News and Views

INSOMNIA AND RISK OF STROKE

People who find it difficult to fall asleep or stay asleep may be at higher risk of having a stroke, according to a study of over 31,000 people published in the journal *Neurology*.

Researchers from the Virginia Commonwealth University, School of Medicine, Richmond in Virginia set out to examine the association between insomnia and incident stroke. For this they sourced data of 31,126 individuals with an average age of 61 years from the Health and Retirement Study between 2002 and 2020. 57% were female. None of the selected participants had ever suffered a stroke. Symptoms of insomnia like difficulty falling asleep, waking up often during the night, waking up too early and nonrestorative sleep (i.e., not feeling rested in the morning) were self-reported through a questionnaire. The scores ranged from 0 to 8; higher scores indicated more severe insomnia.

Over a follow-up period of 9 years, 2101 cases of stroke occurred. After adjusting for other risk factors for stroke such as smoking, alcohol and sedentary life, the risk of stroke was increased 16% in people with 1 to 4 symptoms of insomnia compared to those who did not have insomnia with hazard ratio (HR) of 1.16.

A total of 19,149 participants reported one to four symptoms; of these, 1,300 had a stroke. There were 6,282 people without any symptoms of insomnia; among these, 365 had a stroke. Those who had 5 to 8 symptoms of insomnia were at a 51% increased risk of stroke with a HR of 1.51. Out of the 5,695 subjects with 5 to 8 symptoms, 436 developed a stroke.

Subjects younger than 50 years were nearly 4 times more likely to experience a stroke (HR 3.84) compared to those older than 50 years (HR 1.38) when participants with 5 to 8 symptoms were compared with those without any symptoms of insomnia. Of the 458 subjects younger than 50 years having 5 to 8 symptoms, 27 had a stroke. And, out of the 654 people aged ≥50 years with the same number of symptoms, 33 had a stroke.

This study demonstrates the link between insomnia and risk of stroke; however, it does not establish causality. Greater the number of insomnia symptoms, higher was the risk indicating a dose-response relationship. Individuals younger than 50 years were particularly at risk. This risk was mediated by comorbid diseases such as hypertension, heart disease, diabetes and depression. Physicians should be aware of this association and assess their patients for insomnia. Management of insomnia with medications or psychotherapy may help prevent stroke.

Reference

1. Wendemi Sawadogo, et al. Association between insomnia symptoms and trajectory with the risk of stroke in the Health and Retirement Study. Neurology. 2023;101(5):e475-e488.

EARLY HYSTERECTOMY AND RISK OF HEART DISEASE

The risk of heart disease is known to be higher among postmenopausal women. A new study from South Korea has shown that women who had a hysterectomy done before 50 years of age were at a higher risk for heart disease, stroke in particular. The study findings are published in *JAMA Network Open*.

Jin-Sung Yuk from the Dept. of Obstetrics and Gynecology, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Republic of Korea and co-researchers conducted this retrospective study to examine if hysterectomy before age 50 years increased the risk of new onset cardiovascular disease (CVD). For this they sourced data of 55,539 women who underwent a hysterectomy, with a median age of 45 years, from the national health insurance database from January 2011 to December 2014 and matched them with 55,539 women, who did not undergo a hysterectomy.

Over nearly 8 years (median) of follow-up, the hysterectomy group had a greater risk of CVD with the incidence of heart disease being 115 per 100,000 person-years compared with 96 per 100,000 person-years in the non-hysterectomy group. After adjustment for multiple variables, women who underwent hysterectomy were at a higher risk of developing heart disease compared to those who did not have the surgery with hazard ratio (HR) of 1.25. The risk of stroke was found to be significantly increased among women in the hysterectomy group with HR of 1.31. But the occurrence of MI (HR 1.06) and coronary artery revascularization (HR 1.03) were similar between both groups. When women who also had an oophorectomy were excluded from the analysis,

the risk of heart disease was still higher in women with hysterectomy (HR 1.24).

These findings suggest that hysterectomy in women younger than 50 years resulting in early menopause is associated with increased risk of heart disease, especially stroke. The authors write that "because the incidence of CVD was not high, a change in clinical practice may not be needed". Nevertheless, women undergoing early hysterectomy should be educated about the risk of heart disease and recommended a healthy lifestyle to prevent a cardiovascular event.

Reference

1. Jin-Sung Yuk, et al. Association of early hysterectomy with risk of cardiovascular disease in Korean women. JAMA Netw Open. 2023;6(6):e2317145.

NIGHT OWLS AT RISK OF EARLY DEATH

People who are night owls or those who stay up late at night and get up late in the day are at risk of dying at an early age compared to the early birds or those who sleep early and also wake up early, according to results of a 37-year follow-up study published in the journal *Chronobiology International*.

This study, which was a follow-up of the 2002 Finnish Twin Cohort study, included 23,854 twins from 1981 to 2018. To assess whether they were a morning or an evening person and to what extent, the participants were asked to choose one out of the four responses at the time of enrollment: "clearly a morning or evening person" or "to some extent a morning or evening person". Deaths till 2018 were ascertained from national registers. Just 10% were clearly evening persons, while 33% were to an extent evening people. Over 29% were clearly morning persons and 27.7% described themselves as morning people to an extent.

There were 13,123 morning persons or early birds (6,354 "clear" and 6,769 "to some extent"), while 9,853 were evening types or night owls (7,591"clear" and 2,262 "to some extent"). Compared to the morning persons, the evening people tended to be younger in age and more likely to be consuming alcohol or smoking. A total of 8728 deaths occurred by 2018 when the study ended. Results showed that the all-cause mortality increased by 9% among the clearly evening people compared to the definite morning people with hazard ratio of 1.09. However, the deaths could mostly be attributed to smoking and alcohol intake in larger amounts and not the chronotype of the individual since non-smokers in this group were not at higher risk of death and no association was noted between chronotype and mortality.

This study shows no or minimal independent impact of the chronotype of an individual on mortality suggesting that other factors such as smoking, alcohol or sleep deprivation could be contributing to the increased mortality risk. But the 9% increase in risk of premature death, though small, is significant enough to warrant change in lifestyle and behaviors to reduce one's risk.

Reference

1. Hublin C, et al. Chronotype and mortality - a 37-year follow-up study in Finnish adults. Chronobiol Int. 2023;40(7): 841-49.

IS TESTOSTERONE CARDIAC SAFE? THE JURY IS STILL OUT

Use of testosterone in middle-aged and older men with hypogonadism and pre-existing heart disease or with risk factors for heart disease did not increase the risk of major adverse cardiac events compared to placebo, according to the TRAVERSE trial published in the *New England Journal of Medicine*.[1] These findings were also presented at ENDO 2023, the ongoing Annual Meeting of the Endocrine Society.

A total of 5,246 men, ages ranging from 45 to 80 years (mean age 63 years), were recruited for this multicenter study from May 2018 to February 2022. More than half of the selected participants had either pre-existing heart disease, while the remaining were at high risk of heart disease with presence of risk factors such as hypertension, diabetes, dyslipidemia or active smoking. They also had symptoms of hypogonadism and fasting testosterone levels <300 ng/dL on two separate occasions. The study subjects were randomized to daily treatment with transdermal testosterone gel 1.62% or a placebo gel for a period of 21.7 months (mean). The testosterone levels were maintained between 350 and 750 ng/dL. The mean follow-up was 33.0 months.

After a mean follow-up of 33 months, the primary cardiovascular safety endpoint, which was the first episode of any component of a composite of cardiac-related mortality, nonfatal myocardial infarction or nonfatal stroke was comparable between the two groups; 7.0% in the testosterone group vs 7.3% in the placebo group (hazard ratio 0.96). The secondary endpoints, which had components similar to the primary endpoint, but additionally included coronary revascularization, were also similar between the two groups. However, the incidence of atrial fibrillation (3.5% vs 2.4%), acute kidney injury (2.3% vs 1.5%) and pulmonary embolism (0.9% vs 0.5%) was higher in patients on testosterone compared to those receiving placebo.

These much-awaited results show that testosterone replacement therapy was non-inferior to placebo with regard to the first occurrence of acute cardiac events in men with hypogonadism with diagnosed heart disease or those who are at high risk of developing heart disease. But the risk of atrial fibrillation and pulmonary embolism was increased in the testosterone group. The US FDA has cautioned about the use of testosterone replacement therapy in aging men with low testosterone levels. It also requires a warning about the increased risk of acute cardiac events such as heart attack and stroke associated with the use of testosterone. The findings of the present study are reassuring, but they do not totally refute the current guidance about exercising caution when prescribing testosterone. Nonetheless, they do enable a more informed decision making after taking into consideration the potential risks and benefits.

Reference

1 Lincoff AM, et al; TRAVERSE Study Investigators. Cardiovascular safety of testosterone-replacement therapy. N Engl J Med. 2023;389(2):107-17.

A NEW DRUG FOR HEART FAILURE

Physicians treating patients with heart failure now have a new treatment option for reducing rehospitalizations for heart failure. The US FDA has approved sotagliflozin to reduce the risk of cardiovascular death, hospitalization for heart failure and urgent heart failure visits in patients with heart failure, both with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF). It has also been approved in patients with type 2 diabetes, chronic kidney disease (CKD), and other cardiovascular disease risk factors to prevent these events.

Sotagliflozin is the first dual sodium-glucose cotransporter 1 and 2 (SGLT1/2) inhibitor.

The approval of sotagliflozin is based on the results from the SOLOIST-WHF (Worsening Heart Failure) trial in which sotagliflozin treatment of type 2 diabetes patients who had been recently hospitalized for worsening heart failure led to 33% reduction in the risk of the composite of hospitalizations for heart failure, urgent visits for heart failure and cardiovascular death over a median follow-up of 9 months compared to controls. The drug was also safe. In an exploratory post hoc analysis of the SOLOIST-WHF trial, sotagliflozin reduced 30- and 90-day rehospitalization rates by nearly 50%.

Side effects: Urinary tract infection, volume depletion, diarrhea, hypoglycemia

Contraindication: Patients with hypersensitivity to sotagliflozin or any of its components

Warning and precautions

- Assess renal function and volume status before starting treatment. In patients with decompensated heart failure, start treatment when they are hemodynamically stable.
- Increased risk of ketoacidosis in patients with type 1 diabetes mellitus. Type 2 diabetes mellitus (T2DM) and pancreatic disorders are also risk factors. Hence, monitor for ketones in T1DM patients and others at risk for ketoacidosis.
- Elderly patients, patients on loop diuretics or those with impaired renal function (eGFR < 60 mL/min/1.73 m^2) are at higher risk for hypotension.
- Evaluate patients for signs and symptoms of urinary tract infections and monitor and genital mycotic infections.
- Concomitant use in patients on insulin or insulin secretagogues may increase the risk of hypoglycemia.

Sources

1. Available from: https://www.lexpharma.com/media-center/news/2023-05-26-lexicon-announces-fda-approval-of-inpefa-sotagliflozin-for-treatment-of-heart-failure.
2. FDA approves new drug, sotagliflozin, for heart failure - Medscape - May 26, 2023.

SUBCLINICAL HEART DISEASE IN DIABETES

Nearly one-third of patients with type 2 diabetes have subclinical or silent cardiovascular disease (CVD) indicated by raised levels of high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) compared to those who do not have diabetes, according to a study published online May 31, 2023 in the Journal of the *American Heart Association*. The high burden of subclinical CVD in this patient group considerably increased mortality risk even after adjustment for demographic and traditional CV risk factors like smoking, high BP/cholesterol, overweight or obesity and a positive family history of heart disease.

Researchers from Johns Hopkins University and University of Maryland Medical Center in Baltimore, United States sought to examine the prevalence of subclinical cardiovascular disease. For this they sourced data of 10,304 participants without a history of CVD from the 1999-2004 National Health and Nutrition Examination Survey (NHANES). For this, they measured the levels of hs-cTnT and NT-proBNP in the stored serum samples

and estimated the prevalence of raised levels of these biomarkers among those with diabetes and without diabetes. The cut-offs to diagnose CVD were hs-cTnT (≥14 ng/L) or NT-proBNP (≥125 pg/mL).

The study group was categorized as having no diabetes, newly diagnosed diabetes (≤1 year or no self-reported diagnosed diabetes and HbA1c ≥6.5%), short diabetes duration (self-reported diagnosis between 1 and 10 years) and long diabetes duration (≥10 years).

On analysis, 33.4% patients with diabetes had higher prevalence of either raised hs-cTnT or NT-proBNP levels compared to 16.1% of those who did not have diabetes; 19% had elevated levels of hs-cTnT and 23% had elevated NT-proBNP levels. Adults with diabetes were also more likely to have elevated levels of both biomarkers compared to those without diabetes (9% versus 3%). But after adjusting for age, sex, race/ethnicity and traditional CVD risk factors, only raised hs-cTnT was found to be positively associated with diabetes. Those who had long-standing diabetes and poorly controlled diabetes were more likely to have significantly elevated hs-cTnT levels.

Researchers also studied the associations between the two raised biomarkers and all-cause mortality as well as CVD-related mortality, whether heart disease or cerebrovascular disease. After adjustment for demographics and traditional cardiovascular risk factors, elevated hs-cTnT levels were associated with 77% increased risk of all-cause mortality with adjusted hazard ratio (aHR) of 1.77 and elevated NT-proBNP were associated with 78% increased risk with aHR 1.78. The risk of CVD-related mortality was increased 54% for elevated hs-cTnT with aHR of 1.54 and the increase in risk was more than 2-folds for NT-proBNP (aHR 2.46).

This study shows that many patients with type 2 diabetes who do not have a diagnosed heart disease are still at high risk of developing cardiac complications such as heart attack, stroke, heart failure. It further suggests that cardiac biomarkers, hs-cTnT in particular, should routinely be measured in patients with type 2 diabetes to assess and monitor their risk for heart disease along with other traditional CV risk factors. Doing so will enable timely institution of preventive strategies for patients with type 2 diabetes at higher risk.

Reference

1. Fang M, et al. Subclinical cardiovascular disease in US adults with and without diabetes. J Am Heart Assoc. 2023;12(11):e029083.

ATOPIC DERMATITIS AND RISK OF THROMBOSIS

Patients with atopic dermatitis are at increased risk of venous thromboembolism (VTE), suggests a study from Taiwan published online May 31 in *JAMA Dermatology*.[1]

In this study, Tai-Li Chen and coauthors investigated the risk of new onset VTE in patients with atopic dermatitis. For this they selected adults who had been newly diagnosed with AD between 2003 and 2017 and matched controls from the National Health Insurance Research Database. A total of 284,858 matched participants were recruited for the study; both groups had 142,429 participants each. AD patients were further categorized into subgroups according to the disease severity. Both groups had female preponderance. The average age of participants was around 44 years in both groups.

Over the follow-up period, it was found that 0.7% of patients with AD developed VTE corresponding to incidence rate of 1.05 per 1,000 person-years, while in the control group, 0.6% patients developed VTE with incidence rate of 0.82 per 1000 person-years. Compared to those without AD, the risk of incident VTE was considerably higher among patient with AD with hazard ratio (HR) of 1.28. The HR for deep vein thrombosis (DVT) was 1.26 and that for pulmonary embolism (PE) was 1.30.

AD is a chronic inflammatory condition of the skin and inflammation increases prothrombotic factors and may trigger VTE. This study demonstrates the increased risk of VTE in AD, which can potentially be fatal. Hence, all adult patients with AD should be regularly assessed for cardiovascular risk and they should undergo prompt evaluation if they have symptoms suggestive of VTE such as swelling and tenderness in the legs (DVT) or sudden onset of shortness of breath and pain on breathing (PE). Although the difference between the two groups was small, nevertheless physicians treating these patients should be aware of this association and remain alert to these symptoms and also educate their patients about the same.

Reference

1. Chen TL, et al. Risk of venous thromboembolism among adults with atopic dermatitis. JAMA Dermatol. 2023;159(7):720-27.