うつ病の重症度が心疾患リスクを増大させる (Poster presentation Sa3055)

うつ病の重症度と心血管疾患との強力な関連が認められた

Strong link found between level of severity of depression and cardiovascular disease

うつ病の重症度が心疾患または脳卒中の発症率を上昇させる可能性がある、との予備研究の結果がAmerican Heart Association's Scientific Sessions 2019で発表された。米国国民健康栄養調査（NHANES）において解答されたうつ病アンケートを用いて、うつ病と診断された成人11,000人超が同定された。そのうちの約1,200人が、心疾患または脳卒中の診断を受けている、と報告した。うつ病と非致死性心疾患および脳卒中との関連を定量化した解析によると、うつ病レベル（軽症、中等症、やや重症または重症）が上がる毎に、非致死性心疾患または脳卒中の確率が24%上昇した。

Full Text

The severity of a person's depression may increase their odds of having heart disease or stroke, according to preliminary research presented at the American Heart Association's Scientific Sessions 2019 — November 16-18 in Philadelphia.

"Cardiovascular diseases are impacted by and related to a variety of aspects of health and well-being including mental health," said study author Yosef M. Khan, M.D., Ph.D., M.P.H., national director of Health Informatics and Analytics for the American Heart Association in Dallas, Texas. "We found that the level of depression was strongly tied to living with heart disease and stroke, even after accounting for other factors that could impact risk, including the American Heart Association's Life's Simple 7 and variables of age, income, education, sex and race/ethnicity."

Researchers examined the connection between depression and non-fatal heart disease such as heart failure, coronary heart disease, angina, myocardial infarction or stroke in U.S. adults age 20 years and older. Using depression questionnaires completed in National Health and Nutrition Examination Surveys (NHANES), more than 11,000 adults diagnosed with depression were identified. This represents 231 million adults in the general population. Of these, about 1,200 people (translated to 20 million in the general population) said they had been diagnosed with heart disease or stroke.

An analysis to quantify the link for depression and non-fatal heart disease and stroke found that the odds increased by 24% with each additional level increase of depression — mild, moderate, moderately severe or severe.

"The implications of such an increase are vast," Khan said. "By understanding the relationship and degree of impact we can properly identify, prevent, treat and create policies and strategies to help decrease cardiovascular diseases and improve lives by tackling mental health and heart disease together."

More studies are needed to determine if depression causes cardiovascular disease or cardiovascular disease causes depression, according to the authors.

Co-authors are Remy Poudel, M.P.H., M.S., and Kim Stitzel, M.S., R.D. Author disclosures are in the abstract.

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女性のストレスに対する反応が心血管リスクを増大させる(Oral presentation RF229)

心理的ストレスは心疾患を有する女性の重篤な心血管イベントリスクを増大させる可能性がある

Psychological stress may increase risk for a serious cardiovascular event in women with heart disease

心疾患を有する女性の心理的ストレスへの反応の仕方は心筋梗塞および他の心血管イベントリスクを増大させるが、これは男性には当てはまらないようである、とAmerican Heart Association's Scientific Sessions 2019で発表された。ストレス反応においてIL-6バイオマーカーが1単位上昇する毎に、女性における主要な心関連イベントは41%上昇したが、このバイオマーカーの上昇によるリスク増大は男性においては認められなかった。ストレス反応においてMCP-1バイオマーカーが10単位上昇する毎に、女性においてのみ主要な心関連イベントが13%上昇した。

Full Text

The way women with heart disease respond to psychological stress puts them at increased risk for myocardial infarction (MI) and other cardiovascular events, yet the same doesn't appear to be true for men, according to preliminary research presented at the American Heart Association's Scientific Sessions 2019 — November 16-18 in Philadelphia.

Stress is known to increase inflammation throughout the body, which may contribute to heart disease risk, as well as heart attacks and other major cardiovascular events.

Researchers measured changes in inflammatory biomarkers in blood that are associated with stress in 615 men and women (average age of 63, 25% women) with stable heart disease before and after a psychologically stressful activity. To induce stress, participants were given a short speech test including two minutes of preparation time and three minutes of speaking.

The known inflammatory biomarkers interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1) and matrix metallopeptidase-9 (MMP-9) were measured in participants while they were at rest before the speech and then again 90 minutes after their speech to give the body time to produce and release inflammatory molecules into the circulatory system.

Researchers then tracked participants for a median follow-up of three years, during which time 82 participants (13%) either died, had MIs, were treated for unstable angina or had heart failure.

While there were no significant associations between inflammatory response to stress and risk of major cardiovascular events in the overall sample, there were sex-based interactions for some specific biomarkers, specifically:

- Each unit increase in the IL-6 biomarker in response to stress was associated with a 41% higher risk of major heart-related events among women, yet there was no increased risk for major cardiovascular events among men with increases in this biomarker.
- Each 10-unit increase in the MCP-1 biomarker in response to stress was associated with a 13% increase in risk of a major heart-related event among women only.

These findings align with prior research showing women with existing heart disease have distinct biological responses to stress that may increase their risk of major cardiovascular events compared to men.

"In clinical care, the role of psychosocial stress, or stress during daily life, is often under-recognized and has not yet been incorporated in cardiovascular risk prevention guidelines," said study author Samaah Sullivan, Ph.D., an instructor in epidemiology at Emory University's School of Public Health in Atlanta, Georgia.

"We hope health professionals can advise patients with heart disease, particularly female patients, about the importance of reducing stress through suitable interventions or techniques and refer patients for appropriate mental health care and support."

Co-authors are An Young, M.D., M.P.H.; Muhammad Hammadah, M.D.; Bruno B. Lima, M.D., Ph.D.; Yi-An Ko, Ph.D., M.S.; Brad D. Pearce, Ph.D.; Amit J. Shah, M.D., M.S.C.R.; Jeong Hwan Kim, M.D.; Kasra Moazzami, M.D., M.P.H.; Nancy Murrah, R.N., B.S.N.; Emily G. Driggers, M.A.; Belal Kaseer, M.D.; Oleksiy Levantsevych, M.D.; Ammer Haffar; Laura Ward, M.S.P.H.; Allison Hankus, B.S.; Tene T. Lewis, Ph.D.; Puja K. Mehta, M.D.; J. Douglas Bremner, M.D.; Paolo Raggi, M.D.; Arshed A Quyyumi, M.D.; and Viola Vaccarino, M.D., M.P.H. Author disclosures are in the abstract.

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週末の突然の心停止は死亡率が高い (Abstract 128)

週末に心停止を来した患者は生存入院率が低い

People suffering cardiac arrest on the weekend are less likely to survive to hospital admission

週末に心停止を来した者は、これを平日に来した者に比べ生存入院率が低い、とAmerican Heart Association's Resuscitation Science Symposium 2019で発表された。英国の研究者らは、院外で突然の心停止を来し公共施設の自動体外式除細動器（AED）で処置された患者が、"生存して入院する"ことについて調査した。土曜日の午前1時から日曜日午後11時59分の間に心停止を来した者は、月曜日から金曜日までに心停止した者に比べ、生存率が20%低かった。また、生存率は自宅で心停止を来した場合や患者が高齢である場合は低下した。

Full Text

People who experience cardiac arrests over the weekend are less likely to survive long enough to be admitted to a hospital, compared to those who had the same medical event on a weekday, according to preliminary research presented at the American Heart Association's Resuscitation Science Symposium 2019 — November 16-17 in Philadelphia.

U.K. researchers investigated "survival-to-hospital admission" for patients who suffered an out-of-hospital sudden cardiac arrest and were treated by a publicly accessible automated external defibrillator (AED). They analyzed data of nearly 3,000 patients worldwide and noted that 27% survived to hospital admission, in line with other independent studies. Overall, researchers found that patients who suffered a cardiac arrest between 12 a.m. Saturday to 11:59 p.m. Sunday were about 20% less likely to survive than those patients who suffered a cardiac arrest between Monday and Friday. Survival also decreased for cardiac arrests occurring at home and as the patient's age increased.

"It is often said that sudden cardiac arrest can happen to anyone, anytime, anywhere. These results suggest that there is an opportunity to address sudden cardiac arrests that occur during the weekend by improving AED awareness, availability and training and quick response by rescuers," said Hannah Torney, the study's lead author, who is studying for her Ph.D. at Ulster University in Northern Ireland and is a clinical engineer at HeartSine Technologies/Stryker in Belfast, Northern Ireland.

Researchers noted weekend survival may be reduced because individuals may be less likely to be near a publicly accessible AED and their sudden cardiac arrests may not be witnessed. They added that this data analysis could help guide the strategic placement of AEDs to improve accessibility.

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早期閉経は複数の心疾患リスクを増大させる可能性がある(Poster Presentation MDP451)

早期閉経歴を有する女性に対し医師は推定される将来的な心疾患リスクを精査すべきである

History of premature menopause should prompt physicians to refine the patient's estimated future risks for heart disease

40歳前に閉経した女性は複数の心疾患リスクが高い、とAmerican Heart Association's Scientific Sessions 2019のポスターセッションで発表された。平均7年間の追跡期間中、早期閉経を来した女性は、従来のリスクファクターを考慮しても、冠動脈疾患、心不全、大動脈弁肥厚および狭窄、心房細動、さらに深部静脈血栓症のリスクが有意に高かった。心疾患リスクは、自然閉経よりも手術により閉経した女性で高かった。このリスクの差の一部は、心血管疾患リスクファクターの違いで説明できる可能性がある。

Full Text

Women who experience menopause before age 40 are at higher risk for several heart conditions, according to preliminary research presented at the American Heart Association's Scientific Sessions 2019 — November 16-18 in Philadelphia.

In the largest, single study to-date of diverse heart disease risks relative to age at menopause, researchers used the UK Biobank to examine data on more than 144,000 postmenopausal women (average age 60), including about 4,900 women who experienced menopause "naturally" (i.e., spontaneously) before age 40 and about 640 who entered menopause before age 40 after oophorectomy.

During an average of seven years of follow-up, researchers found:

- Women who had experienced premature menopause were significantly more likely to develop conventional heart disease risk factors, such as hypertension, high LDL-cholesterol, and Type 2 diabetes.
- Even after accounting for conventional risk factors, women with premature menopause still had a significantly increased risk of coronary artery disease, heart failure, thickening and narrowing of the aortic valve, atrial fibrillation, and deep vein thrombosis.
- The heart disease risks were higher for women who experienced menopause due to surgery compared to natural menopause. Some of this risk difference may be explained by differences in cardiovascular disease risk factors.
- Whether or not a woman took hormones for menopausal symptoms did not change the cardiovascular risks.
- Menopausal age prior to age 50 had a dose-dependent effect on cardiovascular disease risk, meaning risk continued to increase with younger menopausal ages.
- Increased cardiovascular risks lasted for decades after menopause.

"Our study reinforces the importance of menopause history in informing a woman's risk of future heart disease," said Michael Honigberg, M.D., M.P.P., lead author of the study and a cardiology fellow at Massachusetts General Hospital and Harvard Medical School in Boston. "Women should make sure their physician knows their menopause history, particularly if they experienced menopause before age 40. History of premature menopause should prompt physicians to refine the patient's estimated future risks for heart disease and to work toward lowering their heart disease risks."

He said early evaluations could lead to intervention and medication recommendations. "Whether or not medications are warranted, eating a heart-healthy diet and exercising regularly may be especially important for women with a history of premature menopause," Honigberg said.

Guidelines published in 2018 by the American College of Cardiology and the American Heart Association on management of cholesterol and in 2019 on the prevention of heart disease both recommend that physicians consider a history of premature menopause (defined as menopause before age 40) when making decisions about prescribing a statin medication for middle-aged women who have not yet developed heart disease or stroke.

The UK Biobank has the advantage of extensive and detailed information on a large number of people; however, because most participants are white, the results of this study may not be generalizable to other ethnic groups. In addition, UK Biobank participants as a group are healthier than the general public, therefore, it is possible that these results underestimate the true effects of premature menopause.

Co-authors are Seyedeh Maryam Zekavat, M.D., Ph.D.; Krishna Aragam, M.D.; Derek Klarin, M.D.; Nandita Scott, M.D.; and Pradeep Natarajan, M.D., M.M.Sc. Author disclosures are in the abstract.

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大麻は若年者の脳卒中と関連がある (Oral presentation 333)

大麻を頻回に使用する若年者は非使用者に比べ脳卒中リスクが有意に高い

Young people who use cannabis frequently had significantly higher risk of stroke than non-users

若年者における大麻の頻回使用は脳卒中リスクの増大と関連する、と American Heart Association's Scientific Sessions 2019で発表され、American Stroke Associationの*Stroke*に掲載された。大麻を頻回に使用し、タバコまたは電子タバコも吸う若年者は、大麻の非使用者に比べ、脳卒中発症率が3倍であった。またスタディの結果、タバコは吸わないが1か月に11日以上大麻を使用すると報告した大麻使用者は、非使用者に比べ、脳卒中発症率が2.5倍であることも示した。

Full Text

Frequent cannabis (marijuana) use among young people was linked to an increased risk of stroke according to a study presented at the American Heart Association's Scientific Sessions 2019 and published in *Stroke*, *a Journal of the American Stroke Association*, a division of the American Heart Association.

"As cannabis products become increasingly used, getting clearer, scientifically rigorous data is going to be important as we try to understand the overall health effects of cannabis," said Robert Harrington, M.D., president of the American Heart Association and the Arthur L. Bloomfield professor of medicine and chairman of the department of medicine at Stanford University in Stanford, California.

Young people who used cannabis frequently and also smoked cigarettes or used e-cigarettes were three times more likely to have a stroke compared to non-users.

The study also showed that cannabis users who did not use tobacco products but reported using cannabis for more than 10 days a month were nearly 2.5 times more likely to have a stroke compared to non-users.

The cannabis users were also more likely to be heavy drinkers, current cigarette users and e-cigarette users, which may have also influenced their risk, even though the researchers adjusted for those factors in their analysis.

Participants in the study included more than 43,000 adults aged 18 to 44, of whom nearly 14% reported using cannabis in the last 30 days. Compared with non-users, marijuana users were often younger, non-Hispanic white or black, were less likely to be college graduates and were often physically active.

"Young cannabis users, especially those who use tobacco and have other risk factors for strokes, such as high blood pressure, should understand that they may be raising their risk of having a stroke at a young age," said lead study author Tarang Parekh, M.B.B.S., M.S., a health policy researcher at George Mason University in Fairfax, Virginia. "Physicians should ask patients if they use cannabis and counsel them about its potential stroke risk as part of regular doctor visits."

The study was observational and did not examine the biological mechanism connection between stroke and cannabis use, so it identified a potential link, rather than proving cause and effect. The data analyzed was from the behavioral risk factor surveillance system (BRFSS) (2016-17), a nationally representative cross-sectional survey collected by the U.S. Centers for Disease Control and Prevention.

Co-authors are Sahithi Pemmasani, M.B.B.S., and Rupak Desai, M.B.B.S. Author disclosures are in the abstract and manuscript. This study did not receive outside funding.

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心疾患とがんリスクは関連する可能性がある (Poster presentation Mo3058)

10年間の心血管疾患リスクが高いと、がん発症リスクは3倍に増大する

A high 10-year cardiovascular disease risk score triples the risk of developing cancer

心筋梗塞既往者は心血管疾患を有さない者に比べがん発症リスクが高い可能性がある、とAmerican Heart Association's Scientific Sessions 2019で発表された。10年動脈硬化性心血管疾患（ASCVD）リスクが20%以上の者は、ASCVDリスクが5%以下の者に比べ、何らかのがんを発症するリスクが3倍以上であった。BNPが高い者は、BNPが低い者に比べ、15年間の追跡期間中にがんを発症する確率が高かった。今回のスタディは、ベースライン時のBNP上昇が将来のがんリスクと関連があることを示した初めてのものである。

Full Text

Survivors of myocardial infarction (MI) may have an increased risk of developing cancer compared to people without cardiovascular disease, according to research presented at the American Heart Association's Scientific Sessions 2019 — November 16-18 in Philadelphia.

People with more risk factors for cardiovascular diseases were also at higher risk for developing cancer compared to people with lower cardiovascular disease risk.

"Heart disease and cancer are the two leading causes of death. We now recognize that they are intimately linked. This tells us that we, as physicians, should be aggressive in trying to reduce cardiovascular risk factors not only to prevent heart disease, but also to consider cancer risk at the same time," said study lead author Emily Lau, M.D., a cardiology fellow at Massachusetts General Hospital in Boston.

Using data from the Framingham Heart Study, researchers evaluated data from 12,712 participants (average age 51) without cardiovascular disease or cancer at the start of the study. The American Heart Association/American College of Cardiology's Atherosclerotic Cardiovascular Disease (ASCVD) Risk Estimator and biomarkers were used to measure cardiovascular risk. The ASCVD risk estimator is a tool to help predict a person's risk of developing heart disease within ten years.

During the study period of nearly 15 years, 1,670 cancer cases occurred (19% gastrointestinal; 18% breast; 16% prostate; 11% lung). The researchers found:

- Cardiovascular risk factors, including age, sex, hypertension and smoking status, were independently associated with cancer.
- Those with a 10-year ASCVD risk of 20% or higher were more than three times as likely as those with 10-year ASCVD risk of 5% or lower to develop any type of cancer.
- People who developed cardiovascular disease (a myocardial infarction, heart failure or atrial fibrillation) during the study period had more than a sevenfold increased risk for subsequent cancer compared to those who did not experience any cardiac event.
- Similarly, those with high levels of BNP, a biomarker frequently elevated in heart failure, were more likely to get cancer during the 15-year follow-up period than participants with low levels of BNP.

"I think it's interesting that BNP, a cardiac marker linked to heart failure risk, was associated with the risk of cancer in the future. Currently we use BNP to determine if a person has developed heart failure from chemotherapy drugs used to treat cancer," said Tochi M. Okwuosa, D.O., Vice Chair, American Heart Association Council on Clinical Cardiology and Genomics and Precision Medicine Cardio-Oncology Subcommittee and associate professor at Rush University, Chicago.

"This is the first study that has shown that BNP that's elevated at baseline is associated with the future risk of cancer."

"Cancer and cardiovascular disease share many of the same risk factors, such as tobacco use, poor nutrition and lack of physical activity. The next step is to identify the biological mechanisms driving the link between cardiovascular disease and cancer," said Lau.

Many of the same lifestyle habits that reduce the risk of heart disease also reduce the risk of some kinds of cancer, so following the American Heart Association Life's Simple 7 may help prevent both diseases. Life's Simple Seven includes recommendations to eat a healthy diet (more fruits and vegetables, whole grains and lean protein), be physically active; avoid all tobacco/nicotine products and attain and maintain a healthy body weight, cholesterol, glucose and blood pressure," said Eduardo Sanchez, M.D., M.P.H., chief medical officer for prevention for the American Heart Association.

Lau said this was an observational study, so it doesn't prove cause and effect, but it does shed light on the connection between heart disease and cancer.

Co-authors are Samantha M. Paniagua, M.P.H.; Elizabeth Liu, B.S.; Manol Jovani, M.D., M.P.H.; Shawn Li, M.D.; Katherine Takvorian, M.D.; Vasan S. Ramachandran, M.D.; Greta L. Splanksy, M.A.; Bernard Kreger, M.D.; Martin Larson, Sc.D.; Daniel Levy, M.D.; and Jennifer E. Ho, M.D. Author disclosures are in the abstract.

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インターベンション治療は薬物療法と大して変わらない(Late breaking Science II)

ISCHEMIA試験：インターベンション治療を施行された患者が薬物療法施行患者に比べ心イベント発生率が低い、とのエビデンスはない

ISCHEMIA: No evidence of lower cardiac event rates in patients treated with interventional procedures compared to medication

重症ではあるが安定した心疾患患者に対する早期の侵襲的治療は至適薬物療法に比べ有益性はない、とAmerican Heart Association's Scientific Sessions 2019のLate Breaking Science sessionで報告された。ISCHEMIA試験では、ルーチンのステント留置やバイパス手術などの侵襲的治療を施行された患者において、薬物投与および生活習慣改善のアドバイスのみを受けた患者に比べ、主要な冠動脈疾患関連イベントの発生率は低下しなかった。しかし、狭心症症状を有する患者においては、侵襲的治療により症状の緩和およびQOLの改善が良好であり、それは4年間持続した。

Full Text

An international study found no benefit of an early invasive strategy compared to optimal medical therapy for patients with severe but stable heart disease according to a Late Breaking Science presentation at the American Heart Association's Scientific Sessions 2019.

Presented in a Late Breaking Science session at the American Heart Association's Scientific Sessions 2019, the study found that patients who underwent routine, invasive procedures – like stent implants or bypass surgery – when compared with patients that received only medications (e.g. aspirin, statins) and lifestyle advice, saw no reduction in the rate of occurrence for a group of five events: cardiovascular death, myocardial infarction (MI), hospitalization for unstable angina, hospitalization for heart failure, or resuscitation after cardiac arrest.

Called ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches), the trial also found no overall difference between the two treatment strategies in the rates of cardiovascular death or MI.

At the same time, the investigators found that for patients with symptoms of angina, invasive treatments resulted in better symptom relief and quality of life that persisted for four years. Among those with daily or weekly angina at the start of the study, 50 percent of those treated invasively were angina- free after a year, compared to 20 percent of those treated with medications and lifestyle advice alone.

Both patient groups in the study received "optimal medical therapy" (OMT), the term for medications and lifestyle advice, with one group undergoing invasive procedures soon after having an abnormal stress test, and the other treated invasively only if symptoms worsened despite drug therapy, or in the case of an MI.

Led by researchers at NYU Grossman School of Medicine and Stanford University, with data management and statistics led by the Duke Clinical Research Institute (DCRI), the study randomly assigned 5,179 patients at 320 sites in 37 countries to receive one of the two treatment strategies, making it more than twice as large as any previous study of its kind. The quality of life component was led by researchers at Saint Luke's Mid America Heart Institute and DCRI.

"In line with evidence from prior studies, our results suggest that routine use of heart procedures was not superior in reducing risk for the five-part disease endpoint or death overall compared to treatment only with optimal medical therapy," says ISCHEMIA study chair Judith Hochman, MD, the Harold Snyder Family Professor of Medicine and Senior Associate Dean for Clinical Sciences, at NYU Langone Health. "On the other hand, patients symptomatic to start that got heart procedures, over the years, had fewer symptoms and felt better."

Funded by the National Heart, Lung, and Blood Institute, ISCHEMIA studied patients with stable ischemic heart disease (SIHD). The "vast majority" of patients in the study were determined to have moderate or severe ischemia caused by atherosclerosis.

For the study, "invasive" treatment meant routine catheterization, followed by revascularization when suitable – in most cases involving angioplasty followed by the placement of a rigid stent. In other cases, improved blood flow was accomplished by cardiac bypass surgery.

The study design reflects clinical practice, where patients with abnormal stress tests often undergo an angiogram and revascularization, with a stent implant or bypass surgery.

The rate of procedure-related stroke and death was "extremely" low in ISCHEMIA, but the risk of MIs related to procedures may explain, says Hochman, why those that had an invasive procedure had a rate of events higher by two percentage points over the first year than those that received optimal medical therapy alone (5.3 percent with invasive vs. 3.4 percent for the five-part endpoint).

By year two, the event rate for the study disease endpoints was roughly the same between the two approaches (9 percent vs. 9.5 percent). By four years, the rate of events was two percentage points lower in patients treated with heart procedures than in those that received medications and lifestyle advice alone (13.3 percent with invasive vs. 15.5 percent). Overall, say the investigators, the trend shifts over time showed no significant evidence of a difference in rates between strategies.

Lastly, the team was surprised to see that the overall rate of heart-related events over the duration of the ISCHEMIA trial was lower than projected ten years ago. This is a testament, say the investigators, to recent advances in drug therapies and revascularization techniques.

"Based on our results, we recommend that all patients take medications proven to reduce the risk of a heart attack, be physically active, eat a healthy diet, and quit smoking," says ISCHEMIA co-chair David Maron, MD, Director of Preventive Cardiology and the Stanford Prevention Research Center at Stanford University. "Patients without angina will not see an improvement, but those with angina of any severity will tend to have a greater, lasting improvement in quality of life if they have an invasive heart procedure. They should talk with their physicians to decide whether to undergo revascularization."

Moving forward, the research team plans to follow the study patients for another five years, to determine whether either strategy is associated with better survival over a longer observation period.

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慢性腎臓病患者において侵襲的治療戦略により得るものはない(Late breaking Science II)

ISCHEMIA-CKD試験：進行する慢性腎臓病に侵襲的心臓手術を施行しても心イベント率は低下しない

ISCHEMIA-CKD: Advanced chronic kidney disease treated with invasive heart procedures show no reduction in rate of cardiac events

中等度から重度の心筋虚血を有する慢性腎臓病（CKD）患者にルーチンの侵襲的血行再建術を施行しても、至適薬物療法（OMT）のみを施行された患者に比べ、死亡または心筋梗塞（MI）のリスクは低下しない、とAmerican Heart Association's Scientific Sessions 2019で発表された。対照的に、脳卒中などある一定のアウトカム発症率は侵襲的施術群で上昇したが、施術直後の脳卒中発症は稀であった。またこのISCHEMIA-CKD試験の結果、狭心症症状を有する患者に対する侵襲的治療は、OMTのみの患者に比べ長期症状緩和やQOLを改善しなかった。

Full Text

Heart disease is the leading cause of death for the roughly 500 million people worldwide with chronic kidney disease (CKD). Yet such patients have been excluded from most of the major, relevant cardiovascular clinical trials that are meant to guide treatment approaches for them.

Today, an international, federally funded study reported on comparing the value of two treatment strategies specifically for patients with advanced chronic kidney disease that also had significant, but stable disease in their coronary arteries.

Presented in a Late Breaking Science session at the American Heart Association's Scientific Sessions 2019, the study found that patients with CKD that underwent routine, invasive procedures – like stent implants or bypass surgery – when compared with patients that received only the lifestyle advice and medications (e.g. aspirin, statins), saw no reduction in risk for two disease-related outcomes: death and myocardial infarction (MI). In contrast, rates of certain outcomes such as stroke was increased in the invasive procedure group, although strokes immediately following the procedure were rare.

Called ISCHEMIA-CKD (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches - Chronic Kidney Disease), the study also found that for patients with symptoms of angina, invasive treatments did not result in better, long-term symptom relief and quality of life than among those that received only optimal medical therapy (OMT – medications and lifestyle advice).

Both patient groups in the study received OMT, with one group undergoing invasive procedures soon after having an abnormal stress test, and the other treated invasively only if symptoms worsened despite intensive drug therapy, or in the case of an MI. Several forms of stress test were included in the study.

"Physicians and patients need to consider that in our study invasive treatments did not lead to reduction in death or heart attack in patients with CKD," says ISCHEMIA-CKD principal investigator Sripal Bangalore, MD, professor of medicine, at NYU Langone Health, and director of cardiac catheterization laboratory (H+H/Bellevue). "Risks for damage to both the heart and kidneys from invasive procedures are higher in these patients, which makes other options, like intensive medication therapy, more attractive, except in cases of emergencies."

Led by researchers at NYU Grossman School of Medicine with data and statistics managed by Duke Clinical Research Institute, the study randomly assigned 777 patients in 30 countries to receive one of the two treatment strategies, making it the largest study in history for patients with chronic disease in their kidneys. The quality of life component was led by researchers at Saint Luke's Mid America Heart Institute and Duke.

Funded by the National Heart, Lung, and Blood Institute, ISCHEMIA-CKD studied patients with advanced CKD and stable ischemic heart disease (SIHD).

For the study, "invasive" treatment meant routine catheterization, followed by revascularization when suitable – in most cases involving angioplasty followed by the placement of a rigid stent. In other cases, improved blood flow was accomplished by cardiac bypass surgery.

Measures were in place to reduce procedure-related heart and kidney damage, including proper hydration and careful limits on contrast agents used to create images of heart blockages. Despite these precautions, no long-term benefit was observed in patients who had an invasive procedure soon after a stress test, versus only optimal medical therapy.

Specifically, ISCHEMIA-CKD found that the invasive strategy of catheterization, followed by revascularization, was associated with higher risk of stroke, although strokes immediately or soon after the procedure were rare, suggesting that they were caused by the advanced disease of the patients, versus risk from the procedures, say the investigators. Of the patients enrolled in the trial, one in four died within 3 years.

Investigators also measured whether either treatment strategy reduced symptoms of angina. The patients enrolled in ISCHEMIA-CKD were minimally symptomatic, with nearly half of them having no angina. The investigators say it is well known that patients with advanced CKD are less likely to report symptoms of angina because their nerves do not register chest pain as well. The study found no substantial benefit at reducing angina or improving quality of life in patients treated with the invasive strategy. Further, researchers say, the study may not apply to patients who are very symptomatic or who come into the hospital with an MI.

"Increasing trends in obesity and diabetes have increased the prevalence of CKD significantly throughout the world," says ISCHEMIA studies chair Judith Hochman, MD, the Harold Snyder Family Professor of Medicine and Senior Associate Dean for Clinical Sciences, at NYU Langone Health. "Our findings provide guidance on how to best treat this vulnerable patient population."

The team plans to follow the study patients for another five years to determine whether either strategy is associated with better survival over this longer observation period.

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ダパグリフロジンの有益性が糖尿病を合併しない心不全患者に拡大される(Late breaking Science I)

DAPA-HF試験：ダパグリフロジンはベースラインのHbA1c値に関係なく心不全を改善する

DAPA-HF: Dapagliflozin's improves heart failure outcomes regardless of baseline A1c levels

DAPA-HF試験の新たな解析の結果、SGLT-2阻害薬ダパグリフロジンの有益性が2型糖尿病治療としての効果を超えて拡大されることが示唆された、とAmerican Heart Association's Scientific Sessions 2019で発表された。追跡期間中央値18か月間に、ダパグリフロジン（1日1回10mg）は主要評価項目である心血管死または心不全増悪を、糖尿病を有する患者において25%減少させたのに対し、糖尿病を有さない患者において27%減少させた（p=0.8）。重要なことに、主要評価項目におけるダパグリフロジンの効果は、ベースラインの糖化ヘモグロビン（A1c）値に関わらず実質的に同等であった。その他の結果から、副次的評価項目に対しても同様の有益性が認められた。

Full Text

New analyses of the DAPA-HF trial suggest that the benefits of the SGLT2 inhibitor dapagliflozin extend beyond its effects as a type 2 diabetes therapy according to a Late Breaking Clinical Trial presented at the American Heart Association's Scientific Sessions 2019.

John J.V. McMurray, MD,professor of cardiology at the Institute of Cardiovascular and Medical Sciences at University of Glasgow, Scotland, presented new data that confirm benefits of treatment with dapagliflozin 10 mg once daily in patients with HF with reduced ejection fraction and no type 2 diabetes. Importantly, dapagliflozin's effect on the primary endpoint was virtually the same regardless of baseline glycosylated hemoglobin (A1c) levels.

DAPA-HF (Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure) is an international, multi-center, parallel group, randomized, double-blind trial in patients with heart failure and reduced ejection fraction (LVEF ≤ 40%), with and without T2D, designed to evaluate the effect of Dapagliflozin 10mg, compared with placebo, given once daily in addition to standard of care. The primary composite outcome was time to a worsening heart failure event (hospitalization or equivalent event; i.e. an urgent heart failure visit), or cardiovascular death.

Over a median follow-up of 18 months, dapagliflozin showed benefit for the primary outcome of CV death or worsening HF, with a 27% relative risk reduction in patients without diabetes (HR = 0.73; 95% CI, 0.6-0.88) compared with 25% in patients with diabetes (HR = 0.75; 95% CI, 0.63-0.9; P for interaction = 0.8).

"Even in patients without diabetes, you see very early separation [of the primary outcome curves] — a rapidly developing benefit of dapagliflozin compared to placebo," McMurray said during a press conference.

Additional results presented show similar results for secondary outcomes, including:

- CV death or HF hospitalization: 27% relative risk reduction in patients without diabetes (HR = 0.73; 95% CI, 0.6-0.89) and 25% relative risk reduction in patients with diabetes (HR = 0.75; 95% CI, 0.63-0.9); P for interaction = 0.83.
- Total HF hospitalizations and CV death, including first and repeat hospitalizations: rate ratio = 0.73 (95% CI, 0.59-0.91) in patients without diabetes and 0.77 (95% CI, 0.63-0.94) in patients with diabetes; P for interaction = 0.74.
- Clinically meaningful change (at least 5 points) in Kansas City Cardiomyopathy Questionnaire Total Symptom Score: OR for improvement = 1.12 (95% CI, 1.03-1.22) for patients without diabetes and 1.2 (95% CI, 1.09-1.31) for patients with diabetes; P for interaction = 0.74)
- Worsening renal function, defined as a sustained 50% reduction in estimated glomerular filtration rate, end-stage renal disease or death from renal causes: HR = 0.67 (95% CI, 0.3-1.49) for patients without diabetes and 0.73 (95% CI, 0.39-1.34) for patients with diabetes; P for interaction = 0.86.
- All-cause death: 12% relative reduction in patients without diabetes (HR = 0.88; 95% CI, 0.7-1.12) and 22% relative reduction in patients with diabetes (HR = 0.78; 95% CI, 0.63-0.97); P for interaction = 0.45.

"The relative and absolute risk reductions in death and hospitalization were substantial, clinically important, and consistent in patients with and without type 2 diabetes," McMurray said.

DAPA-HF is the first outcomes trial with an SGLT2 inhibitor investigating the treatment of HF in patients with reduced ejection fraction (HFrEF), with and without type-2 diabetes (T2D). The new analyses showed the consistency of these results across patient subgroups with and without T2D, an early onset of effects, and improvement in patient-reported outcomes of HF-related health status.

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心臓ポンプは一部の患者において合併症を引き起こす(Late breaking Science IV)

インペラ心室補助循環装置はステント治療後の一部の患者において合併症を引き起こす

Impella ventricular assist device associated with complications in some patients after stent procedure

ステント治療の一部として、血液循環を維持するために心室補助装置を必要とする重症患者において、特定の装置が重篤な合併症を引き起こす、とAmerican Heart Association's Scientific Sessions 2019で発表され、同時に *Circulation*に掲載された。研究者らは、インペラポンプ使用後入院中の患者において、死亡、出血、急性腎障害および脳卒中のリスクが、動脈内バルーンポンプ使用患者に比べ高いことを明らかにした。特に、インペラポンプはバルーンポンプに比べ死亡リスクが24%と統計的に有意に高く、脳卒中リスクが34%高かった。

Full Text

In critically ill patients who require a ventricular assist device to support blood circulation as part of stent procedures, specific devices have been associated with serious complications, according to a new study led by cardiologists at Washington University School of Medicine in St. Louis.

Though the observational study does not prove that the ventricular assist devices are the cause of complications, it suggests that with current practice patterns, there is an association between the use of the pumps and an increased risk of bleeding, kidney problems, stroke and death in patients undergoing stent procedures. The study authors are calling for more research evaluating the heart pumps marketed under the brand name Impella.

Results from the study were presented in a Late Breaking Science session at the American Heart Association's Scientific Sessions 2019 in Philadelphia and published simultaneously in the journal *Circulation*.

After statistically adjusting for certain variables, the researchers found an increased risk of death, bleeding, acute kidney injury and stroke among patients while they were still hospitalized after receiving Impella pumps versus balloon pumps. In particular, the Impella pump was associated with a 24% higher risk of death than seen with balloon pumps and a 34% increased risk of stroke compared with the balloon pump. Both of these differences are statistically significant. In no category was the Impella pump associated with improved outcomes.

"These results deserve a closer look to try to better understand the link between the device and its complications," said lead author Amit P. Amin, MD, a Washington University cardiologist and associate professor of medicine, who is presenting the data. "They suggest that perhaps a more measured approach – one that balances risks and benefits – is needed in this critically ill population. These data are observational, so they can't prove causation. But they underscore the need for large, randomized clinical trials and prospective registries to better understand and guide the use of cardiac support devices."

The researchers analyzed data from the Premier Healthcare Database that included information from 48,000 patients treated at 432 U.S. hospitals. Each patient in the study underwent a heart stent procedure to improve blood flow. Some patients undergoing the stent procedure are seriously ill, often having other medical conditions including heart failure, low blood pressure, complex blockages and other cardiac problems that might lead doctors to decide to add a mechanical assist device during the procedure to help the heart pump a greater volume of blood. Of the patients in this study, just under 10% (4,782 patients) received an Impella heart pump. The remaining 90% (43,524 patients) received an intra-aortic balloon pump.

Most patients undergoing stent procedures don't need a ventricular assist device. This study is focused on the small segment (roughly 3% to 5%) of patients undergoing stent procedures for more advanced heart problems – such as complex blockages or heart failure or cardiogenic shock – and need a ventricular assist device. Most patients receive an intra-aortic balloon pump, which rhythmically inflates and deflates in coordination with the heart's natural rhythm, to help push blood through the vessels. These pumps have been in use since the 1960s. But since 2008, a steadily increasing proportion of patients receive the more recently approved Impella pumps, which have small rotors that create a continuous flow of blood.

The data came from patients treated from 2004 to 2016. The Impella pump was introduced into clinical practice in 2008, allowing for comparisons from the time periods before and after this type of pump came into use. Impella use increased steadily from about 1% of patients receiving a pump in 2008 to almost 32% of all patients in 2016 undergoing stent procedures with support devices.

The researchers also found large variations in how often hospitals used Impella pumps. The hospitals that used Impella pumps more frequently had higher adverse outcomes, as well as higher costs associated with caring for these patients, despite controlling for clinical factors. The researchers analyzed the possibility that sicker patients were more likely to receive the Impella pump, perhaps explaining at least part of that association. Instead, they found a trend showing lower Impella use among more critically ill patients.

The authors caution that there are limitations to this observational study, such as physician preference for use of Impella or balloon pumps, or inability to account for factors that were not measured in the observational study. But since the majority of the data suggest no improvement in outcomes linked to the use of the Impella pump as well as serious complications, Amin and his colleagues call for more definitive research to better understand the appropriate role for circulatory support devices in clinical practice.

"These mechanical support devices are innovative and can efficiently pump blood to the body, but in this study, we found no association with improved outcomes with the Impella pumps," Amin said. "This warrants more study so we can understand which patients are likely to benefit from these cardiac assist devices and which are more likely to develop problems."

Dr. Amin has been supported by a comparative effectiveness research KM1 career development award from the Clinical and Translational Science Award (CTSA) program of the National Center for Advancing Translational Sciences of the National Institutes of Health, the National Cancer Institute of the National Institutes of Health, an AHRQ R18 award, and an unrestricted grant from MedAxiom Synergistic Healthcare Solutions.

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10代の先天性心疾患患者が運動耐容能を改善する(Late breaking Science V)

FUEL試験：経口薬が重症の先天性単心室症の若年患者における運動耐容能を改善する

FUEL: Oral drug improves exercise capacity in adolescents with severe, congenital single-ventricle heart defects

小児心疾患患者に対する薬物療法の中で過去最大の臨床試験の結果、経口薬udenafilが重度の先天性単心室症を有する若年患者の運動耐容能を有意に改善したことが明らかになった。FUEL試験の対象患者は、中等度運動中の酸素摂取量および他の運動耐容能測定値が有意に改善した。また、最大運動時の酸素摂取量においても数値的には改善を認めたが、これは統計学的に有意ではなかった。研究リーダーは、今回の生理的有益性はFontan手術施行患者の治療における画期的な出来事である、と述べている。この試験結果はAmerican Heart Association's Scientific Sessions 2019で発表され、同時に *Circulation* に掲載された。

Full Text

The largest-ever clinical trial of a medication for pediatric cardiology patients found that an oral drug significantly improved exercise capacity in adolescent patients with severe, congenital single-ventricle heart defects. A study leader says the physiologic benefits represent a milestone in the care of those who have undergone the Fontan procedure, a palliative operation for single-ventricle disease.

"Exercise capacity is a surrogate for morbidity and mortality outcomes in children with single-ventricle congenital heart disease. It is our hope that an improvement in exercise capacity will translate into better long-term outcomes," said pediatric cardiologist David J. Goldberg, MD, of the Cardiac Center at Children's Hospital of Philadelphia (CHOP) and co-principal investigator of the multicenter Fontan Udenafil Exercise Longitudinal Assessment Trial (FUEL). The principal investigator of the trial, also from CHOP's Cardiac Center, was Stephen Paridon, MD.

Goldberg reported the FUEL Trial results at the 2019 Scientific Sessions of the American Heart Association in Philadelphia and was the lead author of an article published concurrently in the journal *Circulation*.

The Phase 3 randomized, double-blind, placebo-controlled clinical trial, sponsored by Mezzion Pharma Co., Ltd., enrolled 400 male and female participants aged 12 to 18 years old from 30 centers in the United States, Canada and South Korea within the Pediatric Heart Network.

"This study of udenafil provides the first evidence of clinical benefit for a medication in this unique population of children with single-ventricle heart disease," said Goldberg.

Patients born with single-ventricle heart defects have a severely underdeveloped pumping chamber in their hearts. A series of complex childhood surgeries culminating in the Fontan procedure has greatly improved survival of patients with single-ventricle disease. However, the surgical corrections do not provide normal blood circulation, and survivors have low cardiac output and long-term complications. Among those complications is exercise intolerance, associated with increased morbidity and mortality.

The researchers reported that participants in the FUEL trial had statistically significant improvements in oxygen consumption and other measures of exercise capacity during moderate levels of activity. There was also a numeric improvement in oxygen consumption at peak exercise, although this did not achieve statistical significance. "These benefits in exercise capacity reflect better circulatory function and should correlate with better long-term circulatory health for patients who have undergone the Fontan procedure," said Goldberg.

The patients who took udenafil tolerated the treatment well, with side effects limited to those previously known from phosphodiesterase type 5 inhibitors, more commonly including headache, facial flushing, abdominal pain, nosebleed and erection.

A related trial, the FUEL Open-Label Extension (FUEL OLE) Trial is currently proceeding, with the goal of measuring treatment tolerability and safety over a longer period for this patient population. In the meantime, added Goldberg, "For the many patients with heart disease worldwide now living with Fontan physiology, these trial results represent a big step in the right direction."

In addition to sponsorship by Mezzion, other support came from the National Heart, Lung and Blood Institute of the National Institutes of Health.

In addition to their CHOP titles, Goldberg and Paridon are on the faculty of Perelman School of Medicine at the University of Pennsylvania. Drs. Goldberg and Paridon both receive grant support from Mezzion and are co-inventors of patent US10137128B2 which is for the use of udenafil in Fontan physiology. CHOP holds these patent rights in conjunction with Mezzion.

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InclisiranによりLDLコレステロールが58%低下

InclisiranによりLDLコレステロールが58%低下 (Late breaking Science I)

ORION試験：コレステロール低下治験薬はLDLコレステロール低下に有効である

ORION: Experimental cholesterol-lowering drug effective at lowering LDL-cholesterol

コレステロール低下治験薬inclisiranの年2回の注射は、既に最大用量のスタチン製剤を内服している患者の低比重リポ蛋白（LDL）コレステロール低下に有効であるとのORION-10試験のデータがAmerican Heart Association's Scientific Sessions 2019で発表された。Inclisiranは初回投与から3か月後、その後は6か月毎に投与され、その結果510日目にはLDLコレステロールが58%低下し、90～540日の間の時間平均プラセボ補正LDLコレステロールは56%低下した。AHAで発表された他の第3相試験（ORION-9）では、家族性高コレステロール血症患者においてinclisiranはLDLコレステロール値を50%低下させた。

Full Text

Twice-yearly injections of an experimental cholesterol-lowering drug, inclisiran, were effective at reducing low-density lipoprotein (LDL) cholesterol in patients already taking the maximum dose of statin drugs, according to data of the ORION-10 trial presented in a Late Breaking Science session at the American Heart Association's (AHA) Scientific Sessions 2019.

"Maintaining low LDL over a sustained period is essential to reduce the risk of heart attacks and stroke," says R. Scott Wright, M.D., a Mayo Clinic cardiologist and principal investigator of ORION-10 trial.

ORION-10, a phase 3 placebo-controlled, double-blind, randomized study at 145 U.S. sites, enrolled 1,561 participants with established atherosclerotic cardiovascular disease and elevated LDL (greater than 70 milligrams per deciliters), despite maximum tolerated oral statin therapies. Participants received inclisiran or placebo by subcutaneous injections at baseline, and then at three months and every six months thereafter.

Inclisiran, developed by The Medicines Company, is a siRNA (small interfering RNA) drug and the only cholesterol-lowering medication in its class. The medication mimics a gene variant and prevents production of the protein PCSK9, which in turn lowers LDL.

Inclisiran dosed initially, and then again at three months and every six months thereafter, resulted in placebo-adjusted LDL reductions of 58% at day 510 and demonstrated time-averaged, placebo-adjusted LDL reductions of 56% from days 90 through 540.

"The data show that inclisiran dosed twice-yearly achieved durable and potent LDL reductions with an excellent safety profile, and no treatment-related liver or kidney side effects," Dr. Wright says. "Twice-yearly administration by a health care professional coincides with typical patient visits, which can help with medication adherence."

In another phase 3 trial also presented at AHA (ORION-9) inclisiran reduced LDL levels by 50% in patients with familial hypercholesterolemia.

Dr. Wright has received consulting fees from The Medicines Company.

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