イベントが減少する可能性がある、とのAF-ALERTトライアルの結果がAmerican Heart Association Scientific Sessions 2018で発表された。AFまたは心房粗動患者に対するこのプロバイダー向けの警告ベースCDSにより、90日後の死亡、MI、脳血管障害(脳卒中またはTIA)、および全身性塞栓症から成る複合アウトカムの割合が半減した。このコンピュータ警告はまた、90日間のMIおよび脳卒中頻度を、それぞれ87%および88%減少させた。

Full Text

An alert-based computerized decision support system that is designed to increase anticoagulation for stroke prevention in high-risk hospitalized atrial fibrillation (AF) patients may reduce major adverse cardiovascular events.

The AF-ALERT trial evaluated an alert-based computerized decision support (CDS) strategy to increase anticoagulation prescription among 457 hospitalized AF patients at high-risk for stroke. Results were presented during a Late Breaking Clinical Trials session at the American Heart Association Scientific Sessions 2018.

Researchers looked at 457 hospitalized high-risk patients (CHA2DS2-VASc score≥1) ≥21 years with AF or atrial flutter who were not prescribed anticoagulant therapy for stroke prevention. Patients were randomly assigned to an alert-based computerized decision support system vs. usual care.

This provider-directed, alert-based computerized decision support tool for hospitalized high-risk AF halved the rate of a composite outcome of death, MI, cerebrovascular accident (stroke or TIA), and systemic embolic event at 90 days.
The computer alert also reduced the frequencies of MI and stroke at 90 days by 87% and 88%, respectively.

The computer alert increased prescription of anticoagulation for stroke prevention in AF during hospitalization, at discharge, and at 90 days after randomization and encouraged the use of guideline-preferred direct oral anticoagulants.

"This alert-based computerized decision support strategy increased prescription of anticoagulation in hospitalized patients with AF who were not receiving antithrombotic therapy despite an increased risk of stroke." Says Gregory Piazza, MD, FACC of Brigham and Women's Hospital in Boston, MA, USA. He suggests that an alert-based CDS should be considered an indispensable tool to reduce major adverse cardiac events in patients with AF.

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糖尿病治療薬は心臓の構造を改善する (LBS.05 Abstract 19332)

EMPA-HEART：エンパグリフロジンは早期および臨床的に有意なリバースリモデリングを促進する

EMPA-HEART: Empagliflozin promotes early and clinically significant reverse remodeling

糖尿病治療薬エンパグリフロジンは、心疾患を有する2型糖尿病患者の心臓の構造を改善し得る重要な効果を有する、とAmerican Heart Association's Scientific Sessions 2018で発表された。EMPA-HEART CardioLink-6試験は、心血管疾患歴を有する2型糖尿病患者の左室構造および機能へのエンパグリフロジンの効果をMRI検査を用いて6か月間調査した、初めてのランダム化、二重盲検、並行群間試験である。エンパグリフロジンを投与されると、心臓MRIで評価した左室重量が有意に減少した。

Full Text

A study led by St. Michael's Hospital researchers, and presented at a late-breaker session at the American Heart Association meeting in Chicago, indicates that the diabetes medication empagliflozin has important effects that can improve cardiac structure in people with Type 2 diabetes who also have heart disease.

"Empagliflozin is used to reduce glucose in diabetes patients, but it also has profound cardiovascular benefits," said Dr. Subodh Verma, cardiac surgeon-scientist and director of the CardioLink platform at the Keenan Research Centre for Biomedical Science of St. Michael's Hospital, Toronto, Canada.

"The reasons why this medication results in profound reductions in death and heart failure are largely unknown," added Dr. Verma, who led the EMPA-HEART CardioLink-6 trial. "And whether it can directly and favorably remodel the heart has been an important unanswered question."

EMPA-HEART is the first randomized, double-blind, parallel group study to investigate the effect of empagliflozin on the structure and function of the left ventricle in individuals with Type 2 diabetes and a history of cardiovascular disease, using MRI testing over a six-month period.

The study found that when the subjects were given empagliflozin, it caused a significant regression in left ventricular mass index. The left ventricular mass index was assessed using cardiac MRI, the gold standard method for evaluating heart function.

The EMPA-HEART team included many physicians and scientists from St. Michael's, including Dr. Kim Connelly, Dr. Andrew Yan, Dr. David Mazer, Dr. David Fitchett, Dr. Peter Juni, director of the Applied Health Research Centre (AHRC), and Adrian Quan, research manager the CardioLink platform. It is the sixth CardioLink clinical trial. The late-breaker sessions are used for presentations deemed too important to wait for the next AHA meeting.

"The results are truly impressive, since they were observed on top of excellent standard of care and seen within a very short period of time," said Dr. Connelly, one of the co-principal investigators of the EMPA-HEART study. Dr. Mazer added that the data "provide important clues as to how this medication is working, and how it may prevent heart failure in people with Type 2 diabetes."

Boehringer Ingelheim, a pharmaceutical company that manufactures empagliflozin, provided an unrestricted grant to conduct the EMPA-HEART study and the empagliflozin compound used in the study.

アンジオテンシン受容体ネプリライシン阻害薬はACE阻害薬より優れている (LBS.05 Abstract 19328)

PIONEER-HF：sacubitril/バルサルタンは安定した急性心不全のバイオマーカーを改善させる

PIONEER-HF: Sacubitril/valsartan shows biomarker benefit in stabilized acute heart failure

慢性心不全患者に使用される薬物療法は、急性心不全で入院した患者の予後不良マーカーをも改善する、と*New England Journal of Medicine*に掲載され、American Heart Association Scientific Sessions 2018で発表された。アンジオテンシン受容体ネプリライシン阻害薬sacubitril/バルサルタンを内服している患者において、バイオマーカーNT-proBNPは標準治療を行われた患者よりも迅速に低下した。改善の徴候は、1週間と早い段階で認められた。他のバイオマーカーもまた、sacubitril/バルサルタンにより改善した。この結果は、この薬剤が急性に悪化した心不全患者の予後を改善し得ること、およびこれらの患者の標準治療となり得ることを示唆している。

Full Text

A drug therapy used for patients with chronic heart failure also improves markers of poor prognosis in individuals who are hospitalized with acute heart failure, new Yale-led research shows. The findings suggest that the drug can improve outcomes for acutely ill heart patients and potentially become the new standard of care for treating this serious condition, the researchers said.

The study was published in the *New England Journal of Medicine*, and presented at the American Heart Association Scientific Sessions 2018.

Acute heart failure is the leading cause of hospitalizations for older adults. Affected individuals experience high rates of re-hospitalization and death. The standard of care, which consists of diuretics and medications that enhance blood flow, has remained largely unchanged for decades.

To test whether sacubitril-valsartan could improve outcomes for individuals with acute heart failure, the research team conducted a randomized, double-blind clinical trial called PIONEER-HF. More than 800 patients hospitalized with heart failure at 129 U.S. sites were treated with either sacubitril-valsartan or the standard therapy, enalapril, an ACE inhibitor. Over the trial period of eight weeks, the researchers monitored participants' blood pressure and other safety parameters, such as kidney function, and analyzed blood and urine samples.

The research team found that in patients taking sacubitril-valsartan, levels of a key measure of heart failure severity – NT-proBNP – reduced more quickly than with the standard therapy. Evidence of improvement was observed as early as one week into the trial, they said.

"It worked to reduce NT-proBNP rapidly and to a greater extent than enalapril," said corresponding author Eric Velazquez, M.D., the Berliner Professor of Cardiology at Yale School of Medicine and PIONEER-HF principal study investigator. "There were multiple markers including troponin T, a marker of heart cell injury, that suggested substantial improvement."

Velazquez and his co-authors also reported no significant differences between the two therapies in terms of safety, including impact on renal function, blood pressure, and other indicators. "The results of this landmark study should help inform our basic approach to treating hospitalized patients with acute heart failure," said Velazquez. "Once acute heart failure is diagnosed, patients are stabilized, and a low ejection fraction is confirmed, sacubitril/valsartan should be started promptly to reduce NT-proBNP and reduce the risk of post-discharge heart failure hospitalization."

Combined with results of a previous trial, PARADIGM-HF, which showed the drug's effectiveness for patients with chronic heart failure, these findings could make sacubitril-valsartan the go-to standard of care for acute and chronic heart failure, said the researchers.

"There are consistent results from both trials," Velazquez said. "It is safe and there's a rapid outcome. If it becomes the standard, we are likely to reduce the risk of hospitalization for heart failure, and that will have a positive clinical impact and societal impact."

Other study authors are David A. Morrow, Adam D. DeVore, Carol I. Duffy, Andrew P. Ambrosy, Kevin McCague, Ricardo Rocha, and Eugene Braunwald.

PIONEER-HF was supported by Novartis Pharmaceuticals Corporation, which conducted the trial in collaboration with the Duke Clinical Research Institute and the Thrombolysis in Myocardial Infarction Study Group.

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メトトレキサートは心血管イベントを減少させない (Abstract LBCT-17778)

CIRT：低用量のメトトレキサートは二次予防において炎症または心血管イベントを減少させなかった

CIRT: Low dose methotrexate fails to reduce inflammation or cardiovascular events in secondary prevention

炎症軽減による心疾患および脳卒中リスク軽減と言えば、待望のCIRT試験の結果、リスクを有する患者において適切な炎症経路を標的とすることが重要であることが示された。昨年、CANTOS試験において、インターロイキン-1β阻害薬カナキヌマブが特定の炎症経路を標的とし、その後心筋梗塞および心血管死率を低下させることが示された。対照的に、CIRT試験の結果、低用量メトトレキサートは、この炎症経路は阻害せずまた主要な心血管イベント率も低下させないことが示された。この結果は、American Heart Association Scientific Sessions 2018で発表され、*New England Journal of Medicine*に掲載された。

Full Text

When it comes to reducing inflammation to decrease the risk of heart disease and stroke, results from the much-anticipated Cardiovascular Inflammation Reduction Trial (CIRT) indicate that targeting the right inflammatory pathways in at-risk patients is crucial. Last year, the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) showed that the interleukin-1β inhibitor canakinumab both targeted a specific inflammatory pathway and consequently lowered rates of myocardial infarction (MI) and cardiovascular death. By contrast, the findings from CIRT showed that low-dose methotrexate neither inhibited that same inflammatory pathway nor reduced major adverse cardiovascular event rates.

These results were presented by Paul Ridker, MD, director of the Center for Cardiovascular Disease Prevention at Brigham and Women's Hospital, during the American Heart Association Scientific Sessions 2018, and published simultaneously in The *New England Journal of Medicine*.

"The contrasting results between these two contemporary clinical trials demonstrate the importance of considering the mechanistic diversity of inflammatory pathways and of approaches to their inhibition," said Ridker. "Understanding these differences will be crucial for future studies targeting inflammation in atherosclerosis."

Prior to CIRT, observational studies had suggested that low-dose methotrexate, an inexpensive and effective drug widely used to treat rheumatoid arthritis and other inflammatory diseases, might reduce rates of cardiovascular events. The federally-funded CIRT was designed to rigorously test whether low-dose methotrexate could effectively reduce risk of major adverse cardiovascular events - that is, MI, stroke and cardiovascular death.

In parallel, Ridker and colleagues also designed and conducted CANTOS, sponsored by Novartis, to test the same outcomes for canakinumab, a drug that specifically targets interleukin-1β. Interleukin-1 is a pro-inflammatory cytokine that, if over-produced, results in increased inflammation throughout the body as well as elevated levels of interleukin-6 and high sensitivity C-reactive protein (hsCRP), two critical biomarkers of inflammation.

CIRT and CANTOS were both randomized, double-blind, placebo-controlled trials, and both enrolled stable but high-risk atherosclerosis patients. CANTOS, however, was designed to include only patients with persistently elevated hsCRP levels. CIRT did not employ this criterion, and the average hsCRP level for the population was well within the normal range. CIRT enrolled 4,786 North American patients with prior heart attack or multi-vessel coronary disease who additionally had either type 2 diabetes or a metabolic syndrome. The trial stopped after a median follow-up of 2.3 years.

Unlike canakinumab as used in CANTOS, low-dose methotrexate as used in CIRT did not reduce the inflammatory pathway leading from interleukin-1 to interleukin-6 and on to hsCRP. Concordantly, and in contrast to canakinumab, low-dose methotrexate did not lower cardiovascular event rates compared to placebo. The team reports that 201 patients taking methotrexate suffered a major cardiovascular event compared to 207 patients taking the placebo. Yet, methotrexate was associated with elevations of liver enzymes, reductions in leucocytes and hematocrit, and a higher incidence of non-basal cell skin cancers.

"The results from CIRT and CANTOS, when considered together, tell us something critically important: Not all inflammation is the same, and not all drugs that target inflammation are the same," said Ridker. "While it is disappointing that an inexpensive drug like methotrexate did not have the effects we previously saw in CANTOS, the results from CIRT shed crucial light on the underlying biology that connects inflammation with cardiovascular disease. The divergent trial results provide a clear roadmap to guide our efforts going forward."

Despite its wide clinical use, the biological mechanisms underlying the anti-inflammatory effects of methotrexate in rheumatoid arthritis and other inflammatory conditions remains poorly understood. Drugs such as colchicine and oral NLRP3 inhibitors that may intersect with the interleukin 1 to interleukin-6 to CRP pathway are currently under investigation or in development.

"CANTOS and CIRT provide the cardiovascular community proof-of-principle that specific targeting of the interleukin-1 to interleukin-6 pathway of innate immunity is crucial for preventing atherothrombotic events. The research goal now and the clinical need of our patients is to find inexpensive and widely applicable agents that can safely target this pathway," Ridker said.

Ridker and co-authors received investigator-initiated grants from the National Heart Lung and Blood Institute to conduct CIRT. They also received an investigator-initiated grant from Novartis to conduct CANTOS. Ridker is listed as a co-inventor on patents held by Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes that have been licensed to AstraZeneca and Siemens, and has served as a consultant to Novartis and Inflazome. Co-authors have received compensation for their site efforts enrolling participants into the trial.

This research was supported by the NIH/National Heart Lung and Blood Institute and Novartis.

Cardiology特集

AHA2018 (第91回米国心臓病協会)

トピックス一覧

エゼチミブは一次予防目的の標準治療として最良である(Abstract 17581)

EWTOPIA 75：日本人高齢患者における動脈硬化性疾患の一次予防目的としてエゼチミブは標準治療よりも優れている

EWTOPIA 75: Ezetimibe better than standard care for primary prevention of atherosclerotic disease in elderly Japanese patients

コレステロール吸収阻害薬エゼチミブで治療された高齢患者は、標準治療を受けた患者に比べ動脈硬化性心血管イベントのリスクが有意に低かった。EWTOPIA 75試験は、高LDLコレステロール値（≧140 mg/dL）で心血管疾患歴を有さない患者3,796人を、栄養指導を受けエゼチミブを内服するまたはしない群に組み入れた。両群とも5年にわたりLDLコレステロールが低下したが、エゼチミブ治療群で低下度が高かった（p<0.001）。エゼチミブは心血管イベント（突然死、心筋梗塞、PCIまたはCABG、および／または脳卒中、p=0.002）を有意に予防した。この結果は、American Heart Association Scientific Sessions 2018で発表された。

Full Text

Elderly patients treated with the cholesterol-absorption inhibitor ezetimibe had a significantly lower risk of atherosclerotic cardiovascular events over 5 years when compared with patients who received standard care, according to the results of the EWTOPIA 75 trial presented at a Late Breaking Science session at the American Heart Association 2018 Scientific Sessions.

The EWTOPIA 75 trial was a multicenter, prospective, open-label randomized controlled trial in Japan. It evaluated the effect of lipid-lowering therapy by ezetimibe on the primary prevention of atherosclerotic cardiovascular disease (ASCVD) events in 3,796 old-old patients (75 years or older) with elevated LDL-cholesterol level (≥ 140 mg/dL) and no history of cardiovascular disease. Mean patient age was 80.7 years, and 74% of the population was female. Patients in the study received dietary counseling with or without a daily dose of ezetimibe 10 mg.

Both groups saw reductions in LDL cholesterol over 5 years, but there was a larger reduction observed in the ezetimibe-treated patients. For those treated with ezetimibe, LDL cholesterol was reduced from 161.3 to 120.1 mg/dL, while patients just counselled on diet reduced their LDL levels from 162.0 to 131.4 mg/dL (P < 0.001 for interaction).

Lowering LDL cholesterol by ezetimibe monotherapy significantly prevented ASCVD events (sudden cardiac death, MI, PCI or CABG, and/or stroke, hazard ratio 0.66, p=0.002).

The study was led by Yasuyoshi Ouchi, M.D., Ph.D., Tokyo Metropolitan Institute of Gerontology, Japan. Dr. Ouchi reports no relevant conflicts of interest.

PTSDは心停止後のリスクを上昇させる (American Heart Association's Resuscitation Science Symposium 2018, Abstract 13)

心的外傷後ストレス障害は心停止後1年の合併症や死亡増加と関連がある

Post-traumatic stress disorder linked to increased complications and death a year after cardiac arrest

心的外傷後ストレス障害（PTSD）症状は心停止経験者の主要心血管イベントおよび死亡のリスクを、初回医学的危機後最長1年間有意に上昇させる可能性があるとの予備的研究結果が、American Heart Association's Resuscitation Science Symposium 2018で発表された。軽度から中等度の脳傷害を負った連続114人の患者のうち、31.6%が退院時（心停止後平均21日後）に心停止によるPTSDと診断された。1年以上の追跡期間中に、8.8%が死亡し、25.4%が心筋梗塞、重症狭心症、心不全または緊急血行再建術施行、あるいは除細動／ペースメーカー植込みによる入院などの重大な心血管有害イベントを再発した。

Full Text

Post-traumatic stress disorder (PTSD) symptoms may significantly increase cardiac arrest survivors' risk of major cardiovascular events and death up to a year after the initial medical crisis, according to preliminary research presented at the American Heart Association's Resuscitation Science Symposium 2018 – an international conference highlighting the best in cardiovascular resuscitation research. The Resuscitation Science Symposium is part of the American Heart Association's Scientific Sessions 2018.

PTSD, which is common following cardiac arrest, was associated with a three-fold increased risk of death from any cause or a major heart event in a review of 114 patients who had been resuscitated after in-hospital or out-of-hospital cardiac arrest between 2015 and 2017.

Of 114 consecutive patients who survived with mild to moderate brain injury, 36 (31.6 percent) were diagnosed with cardiac-arrest-induced PTSD at discharge, which was an average of 21 days after the cardiac arrest. During the follow up of more than a year, 10 patients (8.8 percent) died and 29 (25.4 percent) experienced a recurrent major adverse cardiovascular event, such as rehospitalization due to myocardial infarction, severe angina, heart failure or an emergency revascularization procedure or defibrillator/pacemaker implantation.

The primary author is Sachin Agarwal, M.D., MPH of Columbia University Medical Center, New York, NY.

Researchers recommend further study to understand the underlying mechanisms.

冠動脈石灰化は冠動脈リスクの優れた予測因子である(AHA 2018)

冠動脈石灰化レベルは冠動脈疾患リスク患者の優れた予測因子である

Coronary calcium levels a better predictor of patients at risk for coronary heart disease

American Heart Association Scientific Session 2018で発表された新たなスタディの結果、冠動脈石灰化レベルを検査することは、今日の臨床で用いられている標準的なリスク評価式よりも、心筋梗塞のリスクである冠動脈狭窄および血行再建術の必要性を予測する優れた予測因子であることが明らかにされた。冠動脈石灰化計測値（MESAスコアおよび冠動脈石灰化リスクスコアなど）を含む計算式は、年齢、性別、血圧、およびコレステロール計測値などの標準的なリスクファクターのみに依存するPooled Cohort Equationよりも血行再建術を要する症候性冠動脈疾患の存在を予測する能力が優れていた。

Full Text

A new study presented at the American Heart Association Scientific Session 2018 conference found that testing a patient's coronary calcium levels is a better predictor of blocked coronary arteries at risk for a myocardial infarction (MI) and the need for revascularization than standard risk-assessment equations used in medical practice today.

"With coronary calcium, we're looking at a marker indicating the actual presence of anatomic disease – we're not just looking at probabilities of disease based on a patient's standard risk factors," said Jeffrey L. Anderson, MD, a cardiologist and cardiovascular researcher at the Intermountain Medical Center Heart Institute in Salt Lake City, Utah. "The risk factors are worth knowing, but they don't tell whether or not you actually have the disease."

In the new study, researchers at the Intermountain Medical Center Heart Institute identified 1,107 symptomatic patients who presented to the healthcare system without any known coronary artery disease and who had a PET-stress test to measure coronary flow, conducted as part of their diagnostic evaluation.

The PET/CT test also enabled a coronary calcium score to be measured. Based on the coronary calcium score and standard risk factors documented in their medical records, three different atherosclerotic cardiovascular disease risk scores were calculated: the standard Pooled Cohort Equation (based on traditional risk factors), the Multi-Ethnic Study of Atherosclerosis (MESA) Risk Score (which combines coronary calcium and traditional risk factors), and the Coronary Calcium Score alone

Researchers tracked those patients to identify who, based on PET scan results suggesting a blocked artery, went on to revascularization and who had a subsequent MI or died during the subsequent two years.

They found that risk equations that included coronary artery calcium measurements, i.e., the MESA Score and the Coronary Calcium Risk Score, were better able to predict the presence of symptomatic coronary artery disease requiring revascularization than the Pooled Cohort Equation, which relies only on standard risk factors such as age, gender, blood pressure, and cholesterol measurements.

However, after the PET-scan results were acted upon, all three equations were only moderately successful in determining who over two years of follow-up would go on to die or have a heart attack. Noteworthy though was that of the 29 patients who showed no coronary artery calcium, none had any major heart problems in the time-period tracked.

Researchers presented results from the study at the American Heart Association's 2018 Scientific Session in Chicago.

"Calcium in the artery doesn't tell you the extent of soft plaque, but it does mark that disease is present," Dr. Anderson said. "These results tell us that coronary calcium adds importantly to probability estimates."

He also said the cost of coronary calcium screening is low, in the range of $100 or less, and should be considered in the future as part of routine medical care after age 50 for men and 55-60 for women.

"We accept that mammograms should be done for women and colonoscopies should be done for everybody at a certain age, and they're much more expensive than a calcium scan," he said.

Dr. Anderson hopes the findings lead to coronary calcium tests becoming more accepted as a means to better predict who is at coronary risk, which not only will get high-risk patients into treatment earlier, but also keep patients who aren't truly at risk from being overtreated.

慢性的な騒音への曝露は心血管リスクを上昇させる(Abstract PR.APS.02)

慢性的な騒音への曝露と心血管リスク上昇との関連の背景にあるメカニズムが明らかにされた

Scientists identify mechanism behind relationship between chronic noise exposure and elevated cardiovascular risk

環境騒音への曝露は、ストレス反応に関連する脳領域の活動を刺激することにより心筋梗塞(MI)および脳卒中のリスクを上昇させるようである、との予備研究の結果がAmerican Heart Association Scientific Sessions 2018で発表された。慢性的な騒音への曝露レベルが最大(高速道路や空港)の人々は、扁桃体活性が高く動脈内の炎症がより多かった。注目すべきことに、これらの人々は、騒音への曝露レベルが低い人々に比べ、他のリスクファクターに関係なくMIまたは脳卒中および他の重大な心血管イベント発症リスクも3倍以上高かった。

Full Text

Exposure to environmental noise appears to increase the risk of myocardial infarctions (MI) and strokes by fueling the activity of a brain region involved in stress response. This response in turn promotes blood vessel inflammation, according to preliminary research presented at the American Heart Association's Scientific Sessions 2018, a premier global exchange of the latest advances in cardiovascular science for researchers and clinicians.

The findings reveal that people with the highest levels of chronic noise exposure – such as highway and airport noise – had an increased risk of suffering cardiovascular events such as MI and strokes, regardless of other risk factors known to increase cardiovascular risk.

The results of the study offer much-needed insight into the biological mechanisms of the well-known, but poorly understood, interplay between cardiovascular disease and chronic noise exposure, researchers said.

"A growing body of research reveals an association between ambient noise and cardiovascular disease, but the physiological mechanisms behind it have remained unclear," said study author Azar Radfar, M.D., Ph.D., a research fellow at the Massachusetts General Hospital in Boston. "We believe our findings offer an important insight into the biology behind this phenomenon."

Researchers analyzed the association between noise exposure and major cardiovascular events, such as heart attacks and strokes, among 499 people (average age 56 years), who had simultaneous PET and CT scan imaging of their brains and blood vessels. Diagnostic validation was done in a subset of 281 subjects.

All participants were free of cardiovascular illness and cancer at baseline. Using those images, the scientists assessed the activity of the amygdala - an area of the brain involved in stress regulation and emotional responses, among other functions. To capture cardiovascular risk, the researchers examined the participants' medical records following the initial imaging studies. Of the 499 participants, 40 experienced a cardiovascular event (e.g., MI or stroke) in the five years following the initial testing.

To gauge noise exposure, the researchers used participants' home addresses and derived noise level estimates from the Department of Transportation's Aviation and Highway Noise Map.

People with the highest levels of noise exposure had higher levels of amygdalar activity and more inflammation in their arteries. Notably, these people also had a greater than three-fold risk of suffering an MI or a stroke and other major cardiovascular events, compared with people who had lower levels of noise exposure. That risk remained elevated even after the researchers accounted for other cardiovascular and environmental risk factors, including air pollution, high cholesterol, smoking and diabetes.

Additional analysis revealed that high levels of amygdalar activity appears to unleash a pathway that fuels cardiac risk by driving blood vessel inflammation, a well-known risk factor for cardiovascular disease.

The researchers caution that more research is needed to determine whether reduction in noise exposure could meaningfully lower cardiovascular risk and reduce the number of cardiovascular events on a population-wide scale.

In the meantime, however, the new study findings should propel clinicians to consider chronic exposure to high levels of ambient noise as an independent risk factor for cardiovascular disease.

"Patients and their physicians should consider chronic noise exposure when assessing cardiovascular risk and may wish to take steps to minimize or mitigate such chronic exposure," Radfar said.

Co-authors are: Michael T. Osborne, M.D.; Brian Tung, M.S.; Tomas Patrich, B.A.; Blake Oberfeld, B.S.; Ying Wang, M.D.; Roger Pitman, M.D.; and Ahmed Tawakol, M.D.

This work was in-part funded by the National Institutes of Health and by the American Heart Association.