一次予防に対するアスピリンの価値に関する様々なメッセージ(Abstract 2072)

ARRIVE：心血管イベントに対する一次予防目的でアスピリンを毎日服用することの価値は依然として不明である

ARRIVE: Value of an aspirin a day as primary prevention of cardiovascular events still unclear

初発心筋梗塞（MI）や脳卒中の中等度リスクを有する人々が、リスク軽減目的でアスピリンを毎日内服するべきか否かに関しては依然として不明である、とのARRIVE試験のレイトブレイキングの結果が ESC Congress 2018 で発表され、同時に*Lancet* に掲載された。アスピリンを内服したスタディ参加者は、特に50～59歳においてMIが少ない傾向にあったが、脳卒中に関しては効果がなかった。予想通り、消化管出血およびいくつかの他の小出血はアスピリン群において多かったが、致死的出血は2群間で差はなかった。

Full Text

It is still unclear whether people at moderate risk of a first myocardial infarction (MI) or stroke should take daily aspirin to lower their risk, according to late-breaking results from the ARRIVE study presented in a Hot Line Session at ESC Congress 2018 and with simultaneous publication in the *Lancet*.

Professor J. Michael Gaziano, principal investigator, of the Brigham and Women's Hospital, Boston, US, said: "Aspirin did not reduce the occurrence of major cardiovascular events in this study. However, there were fewer events than expected, suggesting that this was, in fact, a low-risk population. This may have been because some participants were taking medications to lower blood pressure and lipids, which protected them from disease."

The benefit of aspirin for preventing second events in patients with a previous MI or stroke is well established. Its use for preventing first events is controversial, with conflicting results in previous studies and recommendations for and against its use in international guidelines. Recommendations against its use cite the increased risk of major bleeding.

The ARRIVE study assessed the impact of daily aspirin on MIs, strokes, and bleeding in a population at moderate risk of a first cardiovascular event. Moderate risk was defined as a 20–30% risk of a cardiovascular event in ten years. The study enrolled individuals with no prior history of a vascular event, such as stroke or MI. Men were at least 55 years old and had two to four cardiovascular risk factors, while women were at least 60 years old with three or more risk factors. Risk factors included smoking, elevated lipids, and high blood pressure.

A total of 12,546 participants were enrolled from primary care settings in the UK, Poland, Germany, Italy, Ireland, Spain, and the US. Participants were randomly allocated to receive a 100 mg enteric-coated aspirin tablet daily or placebo. The median follow-up was 60 months. The primary endpoint was time to first occurrence of a composite of cardiovascular death, MI, unstable angina, stroke, and transient ischemic attack.

The average age of participants was 63.9 years and 29.7% were female. In the intention-to-treat analysis, which examines events according to the allocated treatment, the primary endpoint occurred in 269 (4.29%) individuals in the aspirin group versus 281 (4.48%) in the placebo group (hazard ratio [HR] 0.96, 95% confidence interval [CI] 0.81–1.13, p=0.60). In the per-protocol analysis, which assesses events only in a compliant subset of the study population, the primary endpoint occurred in 129 (3.40%) participants of the aspirin group versus 164 (4.19%) in the placebo group (HR 0.81, 95% CI 0.64–1.02, p=0.0756).

In the per-protocol analysis, aspirin reduced the risk of total and nonfatal myocardial infarction (HR 0.53, 95% CI 0.36–0.79, p=0.0014; HR 0.55, 95% CI 0.36–0.84, p=0.0056, respectively). The relative risk reduction of myocardial infarction in the aspirin group was 82.1%, and 54.3% in the 50–59 and 59–69 age groups, respectively.

All safety analyses were conducted according to intention-to-treat. Gastrointestinal bleedings, which were mostly mild, occurred in 61 (0.97%) individuals in the aspirin group versus 29 (0.46%) in the placebo group (HR 2.11, 95% CI 1.36–3.28, p=0.0007). The overall incidence of adverse events was similar between treatment groups. Drug-related adverse events were more frequent in the aspirin (16.75%) compared to placebo (13.54%) group (p<0.0001), the most common being indigestion, nosebleeds, gastro-esophageal reflux disease, and upper abdominal pain.

Professor Gaziano said: "Participants who took aspirin tended to have fewer heart attacks, particularly those aged 50–59 years, but there was no effect on stroke. As expected, rates of gastrointestinal bleeding and some other minor bleedings were higher in the aspirin group, but there was no difference in fatal bleeding events between groups."

He concluded: "The decision on whether to use aspirin for protection against cardiovascular disease should be made in consultation with a doctor, considering all the potential risks and benefits."

SOURCES OF FUNDING: Bayer.

DISCLOSURES: R. Coppolecchia is an employee of Bayer Healthcare. All other members of the executive committee are consultants to Bayer and received person fees.

Conference News

糖尿病における一次予防に対しアスピリンは必要ない(Abstract 2315)

ASCEND：糖尿病患者においてアスピリンによる出血と有益性は拮抗しており、がんに対しては効果がない

PRAMI: Preventive PCI results in better outcomes than culprit artery PCI alone in STEMI

心血管疾患の既往のない糖尿病患者においてアスピリンは重篤な血管イベントを予防したが、ほぼ同等の大出血を引き起こし、がんには効果がなかった。これらはESC Congress 2018のレイトブレイキング で発表され、*New England Journal of Medicine* に掲載された。ASCENDトライアルは、アスピリンは心筋梗塞、脳卒中、および微小脳出血などの血管イベントを減少させたが、主に消化管出血による大出血のリスクも上昇させることを示した。アスピリン群において、いずれのがんも減少しなかった。糖尿病患者においてアスピリンを内服することによる有益性はなかった、と筆者らは結論付けている。

Full Text

Aspirin prevented serious vascular events in patients with diabetes who did not already have cardiovascular disease, but it caused almost as many major bleeds and there was no effect on cancers. These are the late breaking findings presented in a Hot Line Session at ESC Congress 2018 and published in the *New England Journal of Medicine*.

Patients with diabetes are, on average, at increased risk of cardiovascular disease. Aspirin reduces the risk of second cardiovascular events and is recommended for patients who have evidence of cardiovascular disease. However, its role in primary prevention is less clear because of the increase in bleeding. It has therefore been unclear whether aspirin should be recommended for cardiovascular prevention in diabetic patients without existing cardiovascular disease.

Professor Jane Armitage, principal investigator, Nuffield Department of Population Health, University of Oxford, UK, said: "Even though we showed clearly that aspirin reduces the risk of vascular events, including myocardial infarction, strokes, and mini-strokes, it also increased the risk of major bleeds, mainly from the gastrointestinal tract, so overall there was no clear benefit. It had been suggested that low-dose aspirin might protect against cancer, but we saw no reduction in any cancers; we are continuing to follow the participants to see whether any benefits appear later."

The ASCEND trial (A Study of Cardiovascular Events iN Diabetes) examined whether aspirin reduced the risk of a first cardiovascular event in patients with diabetes. Between 2005 and 2011, 15,480 patients with diabetes but no history of cardiovascular disease were randomly assigned to aspirin (100 mg daily) or matching placebo.

Serious health outcomes that occurred to participants during follow-up were then recorded, including in particular:

- First serious vascular event (the primary efficacy endpoint), which included non-fatal myocardial infarctions, non-fatal strokes or transient ischemic attacks, or death from a cardiovascular cause (but excluding any intracranial hemorrhage; i.e. bleeding in the head or brain); and
- First major bleed (the primary safety endpoint), which included bleeding in the head or brain, from the gut or from elsewhere in the body that was serious enough to result in hospitalization or be fatal.

During an average of 7.4 years of follow-up, a first serious vascular event occurred in 685 (8.5%) participants allocated aspirin and 743 (9.6%) allocated placebo, which meant 11 of every 1,000 participants avoided a serious vascular event during the trial as a result of allocation to aspirin. This represented a 12% (95% confidence interval [CI] 3–21%, p=0.01) proportional reduction in the risk of serious vascular events.

However, a first major bleed occurred in 314 (4.1%) participants allocated aspirin and 245 (3.2%) participants allocated placebo, which meant that 9 of every 1,000 participants suffered a first major bleed during the trial as a result of allocation to aspirin. This represented a 29% (95% CI 9–52%, p=0.003) proportional increase in the risk of major bleeding.

Consequently, overall, the numbers of participants who avoided a serious vascular event were counterbalanced by the numbers who suffered a major bleed. Even among the participants in the trial at highest vascular risk (over 2% per year), there were similar numbers of serious vascular events avoided as major bleeds caused. It was not possible to identify a group of patients in the trial in whom the benefits clearly outweighed the risks.

Previous studies had suggested that aspirin might produce a reduction in cancers in the gut (especially in the bowel), with the effects increasing over time. A large number of cancers were observed during 7.4 years of follow-up in the ASCEND trial. However, no effect of aspirin on incident gastrointestinal cancer was observed: 157 (2.0%) participants allocated aspirin and 158 (2.0%) participants allocated placebo (p=0.95) reported these cancers. Nor was there any apparent effect of aspirin on the overall risk of cancer (11.6% of those allocated aspirin versus 11.5% of those allocated placebo; p=0.81). Longer-term follow-up is ongoing to see if any effects on cancer emerge later.

Professor Armitage said: "We have shown conclusively in ASCEND that aspirin reduces the risk of vascular events in primary prevention, as it does in people who already have cardiovascular disease, but these benefits are counter-balanced by the number of major bleeds caused by aspirin. This is an important finding with implications for many millions of people who have diabetes but have not yet had cardiovascular events. Current clinical guidelines vary in their recommendations about the use of aspirin for primary prevention because of a previous lack of clear evidence. The results of ASCEND now provide much needed clarity."

"The trial participants were well-managed both for their diabetes and their cardiovascular risk," she added. "Most participants were taking proven safe treatments, such as statins and blood pressure reducing medicines which will be protecting them from heart attacks and strokes. For them, we have shown that there is no added benefit of taking aspirin."

SOURCES OF FUNDING: British Heart Foundation, Medical Research Council Population Health Research Unit (MRC-PHRU), Bayer AG, Solvay, Abbott and Mylan.

DISCLOSURES: The study was designed and run independently of the funders by the Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU) in the Nuffield Department of Population Health (NDPH). The lead investigators abide by the CTSU guidelines not to accept payment or honoraria from drug companies.

Conference News

HDLコレステロール値が非常に高いことは有害である可能性がある(Abstract 50)

HDLコレステロール値が非常に高いと心血管死または非致死性MIのリスクが上昇する

Very high levels of HDL-cholesterol increases risk of cardiovascular death or non-fatal MI

高比重リポ蛋白(HDL)コレステロール値が非常に高いことは心筋梗塞(MI)および死亡のリスクが高いことと関連がある可能性がある、とESC Congress 2018 で発表された。追跡期間中央値4年間におけるMIまたは心血管死のリスクは、HDLコレステロール値が41～60 mg/dL (1.1～1.5 mmol/L)の参加者で最も低かった。リスクは、HDLコレステロールが低値(41 mg/dL未満)および非常に高値(60 mg/dL超)の両者において高かった。HDLコレステロール値が非常に高い参加者は、HDLコレステロール値が41～60 mg/dLの参加者に比べ、心血管死または非致死性MIのリスクが50% 高かった。

Full Text

Very high levels of high-density lipoprotein (HDL) cholesterol may be associated with an increased risk of myocardial infarction and death, according to research presented at ESC Congress 2018.

Study author Dr. Marc Allard-Ratick, of Emory University School of Medicine, Atlanta, US, said: "It may be time to change the way we view HDL cholesterol. Traditionally, physicians have told their patients that the higher your 'good' cholesterol, the better. However, the results from this study and others suggest that this may no longer be the case."

HDL cholesterol has been considered "good" because the HDL molecule is involved in the transport of cholesterol from the blood and blood vessel walls to the liver and ultimately out of the body, thereby reducing the risk of clogged arteries and atherosclerosis. People with low HDL cholesterol have a greater risk of atherosclerosis and cardiovascular disease. But the protective effect of very high HDL cholesterol has been unclear.

This study, conducted as part of the Emory Cardiovascular Biobank, investigated the relationship between HDL cholesterol levels and the risk of heart attack and death in 5,965 individuals, most of whom had heart disease. The average age of participants was 63 years and 35% were female.

Participants were divided into five groups according to their HDL cholesterol level: less than 30 mg/dl (0.78 mmol/L), 31–40 mg/dl (0.8–1 mmol/L); 41–50 mg/dl (1.1–1.3 mmol/L); 51–60 mg/dl (1.3–1.5 mmol/L); and greater than 60 mg/dl (1.5 mmol/L).

During a median follow-up of four years, 769 (13%) participants had a myocardial infarction (MI) or died from a cardiovascular cause. Participants with HDL cholesterol 41–60 mg/dl (1.1–1.5 mmol/L) had the lowest risk of MI or cardiovascular death. Risk was increased both in participants with low levels (less than 41 mg/dl) and very high levels (greater than 60 mg/dl) of HDL cholesterol, which produced a U-shaped curve when plotted graphically.

Participants with HDL cholesterol levels greater than 60 mg/dl (1.5 mmol/L) had a nearly 50% increased risk of dying from a cardiovascular cause or having an MI compared to those with HDL cholesterol levels 41–60 mg/dl (1.1–1.5 mmol/L).

The associations were consistent even after controlling for other risk factors for heart disease such as diabetes, smoking, and low-density lipoprotein (LDL) cholesterol, as well as other factors linked with high HDL cholesterol such as alcohol intake, race, and sex.

The results support findings from several large population-based studies, including a recent publication which found increased cardiovascular and all-cause death when HDL cholesterol reached extremely high levels. Dr. Allard-Ratick said: "Our results are important because they contribute to a steadily growing body of evidence that very high HDL cholesterol levels may not be protective, and because unlike much of the other data available at this time, this study was conducted primarily in patients with established heart disease."

He noted that more research is needed to elucidate the mechanisms of this paradoxical association. "While the answer remains unknown, one possible explanation is that extremely elevated HDL cholesterol may represent 'dysfunctional HDL' which may promote rather than protect against cardiovascular disease," he said.

Dr. Allard-Ratick concluded: "One thing is certain: the mantra of HDL cholesterol as the 'good' cholesterol may no longer be the case for everyone."

SOURCES OF FUNDING: None.

Conference News

降圧薬により長期生存率が改善する (Abstract 1327)

ASCOT：血圧とコレステロールを低下させる薬剤は十年後でも生存率を改善し続けている

ASCOT: Blood pressure and cholesterol lowering drugs continue to improve survival after a decade

血圧とコレステロールを低下させる薬剤は10年以上生存率を改善し続けている、とのASCOTレガシースタディのレイトブレイキングの結果がESC Congress 2018 で発表され、*Lancet* に掲載された。高血圧を有する60代半ばの患者は、カルシウム拮抗薬ベースの降圧剤およびスタチンの両者を内服している場合、75～80歳までに心疾患および脳卒中で死亡する確率が低かった。スタチンはトライアル終了後も長期生存に関する有益性を有することが過去に示されているが、降圧剤で示されたのは今回が初めてである、と筆者らは強調している。

Full Text

Hypertension and lipid lowering drugs continue to improve survival in patients with hypertension after more than a decade, according to late breaking results from the ASCOT Legacy study presented at ESC Congress 2018 and published in The *Lancet*.

Dr. Ajay K. Gupta, of the William Harvey Research Institute, Queen Mary University London, UK, said: "Patients in their mid-60s with high blood pressure were less likely to die from heart disease or stroke by age 75–80 if they had taken both calcium channel blocker-based blood pressure lowering treatment and a statin."

The ASCOT Legacy study is the long-term follow-up of 8,580 patients from the UK who took part in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), which between 1998 and 2000 recruited patients with high blood pressure and three or more additional risk factors for cardiovascular disease.

Patients who took a newer blood pressure lowering treatment (based on a calcium channel blocker) for 5.5 years were 29% less likely to have died from a stroke ten years later than those taking an older regimen (based on a beta-blocker). There was a non-significant trend towards 10% fewer cardiovascular deaths with the newer therapy.

Patients with average (6.5 mmol/l) or below average blood cholesterol levels at the start of the trial who took a statin for 3.3–5.5 years were 15% less likely to have died from cardiovascular causes such as heart disease and stroke 16 years later than those randomized to placebo.

A subgroup of patients with above average cholesterol who received standard lipid-lowering therapy for 5.5 years had 21% fewer cardiovascular deaths over ten years of follow-up with the newer blood pressure therapy compared to the older one. There was a non-significant trend towards lower all-cause and stroke deaths with the newer treatment.

"These results are remarkable," said Professor Peter Sever, of the National Heart and Lung Institute at Imperial College London, UK, who jointly led the study with Dr. Gupta. "We have previously shown that statins confer long-term survival benefits after trials have stopped, but this is the first time it has been found with a blood pressure treatment."

Dr. Gupta said: "The findings provide further support for the use of an effective blood pressure lowering therapy plus a statin in most patients with high blood pressure."

A main objective of the initial ASCOT trial was to find out whether a new treatment strategy for high blood pressure was more effective in preventing heart attacks than an old strategy. Patients with high blood pressure were randomly allocated to the new treatment of amlodipine (a calcium channel blocker) plus perindopril (an angiotensin-converting enzyme inhibitor) if needed to achieve the target blood pressure, or the old therapy of atenolol (a beta-blocker) plus bendroflumethiazide (a diuretic) and potassium if needed. The medicines were taken for a median of 5.5 years, when the trial was stopped because the newer treatment prevented more strokes and deaths. After the trial, patients went on to receive usual (or routine) care.

A second aim of the trial was to discover if a statin would provide added protection against coronary heart disease in patients with high blood pressure and cholesterol levels below 6.5 mmol/L. Patients with a blood cholesterol level of 6.5 mmol/l or less were randomly allocated to atorvastatin or placebo for 3.3 years, when the trial was prematurely stopped because atorvastatin prevented more heart attacks and strokes. Following this, patients were offered atorvastatin for the remainder of the blood pressuring lowering arm of the trial. During this 2.2 year period approximately two-thirds of patients previously assigned to either atorvastatin or placebo took atorvastatin.

A third aim of the trial was to evaluate the effectiveness of the newer versus older blood pressure lowering treatment in patients with high blood pressure and high cholesterol (above 6.5 mmol/l). These patients did not participate in the randomized lipid-lowering arm of the trial and all received standard lipid-lowering therapy for 5.5 years.

Professor Mark Caulfield, Director of the William Harvey Research Institute, said: "This study confirms the importance of lowering blood pressure and cholesterol to prevent disabling and life-shortening cardiovascular disease."

SOURCES OF FUNDING: The original ASCOT study was investigator led with funding provided by Pfizer. The ASCOT Legacy program was investigator led and in part funded by research grants from Pfizer to Imperial College London and the Foundation for Circulatory Health.

DISCLOSURES: Professor Peter Sever is a National Institute for Health Research Senior Investigator and was supported by the Biomedical Research Centre Award to Imperial College Healthcare NHS Trust, from the National Institute for Health Research. Dr. Ajay Gupta has been supported by the Barts Charity and William Harvey Research Institute.

Conference News

魚油は糖尿病患者における心血管イベントを予防しない(Abstract 2317)

ASCEND：オメガ3サプリメントは糖尿病患者の心筋梗塞または脳卒中を予防しない

ASCEND: Omega 3 supplements do not prevent myocardial infarction or stroke in people with diabetes

オメガ3サプリメントは糖尿病患者の心筋梗塞（MI）または脳卒中を予防しない、とのASCENDトライアルのレイトブレイキング結果がESC Congress 2018 で発表され、*New England Journal of Medicine* に掲載された。ASCENDトライアルの平均追跡期間7.4年間に、初回の重篤な血管イベントはオメガ3サプリメント群の689人（8.9%）およびプラセボ群の712人（9.2%）において発現し、2群間に有意差がないことが示された（p=0.55）。糖尿病患者において心血管イベント予防目的で魚油を推奨する根拠はない、と筆者らは結論付けている。

Full Text

Omega 3 supplements do not prevent myocardial infarction (MI) or strokes in patients with diabetes, according to late breaking results from the ASCEND trial presented in a Hot Line Session at ESC Congress 2018 and published in the *New England Journal of Medicine*.

In observational studies, higher consumption of fish is associated with lower risks of coronary artery disease and stroke. However, previous randomized trials have not been able to show that taking fish oil supplements containing omega-3 fatty acids reduce the risk of having cardiovascular events.

The ASCEND trial (A Study of Cardiovascular Events iN Diabetes) examined whether fish oil supplements reduce the risk of a cardiovascular event in patients with diabetes. Between 2005 and 2011, 15,480 patients with diabetes but no history of cardiovascular disease were randomly assigned to fish oil supplementation (1 g daily) or matching placebo.

The primary efficacy outcome was first serious vascular event, which included non-fatal MIs, non-fatal strokes or transient ischemic attacks or deaths from a cardiovascular cause (but excluding any intracranial hemorrhage).

During an average of 7.4 years of follow-up, a first serious vascular event occurred in 689 (8.9%) participants allocated Omega 3 supplements and 712 (9.2%) participants allocated placebo. There was no significant difference between the two groups: rate ratio of 0.97 (95% confidence interval 0.87–1.08, p=0.55).

Dr. Louise Bowman, principal investigator, Nuffield Department of Population Health, University of Oxford, UK, said: "Our large, long-term randomized trial shows that Omega 3 supplements do not reduce the risk of cardiovascular events in patients with diabetes. This is a disappointing finding, but it is in line with previous randomized trials in other types of patient at increased risk of cardiovascular events which also showed no benefit of fish oil supplements. There is no justification for recommending fish oil supplements to protect against cardiovascular events."

SOURCES OF FUNDING: British Heart Foundation, Medical Research Council Population Health Research Unit (MRC-PHRU), Abbott, Bayer AG, Mylan, Solvay.

DISCLOSURES: The study was designed and run independently of the funders by the Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU) in the Nuffield Department of Population Health (NDPH). The lead investigators abide by the CTSU guidelines not to accept payment or honoraria from drug companies.

Conference News

持久系アスリートにおいて左房線維化増加が認められた(Abstract 4602)

持久系アスリートにおける不整脈リスクの増加は左房の線維化で説明できる可能性がある

Left atrial fibrosis may explain increased risk of arrhythmias in endurance athletes

高度にトレーニングをした持久系アスリートにおける不整脈リスク増加は左房の線維化で説明できる可能性がある、とESC Congress 2018 で発表された。全体としてアスリートは、非アスリートのコントロール群に比べ、若年でありBMIが小さく併存疾患が少なかった。左房線維化の平均は、持久系アスリートで13.7% であり、非アスリートでは11.8% であった。年齢やBMIで補正すると、持久系アスリートであることは非アスリートに比べ、左房線維化との関連がより強かった。持久系アスリートであることは、糖尿病、高血圧、および喫煙関連疾患などの併存症よりも線維化の度合いに対する影響が大きかった。

Full Text

Left atrial fibrosis may explain the increased risk of arrhythmias seen in highly trained endurance athletes, according to research presented at ESC Congress 2018.

Study author Dr. David Peritz, of the University of Utah, Salt Lake City, US, said: "Left atrial fibrosis could be the link between endurance training and risk of atrial fibrillation. Ultimately, we hope to use the degree of left atrial fibrosis to help predict how likely it is that an endurance athlete will develop atrial fibrillation, providing an opportunity for prevention."

Through physical activity people can decrease their risk of coronary artery disease by half, while studies suggest that professional athletes live up to six years longer than the general population. However, just as any athlete can develop overuse injuries in their joints, there is concern that endurance athletes may also develop training related cardiac injury. Moderate exercise is well established as better for health than a sedentary lifestyle but vigorous exercise may prove to be harmful in some individuals.

Just like any other muscle, athletic activity modifies the heart in predictable ways. These changes are structural, functional and electrical. This study aims to link structural to electrical changes – namely that highly trained athletes are more prone to developing arrhythmias, specifically atrial fibrillation.

Atrial fibrillation, the most common arrhythmia in the general population, is associated with a five-fold stroke risk and a doubled risk of early death. The relationship between atrial fibrillation and exercise appears to be U-shaped, meaning that moderate exercise is protective but long-term high-intensity activity may be harmful. Studies have shown that the most highly trained athletes had a five-fold increased risk of developing atrial fibrillation compared to non-athletes.

Left atrial fibrosis is commonly found in patients with atrial fibrillation. In an effort to explain why highly trained endurance athletes have such a high risk of arrhythmias, this study investigated whether they have more left atrial fibrosis than non-athletes.

The researchers recruited 16 healthy endurance athletes over 35 years of age currently training in endurance sports at least ten hours per week and who had participated in competitive endurance sports for at least ten years. Endurance activities included running, cycling, rowing, and Nordic skiing. Twenty healthy non-athletes were recruited during screening colonoscopies. Participants completed questionnaires on medical history and physical activity.

Atrial fibrosis was assessed using late gadolinium enhancement magnetic resonance imaging, an established method for visualizing tissue damage in cardiac diseases such as myocardial infarction.

Overall the athletes were younger, had a lower body mass index (BMI), and fewer comorbidities. The mean left atrial fibrosis score was 13.7% in endurance athletes compared to 11.8% in non-athletes. After controlling for age and BMI, both known to affect left atrial fibrosis, being an endurance athlete was associated with significantly more left atrial fibrosis compared to being a non-athlete (p=0.05). Being an endurance athlete had a greater impact on the degree of fibrosis than any comorbidity including diabetes, hypertension, and tobacco use.

Dr. Peritz said: "Despite being younger and having fewer comorbidities, endurance athletes showed more left atrial fibrosis. This was a small study and the clinical significance deserves further investigation, but we think that increased left atrial fibrosis may help explain the higher incidence of atrial fibrillation in endurance athletes. The next step in our research is to see whether the degree of left atrial fibrosis is related to the amount of endurance training."

SOURCES OF FUNDING: The University of Utah CARMA (Comprehensive Arrhythmia Research & Management) Center.

DISCLOSURES: None.

Conference News

左心系心内膜炎において経口抗菌薬への切り替えは安全である(Abstract 5869)

POET：左心系心内膜炎患者において経口抗菌薬に切り替えることによって入院期間を半減させることができる

POET: Treatment with oral antibiotics can halve hospital stays for patients with left-sided endocarditis

一部の左心系心内膜炎患者において新たな治療法により入院期間を半減することが可能である、とのDanish POETトライアルのレイトブレイキングの結果がESC Congress 2018で発表され、*New England Journal of Medicine*に掲載された。10日以上の経静脈的抗菌薬投与の後、臨床的に安定した心内膜炎患者400人が経静脈的抗菌薬投与を継続する群、または経口抗菌薬投与に切り替える群にランダムに割り付けられた。経口抗菌薬投与群は外来患者として治療された。6か月の追跡期間中、主要評価項目発現率は両群ともに10.5%で、有意差はなかった。

Full Text

A new treatment can halve hospital stays for some patients with endocarditis, according to late breaking results of the POET trial presented in a Hot Line Session at ESC Congress 2018 and published in the *New England Journal of Medicine*.

The nationwide Danish POET trial examined if it was feasible and safe to shorten the duration of intravenous antibiotic treatment, and give the remaining antibiotics orally in some patients with left-sided infectious endocarditis. After at least ten days of intravenous antibiotics, 400 clinically stable patients with endocarditis were randomly allocated to continued intravenous antibiotics or to oral antibiotics. Patients in the oral antibiotics group were offered treatment as outpatients.

Professor Henning Bundgaard, principal investigator, of Copenhagen University Hospital, Denmark, said: "It is a huge challenge for patients to stay in hospital for up to six weeks receiving intravenous treatment, which is associated with an increased risk of complications. Reducing the length of hospital stay has improved outcomes in other diseases and oral antibiotics could be a safe way to achieve this."

Endocarditis is an infection of the endocardium and one or more heart valves. Around 15–30% of patients die in hospital. Intensive care is sometimes needed, and up to half of patients require surgery to remove infected tissue and repair or replace infected heart valves. After the initial phase and after surgery most patients are clinically stable and the main reason for staying in hospital is to complete up to six weeks of intravenous antibiotic treatment as recommended by guidelines.

Patients in the POET trial were followed-up for six months after antibiotic treatment had finished for the combined endpoint of all-cause death, unplanned cardiac surgery, embolic events, and reinfection.

After randomization, intravenous or oral antibiotics were taken for a median of 18 days. During the six-month follow-up period, the primary endpoint occurred in 10.5% of patients without any significant difference between the two groups. This means that the non-inferiority criterion was met and a change to oral treatment was as efficient and safe as the conventional continued intravenous treatment for the whole period.

Professor Bundgaard said: "Shifting to oral antibiotic treatment in stabilized patients with endocarditis was as effective and safe as continued intravenous antibiotic treatment and was given during half the antibiotic treatment period. These novel findings may have a significant impact on future clinical practice for the management of patients who are stable."

SOURCES OF FUNDING: The study was supported by unrestricted grants from The Danish Heart Foundation, The Capital Regions Research Council, The Hartmann's Foundation and Svend Aage Andersens Foundation.

DISCLOSURES: None.

Conference News

心房細動における併用療法に疑念が生じた (Abstract 5878)

GARFIELD-AF：心房細動患者において経口抗凝固薬と抗血小板薬の併用は予後不良と関連がある

GARFIELD-AF: Oral anticoagulants plus antiplatelets associated with poor outcomes in atrial fibrillation

新たに心房細動と診断され、明らかな抗血小板薬の適応のない患者において、経口抗凝固薬と抗血小板薬の併用は抗凝固薬単独に比べ予後を悪化させる、とのGARFIELD-AFレジストリのレイトブレイキングの結果がESC Congress 2018で発表された。このスタディは、新たに心房細動と診断された患者25,815人を組み入れた。患者は、抗血小板薬および経口抗凝固薬または経口抗凝固薬のみを初めて処方された。経口抗凝固薬と抗血小板薬併用療法は、抗血小板薬の適応でない患者においては有害であった。抗血小板薬の適応であった患者においては有害ではなかったが、ベネフィットも得られないようであった。

Full Text

Combined oral anticoagulant and antiplatelet therapy is associated with a worse prognosis than anticoagulation alone in newly diagnosed atrial fibrillation patients without a clear indication for antiplatelets, according to late breaking results from the GARFIELD-AF registry presented at ESC Congress 2018.

Professor Keith Fox, principal investigator, University of Edinburgh, UK, said: "These findings challenge the use of combined oral anticoagulant and antiplatelet therapy in patients with atrial fibrillation, especially those without an indication for antiplatelet therapy."

Nearly all patients diagnosed with atrial fibrillation should be started on oral anticoagulation to prevent stroke. Adding an antiplatelet increases the risk of bleeding and is not recommended unless required to prevent coronary or peripheral artery thrombosis – for example in patients who have received a stent, had a myocardial infarction, or have peripheral artery disease.

This analysis of the GARFIELD-AF registry investigated whether adding an antiplatelet to oral anticoagulation therapy in those without a clear indication for an antiplatelet would provide an overall benefit or harm. Patients were excluded if they had previously been prescribed antiplatelets, which included aspirin and P2Y12 receptor inhibitors.

The study enrolled 25,815 patients with newly diagnosed atrial fibrillation from 1,317 sites in 35 countries. Of those, 3,133 patients were prescribed antiplatelet and oral anticoagulant therapy for the first time and 22,682 were prescribed oral anticoagulants alone.

Patients receiving oral anticoagulants and antiplatelets had a higher prevalence of coronary artery disease, acute coronary syndrome, and stroke. However, 1,743 (56%) patients prescribed both drugs did not have coronary artery disease or peripheral artery disease.

Professor Fox said: "More than half of patients prescribed both drugs did not have coronary artery disease or peripheral artery disease, suggesting that they did not have a clear indication for antiplatelet therapy."

Patients were followed-up for a minimum of 12 months. Compared to oral anticoagulation alone, combined treatment with oral anticoagulation and antiplatelet therapy was independently associated with increased risks of major bleeding (hazard ratio [HR] 1.45, 95% confidence interval [CI] 0.94–2.23), all-cause death (HR 1.31, 95% CI 1.05–1.62), and stroke (HR 1.60, 95% CI 1.08–2.35).

Associations between treatment type and outcomes were then examined in patients with an indication for antiplatelet therapy (with coronary artery disease or peripheral artery disease) and those without (no coronary artery disease or peripheral artery disease). Compared to oral anticoagulation alone, combined treatment was independently associated with increased risks of all-cause death (HR 1.37, 95% CI 1.02–1.85) and stroke (HR 1.65, 95% CI 1.02–2.65) in patients without an indication for antiplatelets, but was not harmful in those with an indication.

Professor Fox said: "Combined oral anticoagulant and antiplatelet therapy was harmful in patients without an indication for antiplatelets. In those with an indication, it was not harmful but there did not appear to be any benefit. The results question the use of combined treatment in any patient with atrial fibrillation, but particularly in those without an indication for antiplatelets."

Professor Fox noted that the findings only apply to full dose anticoagulation. He added: "Patients with atrial fibrillation yet neither coronary artery disease nor other forms of atherosclerosis receiving both medications should consult their doctor."

SOURCES OF FUNDING: The GARFIELD-AF registry is funded by an unrestricted research grant from Bayer AG, Berlin, Germany.

DISCLOSURES: Professor Fox's disclosures are grants from Bayer/Janssen and AstraZeneca and consulting for Bayer/Janssen, Sanofi/Regeneron, Verseon.

Conference News

タファミジスは心アミロイドーシスの死亡率を低下させる(Abstract 3235)

ATTR-ACT:トランスサイレチン型心アミロイドーシスの生存率を改善する初めての治療が開発される

ATTR-ACT: Researchers discover first treatment to improve survival in transthyretin amyloid cardiomyopathy

タファミジスはトランスサイレチン型心アミロイドーシスと呼ばれる、まれな心疾患の生存率を改善し入院を減らす初めての治療薬である、とのレイトブレイキング研究が ESC Congress 2018 で発表され、*New England Journal of Medicine* に掲載された。ATTR-ACT トライアルにおいて、タファミジスはプラセボと比較して死亡および心血管疾患関連の入院を有意に減少させた(p=0.0006)。30か月の追跡期間中、実薬群の78人(29.5%)が死亡したのに対し、プラセボ群では76人(42.9%)が死亡した—この結果には、心臓移植施行患者や補助人工心臓を使用された患者も含まれた。この治療薬はまた、プラセボと比較し6分間歩行距離の低下およびQOLの低下を減少させた。

Full Text

Tafamidis is the first treatment to improve survival and reduce hospitalizations in a rare heart condition called transthyretin amyloid cardiomyopathy, according to late breaking research presented in a Hot Line Session at ESC Congress 2018 and published in the *New England Journal of Medicine*.

Professor Claudio Rapezzi, principal investigator, University of Bologna, Italy, said: "There are no medications specifically approved for the treatment of transthyretin amyloid cardiomyopathy. Tafamidis improved survival and quality of life, and reduced hospitalizations, indicating that it could be an effective therapy for these patients. A submission to the regulatory authorities for marketing approval is in process as a consequence of this study."

Transthyretin amyloid cardiomyopathy is a rare, progressive, fatal disease. The hereditary form is caused by mutations in the TTR gene and typically presents in 50–70 year-olds, while the acquired (wild-type) form presents in 60–80 year-olds. The disease is caused when the transport protein, transthyretin, becomes unstable and misfolds, leading to the formation of amyloid, which is deposited in the heart. This causes the heart muscle to become stiff and results in heart failure.

Patients have debilitating symptoms common to heart failure, such as shortness of breath, fatigue, orthostatic hypotension, and syncope, leading to frailty and poorer quality of life. Patients survive an average of three to five years after diagnosis. There are no approved drugs to improve survival, and therapy is limited to managing symptoms.

Tafamidis stabilizes transthyretin, preventing misfolding and the formation of amyloid. Treatment with this therapy delays neurologic progression in transthyretin familial amyloid polyneuropathy, a similar condition in which amyloid is deposited in the nerves after transthyretin misfolding. The drug is approved for this condition in the EU.

The medicine has not been approved for the treatment of transthyretin amyloid cardiomyopathy, but has orphan drug designation from the European Medicines Agency (EMA) and Fast Track designation from the US Food and Drug Administration (FDA).

The ATTR-ACT trial assessed the efficacy and safety of tafamidis in patients with hereditary and acquired transthyretin amyloid cardiomyopathy. The trial enrolled 441 patients aged 18–90 years from 48 centers in 13 countries. Patients were randomized in a 2:1:2 ratio to tafamidis 80 mg, tafamidis 20 mg, or placebo – all taken orally, once a day, for 30 months.

The primary endpoint was the hierarchical combination of all-cause death and cardiovascular-related hospitalizations from baseline to 30 months. The two tafamidis groups were combined and compared with the placebo group. Secondary outcomes included the change from baseline to 30 months in exercise capacity (assessed with the six-minute walk test) and in health-related quality of life (assessed using the Kansas City Cardiomyopathy Questionnaire).

A total of 264 patients received the drug and 177 received placebo. Tafamidis significantly reduced death and cardiovascular-related hospitalization compared to placebo (p=0.0006). During the 30-month follow-up, 78 (29.5%) patients receiving the medicine died compared to 76 (42.9%) receiving placebo – this included patients who underwent heart transplant or received a cardiac mechanical assist device as these were classified as death in the analysis. Rates of cardiovascular-related hospitalizations were 52.3% and 60.5% in the tafamidis and placebo groups, respectively.

The therapy also reduced the decline in six-minute walk distance and quality of life compared with placebo. The incidence of individual adverse events were similar or fewer with drug treatment. Discontinuations of study drug due to treatment-related adverse events were less common with tafamidis than placebo.

Professor Rapezzi said: "ATTR-ACT is the largest randomized clinical trial in patients with transthyretin amyloid cardiomyopathy to date. The trial showed that tafamidis is superior to placebo in reducing the risk of death and cardiovascular-related hospitalizations. Tafamidis also reduced the decline in functional capacity and quality of life and had a favorable safety profile in these patients."

He concluded: "These findings provide strong evidence that tafamidis is an effective therapy for patients with transthyretin amyloid cardiomyopathy and can modify the natural history of this disease."

SOURCES OF FUNDING: Pfizer.

DISCLOSURES: Claudio Rapezzi MD has received research grants, speaker fees and board participation honoraria from Pfizer.

Conference News

心房細動患者において未知の脳障害が認められた (Abstract 1358)

Swiss-AF：心房細動患者10人に4人は未知の脳障害を有している

Swiss-AF: Four out of ten patients with atrial fibrillation have unknown brain damage

脳卒中や一過性脳虚血発作の既往のない心房細動患者の10人に4人が、これまでに気付かなかった脳障害を有しており、これで認知症と心房細動の関連が説明できる可能性があるとのSwiss-AFスタディの初めての結果が、ESC Congress 2018 で発表された。最終解析には、脳卒中または一過性脳虚血発作の既往のない心房細動患者1,389人が含まれた。参加者の平均年齢は72歳であり、26% は女性であった。標準化された脳MRI画像の結果、41% の患者が少なくとも1種類の過去の未知の脳障害を有していた：15% は脳梗塞、19% は微小脳出血、そして16% はラクナ梗塞を有していた。

Full Text

Four out of ten patients with atrial fibrillation but no history of stroke or transient ischemic attack have previously unknown brain damage, according to the first results of the Swiss Atrial Fibrillation Cohort Study (Swiss-AF) presented at ESC Congress 2018.

"Our results suggest that clinically unrecognized brain damage may explain the association between dementia and atrial fibrillation in patients without prior stroke," said Co-Principal Investigator Professor David Conen of McMaster University, Hamilton, Canada.

Patients with atrial fibrillation have a significantly increased risk of stroke, which is why most are treated with oral anticoagulation. This increased stroke risk is probably the main reason why patients with atrial fibrillation also face an increased risk of cognitive dysfunction and dementia. However, the relationship between atrial fibrillation and dementia has also been shown among patients without prior strokes, meaning that additional mechanisms have to be involved.

Clarifying the mechanisms by which atrial fibrillation increases the risk of cognitive dysfunction and dementia is a first step towards developing preventive measures.

Swiss-AF is a prospective, observational study designed to pinpoint the mechanisms of cognitive decline in patients with atrial fibrillation. This analysis investigated the prevalence of silent brain damage in atrial fibrillation patients.

The study enrolled 2,415 patients aged over 65 years with atrial fibrillation between 2014 and 2017 from 14 centers in Switzerland. All patients without contraindications underwent standardized brain magnetic resonance imaging and the images were analyzed in a central core laboratory. Scans were available in 1,736 patients. Of those, 347 (20%) patients had a history of stroke and/or transient ischemic attack and were excluded from the analysis.

The final analysis included 1,389 patients with atrial fibrillation but no history of stroke or transient ischemic attack. The average age of participants was 72 years, and 26% were women. The scans showed that 569 (41%) patients had at least one type of previously unknown brain damage: 207 (15%) had a cerebral infarct, 269 (19%) had microbleeds, and 222 (16%) had lacunes.

"Four in ten patients with atrial fibrillation but no history of stroke or transient ischemic attack had clinically unrecognized 'silent' brain lesions," said Professor Conen. "This brain damage could trigger cognitive decline."

Most study participants (1,234; 89%) were treated with oral anticoagulants. Co-Principal investigator Professor Stefan Osswald of University Hospital Basel, Switzerland, noted that the cross-sectional analysis looked at the data at a single point in time and cannot address the question of whether the cerebral infarcts and other brain lesions occurred before or after initiation of oral anticoagulation. But he said: "The findings nevertheless raise the issue that oral anticoagulation might not prevent all brain damage in patients with atrial fibrillation."

Professor Conen said: "All Swiss-AF participants underwent extensive cognitive testing. These data will be analyzed to see whether patients with silent brain lesions also have impaired cognitive function." Collaborations with other study groups will help to sort out whether these findings are specific to patients with atrial fibrillation.

SOURCES OF FUNDING: Swiss National Science Foundation (SNSF).

DISCLOSURES: David Conen received consulting fees from Servier, Canada.

Conference News

小径冠動脈病変に対するバルーンとステントの比較 (Abstract 5167)

BASKET-SMALL 2：小径の新規冠動脈病変において、着脱可能なバルーンの成績は永久留置型ステントと同様である

BASKET-SMALL 2: Removable balloon is as good as permanent stent implant in small de novo coronary lesions

小径の新規冠動脈病変において、着脱可能なバルーンの成績は永久留置型ステントと同様である、とのBASKET-SMALL 2トライアルのレイトブレイキングの結果が ESC Congress 2018 で発表され、同時に *Lancet* に掲載された。12か月の時点で、主要心血管イベント（MACE）はステント群（7.5%）とバルーン群（7.6%）とで有意差がなかった（p=0.918）。心臓死、非致死性心筋梗塞、標的病変血行再建術、または大出血の発現率は、2群間で統計的有意差はなかった。

Full Text

A removable balloon is as good as a permanent stent implant for opening small de novo coronary lesions, according to late breaking results from the BASKET-SMALL 2 trial presented in a Hot Line Session at ESC Congress 2018 and simultaneously published in *The Lancet*.

Principal investigator Professor Raban Jeger, of the University Hospital Basel, Switzerland, said: "The results of this trial move us a step closer towards treating small blocked arteries without having to insert a permanent implant."

BASKET-SMALL 2 is the largest randomized trial to examine whether drug coated balloons are as good as drug-eluting stents for opening small de novo coronary lesions. The effectiveness of the two treatments was evaluated by comparing the rate of major adverse cardiac events (MACE) at 12 months.

Between 2012 and 2017 the trial enrolled 758 patients with a first-time lesion in an artery smaller than 3 mm in diameter. The average age of study participants was 68 years, 72% had stable coronary artery disease and 28% had an acute coronary syndrome (myocardial infarction [MI] or unstable angina).

Patients were randomized to receive drug coated balloon angioplasty (382 patients) or second-generation drug-eluting stent implantation (376 patients). The balloon was coated with iopromide and paclitaxel, and the stents were covered with everolimus or paclitaxel.

After the procedure, patients were followed-up for 12 months for the occurrence of MACE, which included death from cardiac causes, non-fatal MI, and the need for target vessel revascularization. Secondary endpoints included the single components of MACE at 12 months, and major bleeding at 12 months.

At 12 months, there was no difference in the rates of MACE between patients who received a stent (7.5%) and patients who underwent the balloon procedure (7.6%) (p=0.918). Professor Jeger said: "The BASKET-SMALL 2 trial met its primary endpoint of non-inferiority for major adverse cardiac events at 12 months. This is a long-awaited milestone in clinical evidence for the drug coated balloon technique, which so far has primarily been used for the treatment of in-stent restenosis."

There were no statistical differences between groups in the rates of the individual components of the primary endpoint at 12 months: rates of cardiac death were 3.1% versus 1.3% (p=0.113), rates of nonfatal heart attack were 1.6% versus 3.5% (p=0.112), and rates of target vessel revascularization were 3.4% versus 4.5% (p=0.438) in the balloon versus stent groups, respectively. The rate of major bleeding at 12 months was similar in the balloon (1.1%) and stent (2.4%) groups (p=0.183).

"The potential benefits of a stent-free option to treat small blocked arteries are numerous," said Professor Jeger. "With no permanent implant left after the procedure, the problem of tissue growth and clot formation within the stent is eliminated. In addition, there may be no need for prolonged treatment with anticlotting medicines, which has been controversial since it increases the risk of bleeding."

He concluded: "Drug coated balloon angioplasty has the possibility to become the standard treatment for small blocked arteries. We will continue to monitor patients in the trial for a further two years for major adverse cardiac events, stent thrombosis, and bleeding."

SOURCES OF FUNDING: Swiss National Foundation, Bern, Switzerland; Basel Cardiovascular Research Foundation, Basel, Switzerland; and B. Braun Medical AG, Sempach, Switzerland.

DISCLOSURES: Prof. Jeger has received lecture honoraria and travel support from B. Braun.

Conference News

フェブキソスタットは高尿酸血症患者の有害事象を減少させる(Abstract 5163)

FREED：高齢の高尿酸血症患者において痛風治療薬は尿酸値を低下させ有害事象を減少させる

FREED: Gout drug lowers uric acid and reduces adverse events in elderly patients with hyperuricemia

痛風治療薬フェブキソスタットによる尿酸値低下により、高齢の高尿酸血症患者の有害事象が減少するとのレイトブレイキングの結果が ESC Congress 2018 で発表された。FREEDスタディにおいて、計537人の患者がフェブキソスタット(平均用量29 mg)を投与された。フェブキソスタット非投与群533人中、27% がアロプリノール100 mgを投与された。平均血清尿酸値はフェブキソスタット群で4.4 mg/dL、フェブキソスタット非投与群では6.7 mg/dLであった。主要評価項目(脳、心血管および腎イベント、および総死亡)はフェブキソスタット群の23% において発現したのに対し、フェブキソスタット非投与群では29% であった(p=0.017)。

Full Text

Uric acid reduction with the gout treatment febuxostat reduces adverse events in elderly patients with hyperuricemia, according to late breaking research presented in a Hot Line Session at ESC Congress 2018.

The FREED study examined whether lowering uric acid with febuxostat prevents cerebral, cardiovascular and renal events and death in elderly patients with the condition. The study enrolled 1,070 patients aged 65 years and older with hyperuricaemia (serum uric acid 7–9 mg/dL) and at risk for cerebral, cardiovascular, or renal events as defined by the presence of hypertension, type 2 diabetes, renal disorder, or a history of cerebral or cardiovascular disease.

Patients were randomly assigned in a 1:1 ratio to receive oral febuxostat for 36 months or not. In the febuxostat group, the dose was increased stepwise from 10 to 40 mg per day if tolerated. In the non-febuxostat group, allopurinol 100 mg was considered if serum uric acid was elevated. In both groups, the dose of febuxostat or allopurinol was adjusted to avoid a serum uric acid level less than 2 mg/dL. All patients were advised to consume a healthy diet, quit smoking, and exercise to help manage their hyperuricaemia.

Patients were followed-up for 36 months for the primary endpoint which was a composite of cerebral, cardiovascular, and renal events, and death from any cause. This consisted of death due to cerebral or cardiorenal vascular disease, new or recurring cerebrovascular disease, new or recurring coronary artery disease, cardiac failure requiring hospitalization, arteriosclerotic disease requiring treatment, renal disease (development of microalbuminuria, progression to overt proteinuria, or worsening of overt proteinuria to ≥300 mg/g albumin/creatinine, doubling of serum creatinine level, progression to end stage renal disease defined as estimated glomerular filtration rate <15 mL/min/1.73 m^2), and new atrial fibrillation.

A total of 537 patients received febuxostat and the average dose at the end of the study was 29 mg. Of the 533 patients in the non-febuxostat group, 27% received allopurinol 100 mg. Average serum uric acid levels reached 4.4 mg/dL in the febuxostat group and 6.7 mg/dL in the group not receiving febuxostat.

The primary endpoint occurred in 125 (23%) patients in the febuxostat group and 153 (29%) patients in the non-febuxostat group. Febuxostat significantly reduced the rate of the primary endpoint, with a hazard ratio of 0.75 (95% confidence interval 0.59–0.95, p=0.017).

When the individual components of the primary endpoint were analyzed separately, the most frequent event was renal impairment, which occurred in 16.2% of the febuxostat group and 20.5% of the non-febuxostat group. Among those with renal impairment, the development of microalbuminuria or mild proteinuria was common in both treatment groups.

Adverse events were observed in 132 (24.6%) patients in the febuxostat group and 135 (25.3%) patients in the non-febuxostat group, with no significant difference between the two groups (p=0.83). Two patients in the febuxostat group died. Also in the febuxostat group, mental disorder, headache, hypertension, abdominal pain, diarrhea, maculopapular rash, acute kidney injury, and edema of the extremities occurred in two patients each.

Professor Sunao Kojima, principal investigator, Kawasaki Medical School, Okayama, Japan, said: "We found that patients receiving febuxostat were 25% less likely to die or experience strokes, heart disease, or kidney disease over a three-year period than patients who did not receive febuxostat. The findings suggest that lowering uric acid with febuxostat provides clinical benefit."

SOURCES OF FUNDING: Teijin Pharma Limited.

DISCLOSURES: None.

Conference News

悪化する心不全においてトロンビン阻害薬は無効である(Abstract 3238)

COMMANDER HF：抗トロンビン薬は冠動脈疾患を伴う洞調律の心不全において無効である

COMMANDER HF: Antithrombin drug not effective in heart failure with sinus rhythm and coronary disease

抗トロンビン薬リバーロキサバンは、冠動脈疾患を有する洞調律の心不全患者における心不全悪化後の生存率、心筋梗塞（MI）および脳卒中から成る複合エンドポイントのリスクを減少させない、との COMMANDER HFトライアルの結果がESC Congress 2018 で発表され、*New England Journal of Medicine* に掲載された。追跡期間中央値21.1か月の間に、主要評価項目が発現したのは、リバーロキサバン群の25.0% に対しプラセボ群では26.2%であった（p=0.27）。総死亡または非致死性MIにおいて群間差はなかったが、非致死性脳卒中はリバーロキサバン群においてプラセボ群よりも有意に低かった（p=0.023）。

Full Text

The antithrombin drug rivaroxaban does not reduce the risk of a composite endpoint of survival, myocardial infarction (MI) and stroke after an episode of worsening heart failure in patients with heart failure, sinus rhythm, and coronary artery disease, according to late breaking results from the COMMANDER HF trial presented in a Hot Line Session at ESC Congress 2018 and with simultaneous publication in the *New England Journal of Medicine*.

After an episode of worsening heart failure, patients experience high rates of hospital readmission and death, particularly in the first few months. Previous studies have suggested that the enzyme thrombin may contribute to these poor outcomes by inducing inflammation, endothelial dysfunction, and thrombosis in blood vessels.

Rivaroxaban is an oral, direct factor Xa inhibitor that reduces thrombin generation. Higher doses (10–20 mg daily) are approved to treat and prevent venous thromboembolism, and prevent stroke or systemic embolism in patients with atrial fibrillation. Lower doses (2.5 mg twice daily), combined with antiplatelets, reduce cardiovascular mortality, MI and stroke in patients with acute coronary syndromes or stable coronary artery disease.

The COMMANDER HF trial tested whether, compared to placebo, rivaroxaban 2.5 mg twice daily could reduce thrombin generation and thereby lower rates of death and cardiovascular events in patients with recent worsening of chronic heart failure, who had reduced ejection fraction (40% or less), coronary artery disease and no atrial fibrillation.

Professor Faiez Zannad, study author, University of Lorraine, Nancy, France, said: "COMMANDER HF is not just another trial of oral anticoagulation in heart failure. The aim is to interfere with disease processes that rely on thrombin using a targeted antithrombin drug."

The trial enrolled 5,022 patients from 628 sites in 28 countries. Patients were randomly assigned to rivaroxaban 2.5 mg, taken orally twice daily, or matching placebo. The use of guideline recommended therapies for heart failure and coronary artery disease was well balanced between groups and included diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists. Background therapy included aspirin in virtually all patients and a substantial number were also receiving dual antiplatelet agents at the time either rivaroxaban or placebo was initiated in the trial.

The median age of participants at the start of the study was 66 years, 23% were women, and the median ejection fraction was 34%. Patients were followed-up for the primary efficacy outcome of all-cause mortality, MI, or stroke. The primary safety outcome was the composite of fatal bleeding or bleeding into a critical space with a potential for permanent disability.

During a median follow-up of 21.1 months, the primary efficacy outcome occurred in 626 (25.0%) of 2,507 patients assigned to rivaroxaban compared to 658 (26.2%) of 2,515 on placebo (hazard ratio [HR] 0.94, 95% confidence interval [CI] 0.84–1.05, p=0.27). There were no differences between groups in all-cause mortality (HR 0.98, 95% CI 0.87–1.10, p=0.74) or nonfatal myocardial infarction (HR 0.83, 95% CI 0.63–1.08, p=0.17) but there was a significantly lower rate of nonfatal stroke in the rivaroxaban, compared to placebo, group (HR 0.66, 95% CI 0.47–0.95, p=0.023).

The principal safety outcome occurred in 18 (0.7%) patients assigned to rivaroxaban and 23 (0.9%) assigned to placebo (HR 0.80, 95% CI 0.43–1.49, p=0.48). Patients taking rivaroxaban had a significantly higher risk of major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH) compared to those on placebo (HR 1.68, 95% CI 1.18–2.39, p=0.003). This result was mainly driven by the ISTH criterion of bleeding causing a fall in hemoglobin of 2 g/dL (1.24 mmol/L) or more.

Serious adverse events were reported in 479 (19.2%) patients taking rivaroxaban and 451 (18.0%) on placebo. The percentage of patients who permanently discontinued study medication due to an adverse event was 7.1% in the rivaroxaban group and 5.8% in the placebo group.

Professor Zannad said: "The most likely reason rivaroxaban failed to improve the primary efficacy outcome is that thrombin-mediated events are not the major driver of cardiovascular events in patients with recent heart failure hospitalization. Whether a higher dose of rivaroxaban could have led to a more favorable result is unknown."

SOURCES OF FUNDING: Janssen Research and Development.

DISCLOSURES: Full disclosure available on the paper.

Conference News

抗肥満薬は心血管イベントを増加させない (Abstract 2069)

CAMELLIA-TIMI 61：スタディの結果、心血管リスクの高い患者における体重管理目的でのlorcaserin使用が支持される

CAMELLIA-TIMI 61: Study supports use of lorcaserin for weight management in patients at high cardiovascular risk

抗肥満薬lorcaserinは心血管イベントを増加させないとのCAMELLIA-TIMI 61トライアルのレイトブレイキングの結果がESC Congress 2018 で発表され、*New England Journal of Medicine* に掲載された。食事療法および運動療法に追加することにより、この薬剤はプラセボに比べ軽度の体重減少をもたらし、主要心血管イベント（MACE）を増加させなかった。追跡期間中央値3.3年の時点で、MACEはlorcaserin 群の6.1% およびプラセボ群の6.2%に発現し、非劣性が示された（p<0.001）。これらの結果から、例え患者の心血管リスクが高い場合でも体重管理目的でのlorcaserin 使用は支持される、と筆者らは述べている。

Full Text

The weight loss drug lorcaserin does not increase cardiovascular events, according to late breaking results from the CAMELLIA-TIMI 61 trial presented in a Hot Line Session at ESC Congress and published in the *New England Journal of Medicine*.

Lorcaserin is an appetite suppressant, increasing the sense of fullness after a meal and reducing hunger before meals. It is not approved as a weight loss drug in Europe. The European Medicines Agency has expressed concerns about the potential risk of tumors based on animal data, psychiatric disorders including depression, and problems with heart valves.

The US Food and Drug Administration (FDA) in June 2012 approved the medication for weight loss in overweight adults with a body mass index (BMI) of 30 kg/m^2 or greater, or with a BMI of 27 kg/m^2 or greater and at least one weight-related health condition such as high blood pressure, type 2 diabetes, or high cholesterol. As with all weight loss agents, the FDA's approval was contingent on postmarketing studies assessing the risk for major adverse cardiovascular events.

The CAMELLIA-TIMI 61 trial was conducted as part of the FDA's postmarketing requirement. The trial examined the safety and efficacy of the drug with regard to major adverse cardiovascular events (MACE) and progression to diabetes in overweight or obese individuals with, or at risk for, cardiovascular disease.

The trial enrolled 12,000 adults from 473 centers in eight countries between January 2014 and November 2015. Participants had a BMI of at least 27 kg/m^2 and either 1) established cardiovascular disease (with or without diabetes) or 2) diabetes and at least one other cardiovascular risk factor. Participants were randomly allocated in a 1:1 ratio to lorcaserin (10 mg twice a day) or matching placebo. All participants were advised to exercise and eat healthily.

The primary safety endpoint was noninferiority of the drug compared to placebo for MACE (cardiovascular death, myocardial infarction, or stroke) after 460 events had occurred. If the safety endpoint was met, the trial would proceed to completion and assess the primary efficacy endpoint of superiority of the drug for MACE plus hospitalization for unstable angina, heart failure, or any coronary revascularization. Secondary endpoints included delay or prevention of conversion to type 2 diabetes in those with pre-diabetes at baseline, and the effect on weight, heart rate, blood pressure, lipids, and blood sugar.

The average age of participants was 64 years, 64% were male, and the median BMI was 35 kg/m^2. Three-quarters (8,958; 75%) had a history of at least one established cardiovascular disease: 8,153 (68%) had coronary artery disease, 1,129 (9.4%) had cerebrovascular disease, and 657 (5.5%) had peripheral artery disease. More than half (57%) had diabetes, 90% had hypertension, 94% had hyperlipidemia, and 20% had renal insufficiency.

The interim analysis after 460 events showed that the trial met its primary safety objective. At study completion with a median follow-up of 3.3 years, MACE occurred in 6.1% of those taking lorcaserin and 6.2% of those on placebo, demonstrating noninferiority (p<0.001).

The trial did not meet its superiority endpoint. The composite of MACE plus hospitalization for unstable angina, heart failure, or any coronary revascularization occurred in 11.8% of participants taking the drug and 12.1% of those on placebo (p=0.55).

On top of lifestyle counselling, those taking lorcaserin lost an average of 4.2 kg in the first year compared to 1.4 kg for those taking placebo (p<0.001). At one year, 39% of those taking the drug had lost at least 5% of their body weight compared to 17% of the placebo group (p<0.001) while 15% on the drug lost 10% of their body weight compared to 5% on placebo (p<0.001). The differences between groups remained statistically significant at 3.3-years of follow-up.

Regarding secondary endpoints, compared to placebo, the medication reduced the conversion rate to diabetes in participants with pre-diabetes at baseline. The drug also led to small improvements in levels of triglycerides, blood glucose, heart rate and blood pressure.

In the CAMELLIA-TIMI 61 study, the most common side effects possibly related to the drug and leading to drug discontinuation were dizziness, fatigue, headache and nausea – all of which are listed on the FDA-approved label. There was no difference in the occurrence of malignancy between the drug and placebo groups. In a dedicated echocardiographic substudy, there was a non-significant imbalance in the incidence of valvular disease at one year between the drug and placebo groups (1.8% versus 1.3%; p=0.24). Serious hypoglycemia was more common in patients on lorcaserin, a side effect observed in prior studies.

Lorcaserin is not approved for use in women who are pregnant, breastfeeding, or planning to become pregnant. It should be used with caution in patients with congestive heart failure. If signs or symptoms of valvular heart disease develop, such as dyspnea or a new cardiac murmur, patients should be evaluated and discontinuation of the drug considered. People taking the drug should be monitored for depression, changes in mood, and suicidal thoughts or behaviors – the drug should be discontinued if the latter are experienced.

"We have been able to show for the first time that this weight loss drug does what it is intended to do. It helps people lose weight without causing an increase in major adverse cardiovascular events in a population at higher risk for heart attacks and strokes," said Dr. Erin Bohula, an investigator with the CAMELLIA-TIMI 61 trial and TIMI Study Group investigator at Brigham and Women's Hospital, Boston, US.

"One of our hypotheses was that losing weight with this medication might also lead to a cardiovascular benefit but we did not see that," she continued. "While there were improvements in multiple cardiovascular risk factors, including weight, lipids and blood glucose, the magnitude of impact on these risk factors was relatively small."

Dr. Bohula said: "Nevertheless, the CAMELLIA-TIMI 61 study is notable as it provides the first demonstration of cardiovascular safety of any weight loss agent in a dedicated cardiovascular outcomes trial."

SOURCES OF FUNDING: Eisai Inc.

DISCLOSURES: Dr. Bohula has received personal fees from Servier, Merck, NIH, Lexicon, Medscape, Academic CME, MD Conference Express, Paradigm, and Novartis, and grants from Amgen, Astra Zeneca, and Merck.

Conference News

認知機能検査で認知症リスクの高い高血圧患者を同定できる(Abstract P4785)

Heart-Brain Study：高血圧患者には時計描画による認知機能検査をルーチンに施行すべきである

Heart-Brain Study: Clock drawing cognitive test should be done routinely in patients with hypertension

高血圧患者には認知機能障害検出目的の時計描画検査をルーチンに施行すべきである、とESC Congress 2018 で発表された。スタディグループは、時計描画検査によりMMSE (Mini-Mental State Examination) に比べ、認知機能障害の有病率が上昇することを明らかにした（それぞれ36% vs. 21%）。MMSE正常スコアの患者10人中3人が、時計描画検査の結果では異常であった。これら2つの試験結果の違いは、中年患者において最も大きかった。筆者らは、時計描画検査は無症状の血管障害の代替検査と考えられ、認知症発症リスクの高い患者を同定できると確信している。

Full Text

A clock drawing test for detecting cognitive dysfunction should be conducted routinely in patients with hypertension, according to research presented at ESC Congress 2018.

Patients with high blood pressure who have impaired cognitive function are at increased risk of developing dementia within five years. Despite this known link, cognitive function is not routinely measured in patients with high blood pressure.

"The ability to draw the numbers of a clock and a particular time is an easy way to find out if a patient with high blood pressure has cognitive impairment," said study author Dr. Augusto Vicario of the Heart and Brain Unit, Cardiovascular Institute of Buenos Aires, Argentina. "Identifying these patients provides the opportunity to intervene before dementia develops."

The Heart-Brain Study in Argentina evaluated the usefulness of the clock drawing test compared to the Mini-Mental State Examination (MMSE) to detect cognitive impairment in 1,414 adults with high blood pressure recruited from 18 cardiology centers in Argentina. The average blood pressure was 144/84 mmHg, average age was 60 years, and 62% were women.

For the clock drawing test, patients were given a piece of paper with a 10 cm diameter circle on it. They were asked to write the numbers of the clock in the correct position inside the circle and then draw hands on the clock indicating the time "twenty to four". Patients were scored as having normal, moderate, or severe cognitive impairment. The MMSE has 11 questions and produces a score out of 30 indicating no (24–30), mild (18–23), or severe (0–17) cognitive impairment.

The researchers found a higher prevalence of cognitive impairment with the clock drawing test (36%) compared to the MMSE (21%). Three out ten patients who had a normal MMSE score had an abnormal clock drawing result. The disparity in results between the two tests was greatest in middle aged patients.

Dr. Vicario said: "Untreated hypertension silently and progressively damages the arteries in the subcortex of the brain and stops communication between the subcortex and frontal lobe. This disconnect leads to impaired 'executive functions' such as planning, visuospatial abilities, remembering details, and decision-making. The clock drawing test is known to evaluate executive functions. The MMSE evaluates several other cognitive abilities but is weakly correlated with executive functions."

He continued: "Our study suggests that the clock drawing test should be preferred over the MMSE for early detection of executive dysfunction in patients with high blood pressure, particularly in middle age. We think the score on the clock drawing test can be considered a surrogate measure of silent vascular damage in the brain and identifies patients at greater risk of developing dementia. In our study, more than one-third of patients were at risk."

Dr. Vicario concluded: "The clock drawing test should be adopted as a routine screening tool for cognitive decline in patients with hypertension. Further studies are needed to determine whether lowering blood pressure can prevent progression to dementia."

SOURCES OF FUNDING: None.

DISCLOSURES: None.

Conference News

就寝時にヨガ音楽を聴くことは心臓によい (Abstract P4488)

ヨガ音楽は睡眠前の心拍変動に有益な影響を与える

Yoga music has a beneficial impact on heart rate variability before sleeping

就寝時にヨガ音楽を聴くことは心拍変動に有益な影響を与える、とESC Congress 2018で発表された。スタディには健常者149人（平均年齢26歳）が組み入れられ、別々の夜に3つのセッション（睡眠前に癒しのヨガ音楽；睡眠前に一定テンポのポップミュージック；睡眠前に音楽のない静かな状態）に参加した。心拍変動はヨガ音楽で増加、ポップミュージックで減少、さらに静かな状態で有意な変化はなかった。不安レベルはヨガ音楽の後に有意に低下し、ポップミュージック後に有意に上昇、さらに音楽なしのセッション後には上昇した。

Full Text

Listening to yoga music at bedtime is good for the heart, according to research presented at ESC Congress 2018.

Dr. Naresh Sen, study author, Consultant Cardiologist at HG SMS Hospital, Jaipur, India, said: "We use music therapy in our hospital and in this study we showed that yoga music has a beneficial impact on heart rate variability before sleeping."

Previous research has shown that music can reduce anxiety in patients with heart disease. However, studies on the effects of music on the heart in patients and healthy individuals have produced inconsistent results, partly they did not state what style of music was used.

The body's heart rate changes as a normal response to being in "fight or flight" or "rest and digest" mode. These states are regulated by the sympathetic and parasympathetic nervous systems, respectively, and together comprise the autonomic nervous system. High heart rate variability shows that the heart is able to adapt to these changes. Conversely, low heart rate variability indicates a less adaptive autonomic nervous system.

Low heart rate variability is associated with a 32–45% higher risk of a first cardiovascular event. Following a cardiovascular event, people with low heart rate variability have a raised risk of subsequent events and death. Failure of the autonomic nervous system to adapt may trigger inflammation, which is linked to cardiovascular disease. Another possibility is that people with low heart rate variability already have subclinical cardiovascular disease.

This study investigated the impact of listening to yoga music, which is a type of soothing or meditative music, before bedtime on heart rate variability. The study included 149 healthy people who participated in three sessions on separate nights: soothing yoga music before sleep; pop music with steady beats before sleep; and no music or silence before sleep at night.

At each session, heart rate variability was measured for five minutes before the music or silence started, for ten minutes during the music/silence, and five minutes after it had stopped. In addition, anxiety levels were assessed before and after each session using the Goldberg Anxiety Scale. The level of positive feeling was subjectively measured after each session using a visual analogue scale.

The average age of participants was 26 years. The researchers found that heart rate variability increased during the yoga music, decreased during the pop music, and did not significantly change during the silence.

Anxiety levels fell significantly after the yoga music, rose significantly post the pop music, and increased after the no music session. Participants felt significantly more positive after the yoga music than they did after the pop music.

Dr. Sen noted that holistic therapies such as music cannot replace evidence-based drugs and interventions, and should only be used as an add-on.

He said: "Science may have not always agreed, but Indians have long believed in the power of various therapies other than medicines as a mode of treatment for ailments. This is a small study, and more research is needed on the cardiovascular effects of music interventions offered by a trained music therapist. But listening to soothing music before bedtime is a cheap and easy to implement therapy that cannot cause harm."

SOURCES OF FUNDING: None.

DISCLOSURES: Nothing to disclose,

Conference News

たこつぼ心筋症患者においてがんは予後不良と関連がある(Abstract P6133)

がんを有するたこつぼ心筋症患者においては有害事象がより多い

Adverse events are more common in patients with takotsubo cardiomyopathy who had cancer

たこつぼ心筋症患者において、がんは死亡および再入院リスクが高いことと関連がある、とESC Congress 2018 で発表された。入院中および退院後の有害事象を合わせて調査したところ、がんの既往またはがんを有しているたこつぼ心筋症患者は、がんを有さない患者に比べ臨床イベントのリスクが有意に高かった(p<0.01)。退院後のイベントリスクを別々に評価したところ、がんを有さないグループに比べがんグループでは2倍高かった(p<0.01)。入院中のイベントリスクは、がんグループにおいて有意ではないが高い傾向がみられた。

Full Text

Cancer is linked to an increased risk of death and rehospitalization in patients with takotsubo cardiomyopathy, according to research presented at the ESC Congress 2018.

Dr. Francesco Santoro, study author, University of Foggia, Italy, said: "In our study, patients with takotsubo cardiomyopathy were twice as likely to die or be readmitted to hospital within three years if they had previous or current cancer than if they did not. Patients with broken heart syndrome and cancer need strict monitoring at follow-up."

Takotsubo cardiomyopathy, sometimes referred to as broken heart syndrome, is a type of heart failure that occurs suddenly and goes away within days or weeks. Increased levels of stress hormones are thought to be one of the main drivers. Symptoms are similar to a myocardial infarction and include sudden chest pain and shortness of breath.

Around 30% of takotsubo cardiomyopathy is due to emotional triggers such as death of a spouse, anger, financial problems, or happy life events such as birthdays and weddings. Around 40% of patients have a physical trigger such as surgery, while in 30% the trigger is unknown. Prior studies have suggested that cancer may be a physical trigger.

The current study investigated the association between cancer and poor outcomes in patients with takotsubo cardiomyopathy by combining the results of three published studies on this topic in a meta-analysis. The researchers looked at adverse events that occurred while patients were in hospital with takotsubo cardiomyopathy (life threatening arrhythmias, cardiogenic shock, thromboembolism, respiratory support) as well as all-cause death and re-hospitalization for cardiovascular disease during the first three years after discharge from hospital.

A total of 554 patients admitted to hospital with takotsubo cardiomyopathy were included in the analysis. One in five patients had previous or current cancer (113 patients; 20%). Gastrointestinal cancers were the most frequent (23%), while nervous system and urinary cancers were the rarest (3% for each). Patients who had past or existing cancer were of a similar age to those who had never had cancer.

When the researchers examined the risk of in-hospital and post-discharge adverse events together, they found that takotsubo cardiomyopathy patients with past or existing cancer had a significantly higher risk of clinical events than those without (risk ratio [RR] 1.82, 95% confidence interval [CI] 1.37–2.42, p <0.01).

When evaluated separately, the risk of events after discharge was two-fold higher in the cancer group compared to the cancer-free group (RR 2.08, 95% CI 1.50–2.87, p <0.01). There was a trend towards a higher risk of in-hospital events in the cancer group, but it was not statistically significant (RR 1.30, 95% CI 0.74–2.29, p= 0.36).

Dr. Santoro said: "We found that takotsubo cardiomyopathy patients who had ever had cancer were at greater risk of adverse events, particularly after discharge from hospital. More research is needed to clarify the reasons for this. These patients may benefit from standard therapy for heart failure, especially an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker."

Dr. Santoro noted a limitation of the study was that there was no control group of individuals without takotsubo cardiomyopathy.

SOURCES OF FUNDING: None.

DISCLOSURES: None.

Conference News

抗凝固薬による出血はがんと診断されるリスクを上昇させる(Abstract 1321)

COMPASS：抗凝固薬で治療されている患者が出血した場合は、がんの検索をすべきである

COMPASS: Bleeding in patients treated with anticoagulants should stimulate search for cancer

抗凝固薬で治療されている患者において出血した場合はがんの検索をすべきである、とのCOMPASS試験のレイトブレイキングの結果が ESC Congress 2018 で発表された。重大な消化管出血により新たな消化器がんの診断は20倍となり（9.3% vs. 7%、p<0.0001）、非消化器がんの診断は2倍に増加した（4.6% vs. 3.1%、p<0.0001）。重大な非消化管出血は非消化器がんと新たに診断されるリスクを5倍上昇させた（9.4% vs. 3.0%、p<0.0001）。重大な出血を来した患者の10人に1人以上が後にがんと診断され、新たにがんと診断された患者の20% は出血を来した患者であった。

Full Text

Bleeding in patients treated with anticoagulants should stimulate a search for cancer, according to late breaking results from the COMPASS trial presented at ESC Congress 2018.

Professor John Eikelboom, principal investigator, of the Population Health Research Institute, McMaster University, Hamilton, Canada, said: "In patients with stable coronary artery disease or peripheral artery disease, the occurrence of major gastrointestinal bleeding predicts a substantial increase in new gastrointestinal cancer diagnoses, while major genitourinary bleeding predicts a substantial increase in new genitourinary tract cancer diagnoses."

Up to one in ten patients with cardiovascular disease have recurrent events each year. As previously reported, the COMPASS trial found that in patients with coronary artery disease or peripheral artery disease, the combination of rivaroxaban (2.5 mg twice daily) and aspirin reduced cardiovascular events compared to aspirin alone, but there were more major bleeding events in the combined drug group.

For the first time, the investigators report details on the effect of bleeding on subsequent cancer diagnoses.

Briefly, the trial enrolled 27,395 patients with chronic stable coronary or peripheral artery disease from 602 centers in 33 countries. Patients were randomly allocated to one of three groups: 1) rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily 2) rivaroxaban 5 mg twice daily, or 3) aspirin 100 mg once daily. Results in each of the rivaroxaban groups were compared with the aspirin alone group. The mean duration of follow up was 23 months.

The combination increased major bleeding, as defined by the International Society on Thrombosis and Haemostasis (ISTH), compared with aspirin (3.1% versus 1.9%, hazard ratio [HR] 1.70, 95% confidence interval [CI] 1.40–2.05, p<0.0001), but did not significantly increase intracranial (0.3% versus 0.3%, HR 1.16, 95% CI 0.67–2.00, p=0.60) or fatal bleeding (0.2% versus 0.1%, HR 1.49, 95% CI 0.67–3.33, p=0.32).

Major gastrointestinal bleeding was associated with a 20-fold increase in new diagnoses of gastrointestinal cancer (9.3% versus 0.7%, HR 22.6, 95% CI 14.9–34.3, p<0.0001) and a two-fold increase in non-gastrointestinal cancer (4.6% versus 3.1%, HR 2.55, 95% CI 1.47–4.42, p<0.0001).

Major non-gastrointestinal bleeding was associated with a five-fold increase in new non-gastrointestinal cancers (9.4% versus 3.0%, HR 5.49, 95% CI 3.95–7.62, p<0.0001), but not with new gastrointestinal cancer (0.5% versus 0.8%, HR 0.85, 95% CI 0.21–3.45, p=0.82).

Professor Eikelboom said: "More than one in ten patients with major bleeding were subsequently diagnosed with cancer, and more than 20% of new cancer diagnoses were in patients who experienced bleeding. By reducing major cardiovascular events and mortality, the combination of rivaroxaban and aspirin already produces a clear net benefit, and if bleeding unmasks cancer it could potentially lead to the added benefit of improved cancer outcomes."

SOURCES OF FUNDING: Bayer AG.

DISCLOSURES: John Eikelboom has received honoraria and/or research support from Astra-Zeneca, Bayer, Boehringer-Ingelheim, Daiichi-Sankyo, Janssen, and Pfizer.

Conference News