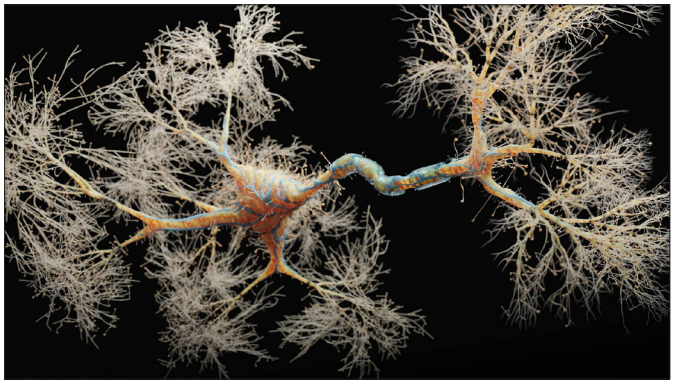
Cellular Stress Enzyme May be a Target for Neurodegenerative Disease Treatments

An enzyme called MARK2 has been identified as a key stress-response switch in cells in a study by researchers at Johns Hopkins Bloomberg School of Public Health, US. Overactivation of this type of stress response is a possible cause of injury to brain cells in neurodegenerative diseases such as Alzheimer's, Parkinson's, and Amyotrophic Lateral Sclerosis. The discovery will make MARK2 a focus of investigation for its possible role in these diseases, and may ultimately be a target for neurodegenerative disease treatments.



In addition to its potential relevance to neurodegenerative diseases, the finding is an advance in understanding basic cell biology. The paper describing the discovery appeared in *PLoS Biology.*

The study focused on the cellular response to "proteotoxic" stress, a buildup of damaged or aggregated proteins within the main part of the cell, which is a central feature of neurodegenerative diseases. It has been known that cells respond to this type of stress by reducing their production of new proteins, and that a signaling enzyme likely mediates this response. The researchers, after ruling out other signaling enzymes, were able to show that the signaling enzyme MARK2 has this role.

"Further studies of this previously unrecognized signaling pathway should expand our understanding of protein regulation in cells and the role of this process in the development of human diseases." Said Jiou Wang, PhD, Professor, Department of Biochemistry and Molecular Biology, Bloomberg School.

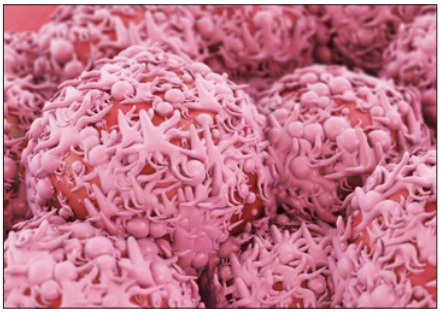
The researchers first identified the kinase MARK2 as one of several candidates for their inquiry by sifting through a large database, produced with prior research, of various kinases and the proteins they potentially act upon. Following up their leads with various cell-free and cell culture experiments, they were able to show that MARK2, and no other candidate kinase, can switch off the protein-making machinery in cells in response to proteotoxic stress, even when the other four known protein-shutdown kinases are absent.

As a preliminary check on the clinical relevance of these findings, the researchers examined a mouse model of familial ALS and samples of spinal cord tissue from human ALS patients. They found evidence that this PKCδ-MARK2 pathway is highly active in these cases compared to non-ALS mice and humans.

"These findings are consistent with the idea that in ALS, for example, this PKCδ-MARK2 pathway is highly active and reducing protein production, which over the long term contributes to the disease process," Wang says.

Chromatin-regulating Enzyme Found to be a Key Driver of Common Lung Cancer

A chromatin-regulating enzyme has been shown by in-depth interdisciplinary investigations to be a key driver of a common type of lung cancer. Drugs that target the enzyme could improve treatment and survival rates for this particular cancer.



"Squamous cell carcinoma represents nearly one third of all lung cancers in humans," says KAUST structural biologist Lukasz Jaremko, who led the research along with colleagues at Stanford University and The University of Texas MD Anderson Cancer Center, U.S. "Our joint structural and dynamics investigations, including enzymatic activity studies, genetic analyses, and mouse

model and human cell results, all point to the enzyme histone-lysine N-methyltransferase (NSD3) as a main driver of cancer," he says.

As part of the investigations, Ph.D. student Vladlena Kharchenko, a member of Jaremko's lab, used nuclear magnetic resonance spectroscopy to experimentally evaluate the structure and dynamics of both normal NSD3 and the hyperactive mutant implicated in driving lung squamous cell carcinoma.

"The mutation did not appear to affect the static structure of the enzyme. However, using the dynamic nuclear Overhauser effect, we were able to show that the hyperactive mutation led to mobility changes in part of the NSD3 enzyme, enabling it to more easily catalyze the addition of two methyl molecules to a histone tail in chromatin. This ultimately deregulates cancer-promoting genes in some forms of lung cancer." Said Lukasz Jaremko, KAUST Structural Biologist

"Our studies explain the molecular foundations of NSD3 enzymatic hyperactivity, its danse macabre, and unequivocally confirm that NSD3, not the previously suspected FGFR1, is the main driver of squamous cell carcinoma of the lung," says Jaremko.

The collaborative investigations also found that NSD3 was susceptible to a category of anticancer drugs called bromodomain inhibitors. But inhibitors that specifically target NSD3 are still needed, making it a prominent target for drug screening campaigns.

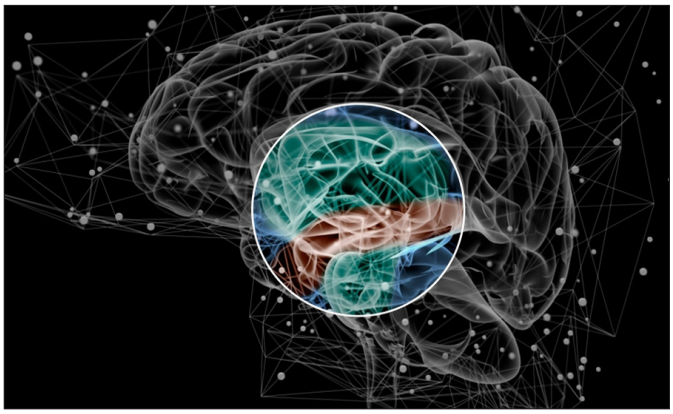
Transporter Imbalance Implicated in Schizophrenia

Alterations in the balance of two chloride ion transporters may be responsible for cognitive deficits in schizophrenia, according to a Northwestern Medicine, US, study published in *Science Advances*.

These alterations cause the most important inhibitory current in the brain, called GABAA, to become excitatory. Inhibiting the transporter activity with bumetanide, an FDA-approved diuretic, rescued cognitive symptoms in mouse models of schizophrenia.

"To our surprise, it completely reversed deficits on three different tests of cognitive performance," said Marco Martina, MD, MsC, Ph.D., associate professor of Physiology and senior author of the study.

GABAA is the major inhibitory current in the adult brain. GABAA currents help maintain inhibitory-excitatory balance in the brain along with excitatory neurotransmitters such as glutamate. However, in early development and until about two years of age in humans, GABAA is excitatory.



The polarity of the GABAA-mediate current is determined by the balance of two chloride transporters: NKCC1 and KCC2.

Attempting to reverse the cognitive symptoms in the mice, the investigators gave these mice bumetanide, a diuretic that inhibits NKCC1. Mice treated with this drug did much better on cognitive tests compared to mice who were untreated. Another experiment, this time using a viral construct to selectively reduce expression of NKCC1 in the cortex, also produced improved cognitive performance, demonstrating that the imbalance in chloride transporters could be a significant contributor to the cognitive symptoms in schizophrenia.

This was supported by the biology of the channels. Other ion channels, such as potassium or sodium channels, have a large difference between their equilibrium potential and resting potential. This means that unless the concentration of ions inside or outside the cells changes drastically, the overall polarity of the currents will not change.

"Most biological mechanisms might have redundancy mechanisms built in, but these chloride channels are engineered to change at a certain stage of development," Martina said. "Therefore, any pathological disturbance may end up affecting polarization."

Further, Martina said he believes this mechanism may be present in other disorders with cognitive deficit symptoms as well, and plans on examining autism-spectrum disorders for any changes in GABAA polarity.

Association Between Dehydration and Falls

The goal of a recent study published in *Mayo Clinic Proceedings: Innovations, Quality & Outcomes* was to determine the association between dehydration and falls in adults, 65 years and older.

In this retrospective cohort study, University of Wisconsin Health's, US, electronic health records were utilized to examine the association between dehydration at baseline and falls within three years after baseline—while accounting for prescriptions of loop diuretic, antidepression, anticholinergic, antipsychotic and benzodiazepine/hypnotic medications and demographic characteristics, using logistic regression. Dehydration was defined as serum urea nitrogen to creatinine ratio > 20; sodium level > 145 mg/dL; urine specific gravity > 1.030; or serum osmolality > 295 mOsm/kg.

The results showed that of the 30634 patients, 37.9% were dehydrated; 11.4% had a fall during follow-up, and 11.7% perished during the follow-up period. A positive association of dehydration was found with

falls alone. For the outcome of falls or death, dehydration was positively associated along with loop diuretics and antipsychotic medications.

The findings showed that more than one-third of older adults in this cohort were dehydrated, with a strong association between dehydration and falls. It was stated that understanding and addressing the risks associated with dehydration, including falls, has the potential for improving the quality of life for patients as they age.

The New Genetic Target for Blood Cancer Treatment

Targeting a pathway that is essential for the survival of certain types of acute myeloid leukemia could provide a new therapeutic avenue for patients, the latest research has found.

Researchers from the Wellcome Sanger Institute, UK, found that a specific genetic mutation, which is linked with poor prognosis in blood cancer, is involved in the development of the disease when combined with other mutations in mice and human cell lines.

The study, published in *Nature Communications*, provides a greater understanding of how the loss-of-function mutation in the CUX1 gene leads to the development and survival of acute myeloid leukemia. The findings suggest that targeting a pathway that is essential for these cancer cells to continue growing could lead to new targeted therapies for some patients.

Acute myeloid leukemia (AML)

is an aggressive blood cancer that affects people of all ages, often requiring months of intensive chemotherapy and prolonged hospital admissions. It typically develops in cells within the bone marrow to crowd out the healthy cells, in turn leading to life-threatening infections and bleeding. Mainstream AML treatments have remained unchanged for decades and fewer than one in three people survive cancer.

Previously through large-scale DNA sequencing analysis, researchers at the Wellcome Sanger Institute found that loss-of-function mutations in the CUX1 gene on chromosome 7q were seen in several types of cancer, including AML, where it is associated with poor prognosis. However, the role of this gene in AML development is unclear.

In this new study, the team used CRISPR/Cas9 gene-editing technology to show that lack of functioning CUX1 leads to expansion of certain types of blood stem cells, which are defective in a type of regulated cell death known as apoptosis. They found that the loss of CUX1 causes increased expression of the CFLAR gene—which encodes a protein that restrains apoptosis—potentially providing a means for mutated cancer cells to evade cell death and propagate. The researchers showed that targeting CFLAR, or apoptosis evasion pathways in general, could be a possible treatment for those living with this type of AML that is linked to poor prognosis. Currently, there are no clinically approved drugs that target CFLAR.

Dr Saskia Rudat, co-first author and Postdoctoral Fellow at the Wellcome Sanger Institute, said: "By investigating the role of CUX1 further, we now have new insight into how this gene, and the lack of it when mutated, plays a key role in the survival of blood cancer cells. While this mutation doesn't seem to cause the development of malignant disease on its own, focusing on the pathways involved with CUX1 is a good target for further research."

'Nerve Zap' Pain Treatment Could Cut Need for Opioids After Surgeries

Emerging technology could eliminate the need of opioids after surgeries.

The technique is called percutaneous peripheral nerve stimulation. It involves inserting a small wire next to a nerve and using a stimulator to deliver a mild electrical current to the affected area, interrupting pain transmission.

A team led by Dr Brian Ilfeld, of the University of California, San Diego, US, tested the device in patients who were having foot, ankle or knee operations, or major shoulder surgery. The wire can be placed while the patient is awake, without the need for sedation.

"It's pretty straightforward," Ilfeld said. "You numb up the skin and place the needle through that location then you use an ultrasound machine to guide the needle towards the target nerve and about one centimeter away from it, you deploy the lead, which is inside the needle. So, you essentially just withdraw the needle, which leaves the lead in place."

Patients then have their procedure and wake up with the device ready to go. They're already comfortable because doctors use nerve blocks to relieve their pain for 10 to 12 hours, Ilfeld said.

"When they're in the recovery room, we attach a stimulator, which is about the size of two half-dollars placed next to each other," he said. "It's small enough that you can just stick it onto the patient."

At home, participants used a battery-powered pulse generator to control the electrical stimulation.

The findings, which were published online recently in the journal *Anesthesiology*, were better than the doctors could have hoped for.

"We decreased opioid use dramatically, by 80%, and we decreased pain scores by about 60%," Ilfeld said. "So, it was far more potent than we had anticipated."The possibilities are promising, but the size of this initial study was too small to make definitive claims, Ilfeld said.

If the method does become the norm, the implications could be revolutionary, according to Dr David Dickerson, chairman of the American Society of Anesthesiologists Committee on Pain Medicine.

BP Reduction Beneficial in CV Risk Management even at Normal Levels

Reducing blood pressure with antihypertensive drugs protects against future cardiovascular (CV) events even in individuals with normal or only mildly raised blood pressure level, suggests a large meta-analysis.

The findings published online in *The Lancet* suggested that each 5mmHg reduction in systolic blood pressure decreased the relative risk for CV events by about 10% across the full spectrum of baseline blood pressures, irrespective of whether the individual had cardiovascular disease (CVD) or not.

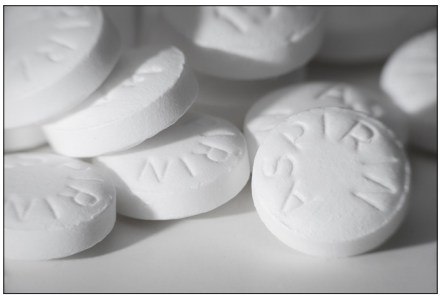
Lead investigator Kazem Rahimi stated that pharmacological blood pressure reduction should be considered in cardiovascular risk management even when the blood pressure is normal or mildly increased, for primary and secondary prevention of CVD.

Short-term Exposure to Air Pollution May Impede Cognition, Aspirin Could Help

Exposure to air pollution, even over just a few weeks, can impede mental performance; however, these adverse effects were lessened in people taking nonsteroidal anti-inflammatory drugs (NSAIDs) like aspirin, according to a new study led by researchers at Columbia University Mailman School of Public Health, US.

The study is published in the journal *Nature Aging* and it is among the first to explore short-term air pollution exposures and the use of NSAIDs to mitigate their effects.

Examples of events that would increase someone's exposure to air pollution over the short term could include forest fires, smog, second-hand cigarette smoke, charcoal



grills, and gridlock traffic.

The researchers examined the relationship between exposures to fine particulate matter (PM2.5) and black carbon, a component of PM, and cognitive performance in 954 older white males from the Greater Boston Area enrolled in the Normative Aging Study.

They also explored whether taking NSAIDs could modify their relationships. Cognitive performance was assessed using the Global Cognitive Function (GCF) and Mini-Mental State Examination (MMSE) scales. Air pollution levels were obtained from a site in Boston.

Elevated average PM2.5 exposure over 28 days was associated with declines in GCF and MMSE scores. Men who took NSAIDs experienced fewer adverse short-term impacts of air pollution exposures on cognitive health than non-users, though there were no direct associations between recent NSAID use and cognitive performance.

The researchers postulate that NSAIDs, especially aspirin, may moderate neuroinflammation or changes in blood flow to the brain triggered by inhaling pollution.

New Neuroimaging Technique Studies Brain Stimulation for Depression

A recent first-in-human study of diffuse optical tomography duringRepetitive transcranial magnetic stimulation(rTMS) suggested treatment target or parameters may need adjustment to benefit more patients with severe depression.

The study was published in the journal *Scientific Reports*. Repetitive transcranial magnetic stimulation, or rTMS, was approved by USFDA as a safe and effective non-invasive treatment for severe depression resistant to antidepressant medications.

A small coil positioned near the scalp generates repetitive, pulsed magnetic waves that pass through the skull and stimulate brain cells to relieve symptoms of depression. The procedure has few side effects and is typically prescribed as an alternative or supplemental therapy when multiple antidepressant medications and/or psychotherapy do not work.

Despite the increased use of rTMS in psychiatry, the rates at which patients respond to therapy and experience remission of often-disabling symptoms have been modest at best.

Now, for the first time, a team of University of South Florida psychiatrists and biomedical engineers applied an emerging functional neuroimaging technology, known as diffuse optical tomography (DOT), to better understand how rTMS works so they can begin to improve the technique's effectiveness in treating depression. DOT uses near-infrared light waves and sophisticated algorithms (computer instructions) to produce three-dimensional images of soft tissue, including brain tissue.

Intensive Treatment for Hypertension Management

The therapeutic blood pressure (BP) targets to be attained have long been a topic of debate. Several clinical studies and meta-analyses, especially the SPRINT trial, have shown the advantages of intensive antihypertensive treatment in reducing major cardiovascular events, myocardial infarction, stroke, heart failure, and all-cause cardiovascular mortality.

These trials were followed by several international Guidelines recommending a BP target of <130/80mmHg for a majority of hypertensive patients till 65 years of age. The guidelines also suggested a reduction of the target for the elderly.

The 2017 American College of Cardiology/American Heart Association (ACC/ AHA) guidelines as well as the European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines identified the new therapeutic goal of 130/80mm Hg for all hypertensive patients 18-65years of age, or lower, if well-tolerated.

Additionally, initiating antihypertensive treatment early helps achieve the recommended BP targets faster, and is also associated with significant benefits in terms of reduction of the incidence of myocardial infarction, heart failure, and major cardiovascular events, especially when BP control is achieved during the first 6 months of treatment. The outcome is even better if BP control is achieved during first 3 months of treatment.

Furthermore, there have been studies showing that combination therapy, particularly a single-pill combination, is better at attaining the recommended therapeutic levels. The ESC/ESH 2018 guidelines strongly support the use of combination therapy in the management of hypertension, particularly the use of renin-angiotensin-aldosterone system inhibitors in combination with calcium antagonist and/or thiazide diuretics.

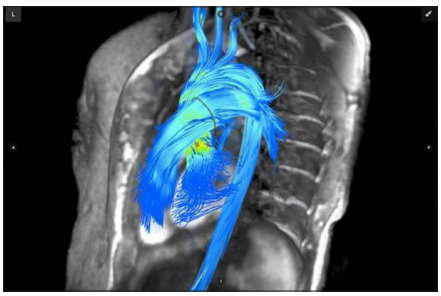
The revised therapeutic goals have particular significance for high-risk patients, such as those with previous cardiovascular events, diabetes mellitus, renal insufficiency, and patients above 65.

Intensive antihypertensive treatment with a therapeutic goal of 130/80mmHg is highly beneficial in reducing major cardiovascular events as well as mortality. Early initiation of antihypertensive treatment, as well as the use of single-pill combination therapy, is of particular significance in realizing the therapeutic goals.

Using Contrast MRI After a Heart Attack Could Increase Survival

According to the British Heart Foundation, heart and circulatory diseases cause more than a quarter (27%) of all deaths in the UK, which equates to more than 160,000 deaths each year—or one death every three minutes.

The research, published in the top science journal *Advanced Science*, found that injection of the trace mineral manganese could enhance MRI scans so that they provided more accurate details of heart function than traditional MRI methods.



These findings, if confirmed in human subjects, could have major implications for the treatment of heart attack patients. The findings could also be of great use in the preclinical evaluation of treatments for patients who suffer from cardiac ischemia—a reduction in blood supply to the heart muscle that could lead to cardiac arrest.

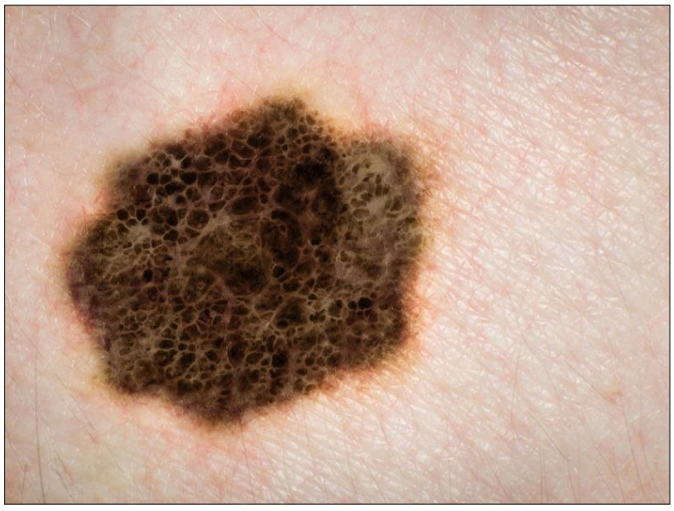
The study also suggests that if manganese-enhanced MRI is performed within the first few hours of a heart attack it could be used to determine the optimal treatment regime for individual patients—helping to regulate changes in the cardiac muscle and thereby further improving survival chances. Findings were evaluated by examining the infarct size and blood supply at three key intervals: one hour, one day and 14 days after myocardial infarction was induced.

Dr Patrizia Camelliti, principal investigator and senior lecturer in cardiovascular science at the University of Surrey said: "Magnetic resonance imaging (MRI) is increasingly used to diagnose and give information on heart conditions. This research using mice allows us to measure the health status of the heart muscle rapidly after a heart attack and could provide important information for optimizing treatments in patients."

Emerging Biomarkers in Stage III Melanoma May Improve Patient Management

Increased effort is needed in the development of reliable predictive biomarkers for stage III melanoma, according to a review published in the International Journal of *Molecular Sciences.*

Gene expression analysis and the identification of a single gene or a signature correlated with patients' outcomes could lead to improved patient stratification. Research has shown an association between mRNA signatures and prognosis in patients with stage III melanoma. MicroRNAs (miRNAs) have been used in the identification of high-risk patients who may benefit from adjuvant therapy. In addition, circulating tumor DNA also may have important clinical implications, as research has shown that it is associated with shorter progression-free survival.



In a recent study of circulating tumor cells (CTCs), Lucci and colleagues found that 1 or more CTCs per 7.5 mL of blood can independently predict disease relapse at 6 months from baseline, as well as up to 54 months of follow-up. DNA methylation and programmed death-ligand 1 (PD-L1) status have also shown promise as potential biomarkers.

The prognostic significance of B-Raf proto-oncogene serine/threonine-protein kinase (BRAF) mutations has been investigated in several studies, but the role of BRAF in predicting patient outcomes in melanoma is controversial, according to the study authors. A majority of studies have found an association of BRAF mutation with poor clinical outcome. García-Silva et al found that extracellular vesicles (EV) derived from exudative seroma (ES) may be a useful surrogate marker for melanoma progression and could be used to detect melanoma-specific mutations.

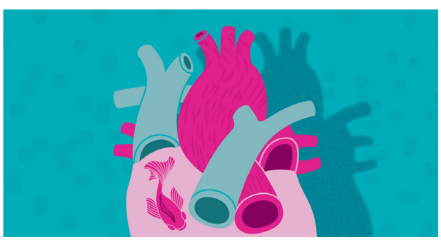
"EVs could be a promising source of mutant DNA and should be considered for the development of next-generation liquid biopsy approaches," according to the study authors.

Radiomics is an emerging and promising technology, as recent research has shown that radiomic images may be predictive biomarkers for immunotherapy response and an important tool for managing patients with cancer.

"A multidisciplinary approach integrating biology with bioinformatics and computational science is fundamental to discover novel predictive and prognostic biomarkers to personalize the treatment of each patient," stated the study authors.

Surgical Snip Might Prevent Stroke in People With A-fib

A simple surgery may help lower the risk for strokes by more than a third in patients with atrial fibrillation, a common irregular heartbeat, a new trial finds.



The reduction in stroke risk is achieved by blocking the left atrial appendage, an unused, finger-like tissue that traps blood in the upper chamber of the heart and increases the risk of clots that can cause strokes, the researchers explained.

"This study was performed in patients who were already under-

going heart surgery for other indications, so it was the addition of a secondary procedure," said lead researcher Dr Richard Whitlock, a professor of surgery at McMaster University in Hamilton, Ontario, Canada.

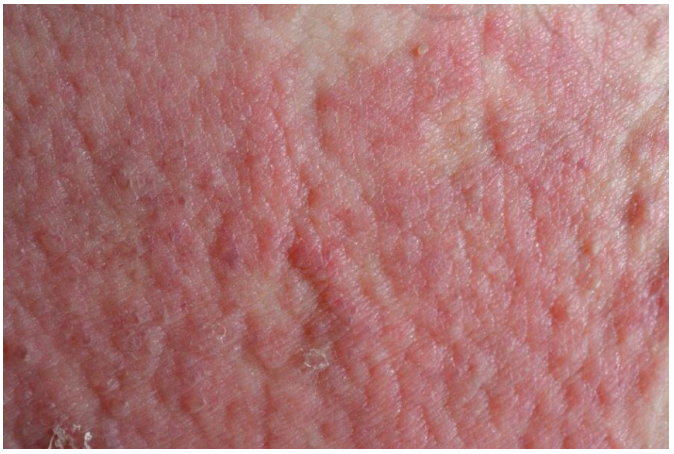
As with most patients with atrial fibrillation, patients in this study were already taking blood thinners to prevent stroke. This study supports this procedure of removal and closure (occlusion) of the left atrial appendage while doing heart surgery. But patients will still need to take blood thinners after the operation, Whitlock noted.

The combination of the surgery plus continuing to take blood thinners is how the additional protection from stroke is achieved, he added.

Baricitinib Shows Long-Term Efficacy for Atopic Dermatitis

Baricitinib demonstrates sustained long-term efficacy in patients with moderate-to-severe atopic dermatitis, according to a study published in *JAMA Dermatology*.

Jonathan I. Silverberg, MD, from the George Washington University School of Medicine in Washington, DC, and colleagues evaluated the long-term (68 weeks) efficacy of baricitinib in adults with moderate-to-severe atopic dermatitis who were treatment responders or partial responders in phase 3 monotherapy studies.



The researchers found that of the responder/partial responder population treated with 4 mg baricitinib (70 patients; mean age, 36.7 years; 60% men), 45.7% achieved validated Investigator Global Assessment for Atopic Dermatitis scores of 0 or 1 (vIGA-AD [0,1]) at week 16; the proportion was 47.1% at week 68. Seventy per cent of participants achieved an improvement of 75% or greater in the Eczema Area and Severity Index (EASI75) at week 16 vs 55.7% at week 68. Among the responder/partial responder population treated with 2 mg baricitinib (54 patients; mean age, 32.8 years; 51.9% men), 46.3% achieved vIGA-AD (0,1) at week 16 vs 59.3% at week 68. At week 16, improvement in the EASI75 score was 74.1% compared with 81.5% at week 68.

"Overall, these findings provide the support that baricitinib may be a longer-term treatment option for patients with moderate-to-severe atopic dermatitis," the authors write.