Study: High-intensity statins lower mortality

By Yasemin Saplakoglu

A large national study has confirmed the value of high-intensity statin treatments for people with cardiovascular disease, according to researchers at the School of Medicine.

Over the duration of a year, the researchers found that patients taking high-intensity statins had an increased chance of survival over those on moderate-intensity statins. The study was published online Nov. 9 in JAMA Cardiology.

Statins, a class of drugs that lowers cholesterol levels in the blood, are commonly prescribed for preventing the acceleration of cardiovascular disease caused by the buildup of plaque in the arteries, which can lead to heart attacks and stroke.

Health-care providers have long debated the benefits of prescribing high-intensity statins to their patients with cardiovascular disease. Patients, in turn, have been hesitant to take them because of equivocal messages from their doctors and internet searches of patient and doctor perspectives.

Conflicting recommendations

"Previously, there was definitely a certain amount of fear on the patient's part because most people don't like taking medication," said Paul Heidenreich, MD, professor of cardiovascular medicine and the study's senior author. Some studies have shown an increased risk of side effects, such as diabetes or muscle damage, associated with higher-intensity statins.

In 2013, the American College of Cardiology and American Heart Association jointly recommended high-intensity statin therapy for patients with atherosclerotic cardiovascular disease who were no older than 75. The ACC/AHA guidelines differed, however, from guidelines established in 2014 by the Veterans Affairs Health Care System, which recommended only moderate-intensity statins, noting the lack of conclusive evidence that higher-intensity statins are more beneficial than those of moderate intensity.

In their study, Heidenreich and his team found evidence to support the ACC/AHA guidelines. They determined that high-intensity statins do not in fact increase rates of survival, not only in younger and middle-aged patients with cardiovascular disease, but also in a patient population not well-studied: adults over 75.

"The greatest strength of this study is that we used a very large, well-defined clinical cohort," said Fatima Rodriguez, MD, a cardiology fellow at Stanford and the study's lead author. "The results show that high-intensity statins confer a survival advantage for patients with cardiovascular disease, including older adults."

Large sample size

The researchers studied the medical records of 509,766 patients across the country receiving care from the Veterans Affairs Health Care System. "This is a very large patient population rich in cardiovascular disease who were no older than 75," Rodriguez said.

The primary purpose was to look at overall patient death rates from 2013 to 2014, the researchers said. They included patients with coronary artery disease, cerebrovascular disease and peripheral artery disease. "There are basically the three main areas affected by plaque buildup — the heart, the brain and the large arteries of the rest of the body," Heidenreich said.

Patients were taking high-intensity, moderate-intensity or low-intensity statins in many

PTSD changes the brains of boys and girls differently

By Erin Digitale

Traumatic stress affects the brains of adolescent boys and girls differently, according to a new brain-scanning study from the School of Medicine.

Among youth with post-traumatic stress disorder, the study found structural differences between the sexes in one part of the insula, a brain region that detects cues from the body and processes emotions and empathy. The insula helps to integrate one's feelings, actions and several other brain functions.

Existence of asymptomatic Ebola confirmed in study in Sierra Leone village

By Ruthann Richter

A year after the Ebola epidemic in West Africa, researchers from the School of Medicine and other institutions identified 14 individuals previously unknown to have had the disease in a Sierra Leone village that was an Ebola hot spot.

These individuals had antibodies to the virus, indicating they had been infected at one time. Yet 12 said they had no symptoms during the time of active transmission in the village.

The research confirms previous suspicions that the Ebola virus does not uniformly cause severe disease, and that people may be infected without showing signs of illness, said Gene Richardson, MD, a former fellow in the Division of Infectious Diseases and Geographic Medicine at Stanford who is now a PhD candidate in anthropology at the university. The findings also suggest that the epidemic was more widespread than previously believed.

Based on the results of the study, the researchers calculated the prevalence of minimally symptomatic infection to be 25 percent.

"The study corroborates previous evidence that Ebola is like most other viruses in that it causes a spectrum of manifestations, including minimally symptomatic infection," Richardson said. "It provides important evidence on that front. It also means a significant portion of transmission events may have gone undetected during the outbreak. This shows there was a lot more human-to-human transmission than we thought."

The study was published online Nov. 15 in PLOS Neglected Tropical Diseases. The study also was presented Nov. 14 at the American Society of Tropical Medicine and Hygiene's annual meeting in Atlanta. Richardson is lead author of the study, and Paul Farmer, MD, PhD, a Harvard professor and director of Partners In Health, is the senior author.

Testing individuals

The research was done in the rural village of Sukudu in Sierra Leone, a small number of villagers in Sierra Leone were infected with the Ebola virus but reported having no symptoms, a study found.

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DNA sequencing determines lymphoma origin, prognosis

By Krista Conger

Sequencing tiny bits of DNA circulating in the blood of patients with lymphoma can accurately identify the cancer subtype and pinpoint mutations that might cause drug resistance, according to researchers at the School of Medicine.

This knowledge could help personalize cancer treatment by revealing which patients are likely to be treated successfully and those who may have a poorer prognosis.

Tracking sequence changes over time could also provide a kind of early warning system to identify the emergence of an aggressive form of the cancer by providing a real-time window into tumor evolution. The findings bolster the growing notion that noninvasive, blood-based biopsies of what’s known as circulating tumor DNA are likely to transform cancer care.

“We now can identify the subtype of the tumor, watch how it changes over time and begin to tailor our chemotherapy choices based on the presence or absence of specific mutations,” said assistant professor of medicine Ash Alizadeh, MD, PhD. “We’ve moved beyond just measuring disease burden based on the amount of tumor DNA in the blood.”

Alizadeh and assistant professor of radiation oncology Maximilian Diehn, MD, PhD, share senior authorship of the study, which was published Nov. 9 in Sciencetranlational Medicine. Postdoctoral scholars Florian Scherer, MD, and David Kurz, MD, and instructor Aaron Newman, PhD, are the lead authors.

The researchers conducted a study of 92 prospectively enrolled patients with diffuse large-B-cell lymphoma. DLBCL is the most common type of non-Hodgkin lymphoma and is highly biologically variable.

As a result, patients vary widely in their response to treatment. About one-third of seemingly successfully treated patients eventually relapse, or their tumors become resistant to treatment. Additionally, a form of indolent B cell lymphoma, which progresses slowly with only mild symptoms, can transform without warning into an aggressive form of the disease.

“Transformation is very difficult to detect,” said Diehn. “This transformation is very difficult to detect, and usually requires an invasive biopsy to diagnose,” said Diehn. “Our approach will allow us to monitor patients over time with a simple blood test, and may help us identify transformation much earlier.”

The researchers used an enhanced version of a technique they developed called CAPP-Seq to isolate and sequence circulating tumor DNA, or ctDNA, from blood samples from the patients. Unlike previous studies, which tracked lymphoma progression by monitoring the sequence of just one cancer-associated protein, CAPP-Seq can identify a much larger range of mutations in the tumor genome.

They then compared the ctDNA sequences obtained from 82 patients who stored blood samples with those of the tumor cells from invasive biopsies, and paired the information with what was known about the course of the patient’s disease and eventual outcome. They found that low levels of ctDNA after diagnosis but before treatment correlated strongly with progression-free survival in the patients. Those with higher levels of ctDNA fared more poorly overall. Furthermore, they were able to determine ctDNA sequences those patients whose disease was transforming over time with a simple blood test, and may help us identify transformation much earlier.”

Determining cancer’s cell of origin

Perhaps even more importantly, however, the researchers found they could use CAPP-Seq to determine the type of B cell from which the cancer originated and predict prognosis. About two-thirds of people with the presence of ctDNA in the blood of relapsing patients on average six months before any clinical symptoms appeared and as long as 2.5 years before clinical signs of relapse.

“Transforming tumor DNA is still evolving. This is a developing field, and so we’re just starting to get a handle on it,” said Diehn. “We’re starting to see that it’s very dynamic, and that it’s possible to track these changes over time.”

The discovery helps to clarify at least one aspect of the brain’s mysterious ways, said Jong Yoon, MD, an assistant professor of psychiatry and behavioral sciences at Stanford and a psychiatrist at the Palo Alto Veterans Affairs Health Care System who sees numerous patients with this disorder.

“Delicits in working memory also characterize various neuropsychiatric conditions and are particularly so in schizophrenia,” said Jong Yoon, MD, an assistant professor of psychiatry and behavioral sciences at Stanford and a psychiatrist at the Palo Alto Veterans Affairs Health Care System who sees numerous patients with this disorder.

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More GABA in one brain region linked to better working memory

By Bruce Goldman

The amount of a particular chemical in a particular part of your brain predicts your ability to simultaneously hang onto several bits of information in your working memory, a School of Medicine scientist and his UC-Davis collaborators have learned.

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Blocking CD47 could boost immunotherapy for canine cancer

By Christopher Vaughan

Blocking a cell surface protein called CD47 may help treat at least one kind of cancer in dogs, according to a study by researchers at the School of Medicine and other institutions.

The work expands on research by Irving Weissman, MD, professor of pathology and of developmental biology, and his colleagues, who found that blocking CD47 might be useful in treating nearly every kind of human cancer.

The study was published online Nov. 14 in Cancer Immunology Research.

Kipp Weiss, MD, a former student at the School of Medicine, is lead author of the study. Weissman, director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine, and Jaime Modiano, VMS, PhD, of the University of Minnesota, share senior authorship.

‘Don’t eat me’

The CD47 protein acts as a “don’t eat me” signal to immune cells called macrophages, which normally engulf and devour cancer cells and other diseased and dying cells. It turns out that nearly every kind of cancer uses CD47 to evade these macrophages. By targeting up the “don’t eat me” protein, researchers hope to allow the immune cells to find and swallow cancer cells. An anti-CD47 antibody is currently in a university-sponsored clinical trial in cancer patients at Stanford and elsewhere.

Weisskopf and his fellow researchers took canine lymphoma, one of the most common cancers in dogs, and put it into laboratory mice. Weisskopf then injected the mice with CV1, a molecule he helped develop to bind tightly to the CD47 receptor and block the “don’t eat me” signal. In some cases, they also used a specially devised antibody against a protein called CD20 to act as an “eat me” signal to attract immune cells to the cancer.

They found that when anti-CD20 antibody alone was used to treat the dog cancer in mice, none of the mice survived. When CV1 was used by itself to treat the cancer, only 20 percent of the mice survived. But when the anti-CD20 antibody and CV1 molecule were used together, 100 percent of the mice survived with no further evidence of disease. They seemed to be cured.

Leading cause of illness in dogs

Cancer is among the leading causes of illness in dogs, and clinical trials will help assess the actual cancer-stricken dogs are the next step. “We hope that these studies help companion animals and further inform us about treating disease in humans,” Weisskopf said.

Weissman noted that it is an important first step that the molecular tools used to target human CD47 also work against dog cancers, at least when tested in a mouse host. “This should provide impetus to produce even more effective anti-CD47 proteins that are designed for optimal targeting of dog — and separately, cat — CD47 molecules and cancers,” he said. Weissman is also director of the OnCore Pre-Clinical Cancer Stem Cell Research and Medicine.

Other Stanford co-authors of the study are graduate student Amira Bialak; former postdoctoral scholar Susan Pro-haska; former medical school student Aaron Steinberg; and former lab technicians Peter Schnorr and Kelly McKenna.

Researchers from the University of Minnesota, Elanco Animal Health U.S. Inc. and the Genomics Institute of the Novartis Research Foundation also co-authored the study.

The work was supported by the National Institutes of Health, the Morris Animal Foundation, the Joseph and Laurie Laob Gynecologic/Ovarian Cancer Fund, Ludwig Cancer Research, the Siebel Stem Cell Institute, the Thomas and Stacey Siebel Foundation, Stanford SPARK, the Skippy Frank Fund for Life Sciences and Translational Research, and an Elanco donor fund.

Stanford’s departments of Pathology and of Developmental Biology also supported the work.

Three faculty members elected fellows of AAAS

Two professors at the School of Medicine and one at the School of Earth, Energy & Environmental Sciences have been elected fellows of the American Association for the Advancement of Science.

They are among 391 new AAAS fellows chosen this year by their peers for scientifically or socially distinguished efforts to advance science or its applications.

Andrew Hoffman, MD, professor of endocrinology, was selected for contributions to the field of epigenetics, particularly for discerning underlying mechanisms of genomic imprinting and long-range chromatin interactions. Hoffman’s lab examines mechanisms of genomic imprinting for discerning underlying mechanisms of normal physiology and in oncogenesis.

Lawrence Steinman, MD, professor of neurology and neurological sciences, was selected for discoveries about the molecular basis for lymphocyte homing to the brain in relapsing multiple sclerosis, which led to the molecular basis for lymphocyte homing to the brain in relapsing multiple sclerosis, which led to an effective approved therapy for multiple sclerosis. Steinman, who holds the George A. Zimmermann Professorship, focuses his research on understanding the pathogenesis of autoimmune diseases, particularly multiple sclerosis.

Steven Gorelick, PhD, professor of Earth system science, was selected for contributions to improving the understanding of ocean and atmosphere transport and for pioneering leadership in developing optimization models for climate modeling, and for pioneering leadership in developing optimization models for hydrodynamic analysis, Gorelick, who holds the Cyrus F. Tolman and Enersen Professorship, studies groundwater management, water resources vulnerability in developing regions, optimal remediation design, hydrography and ecohydrology.

New compliance, study management resources available for researchers

Spectrum, the Stanford Center for Clinical and Translational Research and Education, recently established two new groups to assist Stanford researchers in managing studies and complying with the labyrinth of government regulations associated with clinical research.

OnCore training

The first, Spectrum’s OnCore support team, is currently scheduling training sessions for groups interested in using the OnCore clinical research management system. The schoolwide adoption of OnCore will make it easier for investigators to manage clinical research and monitor participant recruitment. OnCore also provides tools for multisite study management. For more info, contact the manager of this group, Yona Shulaker, at shulaker@stanford.edu, or visit http://medicine.stanford.edu/news/current-news/standard-news/department-wide-roll-out-planned-for-oncore.html.

Clinical research guidance

The second resource, the Clinical Research Quality Office, is staffed with experts who can help research teams understand clinical research regulations and adopt best practices. They can also help groups prepare for audits by industry sponsors or the Food and Drug Administration.

$25 million awarded to joint center for the study of regulatory science

The Food and Drug Administration has awarded the UCSF-Stanford Center of Excellence in Regulatory Science and Innovation a five-year, $25 million grant. The collaborative venture is one of five FDA Centers of Excellence in Regulatory Science and Innovation intended to advance the science of regulation. New technologies in biomedical research require new approaches to evaluating safety and effectiveness.

The UCSF-Stanford center launched in 2014 with an initial $3.3 million grant from the FDA to develop projects that can help with regulating health care. For example, one project, headed by Russ Altman, MD, PhD, professor of bioengineering, of genetics of medicine and of biomedical data science at Stanford, uses natural language processing and machine learning to analyze the contents of enormous databases of adverse effects from drugs reported by patients and clinicians.

Altman and Kathy Giacomini, PhD, professor of bioengineering and therapeutic sciences in the UCSF School of Pharmacy, lead the center. Altman is also director of Stanford’s biomedical informatics training program.

The new $25 million grant supports research, collaboration and education. Researchers will work to address how to regulate the development and approval of new medical products; provide public lectures, panel discussions and workshops on FDA regulations; and provide training in regulatory science.
Stanford’s inaugural health-focused hackathon brings innovators together

By Ula Chrobak

Stanford students, faculty and health professionals, as well as designers and entrepreneurs from across the United States, teamed up for a weekend of health care innovation Nov. 5-6 at the inaugural health++ hackathon.

Participants pitched their projects, formed teams and went from idea to prototype in 36 hours. The goal: create a design, app or business plan that improves health care affordability and access.

Health care systems can be slow to embrace new technologies, said Oliver Aalami, MD, Stanford’s associate professor of surgery, who was a faculty adviser for the event. Aalami said many doctors already rely on smartphones for sharing diagnoses and prescribing advice, making that a good platform for innovations.

Aalami added that while a number of health care technology projects have formed at Stanford, the interdisciplinary connection to bring them to fruition has been lacking. “The left arm doesn’t know what the right arm is doing,” he said.

Interdisciplinary teamwork

Of the 257 hackathon participants, about half were Stanford undergraduates, and a quarter were Stanford physicians, business students and graduate students. The rest were designers, engineers and entrepreneurs from other institutions and private companies.

“It’s incredible to see the energy and interest we’re getting from the engineering school — traditionally I think hackathons appeal the most to engineering students — but the design school and business school have been super-excited as well,” said Sherman Leung, a Stanford business school associate professor of design.

“We have such a perfect ecosystem with the hospital, the graduate schools, the undergraduate school,” Aalami said. “It’s just a perfect ecosystem to have amazing things happen.”

Winning projects

A novel pill-bottle sticker that makes prescription labels more accessible to people with visual impairments, called Pharmassist, won the grand prize at the event. When placed on a smartphone, the sticker’s unique pattern would enable the phone to read aloud the prescribing information, track the number of pills left and help order a refill.

“By getting together at the hackathon with a team of five people, it was so awesome that we could build a working prototype in 36 hours,” said Pharmassist lead team member Zahoor Zafrrulla. Zafrrulla said he would have needed a week to 10 days to complete the project on his own. As a full-time engineer, he said, this was not possible. Zafrrulla’s team included experts in biomedical engineering, biology and computer science.

“They’re coming to the event with very deep experience and an understanding of what the problem is, and basically saying, ‘OK, let’s spend two days and see how we can prototype something to address this problem,’” said Leung.

The other grand prize winners were Foot++, a muscle stimulator for people with a gait abnormality known as foot drop, and Benjamin, an app that informs users of lower-cost options for prescription drugs and insurance plans. A total of 12 teams won prizes.

The prizes were awarded based on problem-solving potential and feasibility to implement. The goal was not to create a finished product, which is hard to do in a mere 36 hours. Instead, the biggest impact of bringing together clinicians, business experts and engineers for the weekend was to create a starting point for future innovation.

“We hope that hackathon can serve as a launching pad, sparking future collaborations and getting people from all departments thinking about health care innovation,” said Wang.

Health++ organizers are already looking forward to next year. Aalami said that Stanford Health Care plans to contribute deidentified medical records next year, which could be used by hackers in big data projects.

The event organizers are excited about the potential for the event to initiate an interdisciplinary community of collaborators on health care issues.

“A ton of problems in health care require interdisciplinary thinking,” Roy said. “We hope health++ can help facilitate that paradigm shift.”

Other advisers for the event were Robert Chang, MD, assistant professor of ophthalmology; Anir Bhatt, MD, PhD, assistant professor of radiology and of genetics; and Marla Zanchi, PhD, a Biodesign faculty member.

Panelists from industry and academia discuss opportunities for innovation in health care affordability at the hackathon, which took place Nov. 5-6.

Fall issue of Stanford Medicine looks at power, limits of diagnostics

By Rosanne Spector

In the future, your toilet might save your life.

Of course, your toilet would have to be very special to accomplish this, but that’s what Sanjiv Gambhir, MD, PhD, professor and chair of radiology, and his colleagues are working on in his lab at the School of Medicine.

Gambhir envisions a future in which we nearly continuously monitor our health. So he’s developing diagnostic tools, such as a “smart” toilet to detect diabetes and a smart bra to detect breast cancer.

As he explains in the new issue of Stanford Medicine magazine, the resulting data might tell each of us, as our health-care team, if something is amiss right away.

“The future is all about being able to intercept diseases early and, ideally, prevent them,” said Gambhir in the lead article of the magazine’s special report on diagnostics.

He and other researchers in the field of diagnostics are taking advantage of advances in biomedical research, engineering and computer technology to make diagnostics more informative and less invasive.

One Stanford team, for example, is helping to create a real-life version of the tricorder, a sci-fi device used by the character Dr. McCoy on Star Trek to diagnose patients. Another team is developing an imaging method for cancer patients that eliminates radiation exposure and might even help fight the disease.

Falling short of potential

At present, however, diagnostic methods fall short of their potential. According to a 2015 National Academy of Medicine report, “The delivery of health care has proceeded for decades with a blind spot: Diagnostic errors — inaccurate or delayed diagnoses — persist throughout all settings of care and continue to harm an unacceptable number of patients.”

Part of the problem, said Gambhir, is that researchers in the field of diagnostics receives much less funding than research on treatments.

The fall magazine, produced with the support of Stanford’s Department of Radiology, includes a Q&A with Travis Tygart, the CEO of the U.S. Anti-Doping Agency. The online version of the magazine includes a live video chat with Tygart about cleaning up sports.

Also in the special report:

• The story of Gambhir’s quest to save his son after he was diagnosed with a brain tumor — and his son’s legacy to diagnostics.

• An article about how School of Medicine Dean Lloyd Minor, MD, discovered the cause of
Magnetic tool makes gallbladder-removal surgery less invasive

By Sara Wykes

Researchers at School of Medicine and three hospitals in Chile have demonstrated the safety of a new magnet-driven device that enables surgeons to make fewer incisions while performing laparoscopic gallbladder surgery.

Each year, more than 1 million people in the United States have their gallbladders removed, putting that procedure, called a cholecystectomy, on the nation’s top-10 list of surgeries. The gallbladder is closely nestled in the curve of the liver, so removing it can be tricky. Even in the most skilled hands, manipulating the laparoscopic instruments used in the surgery poses a risk of causing internal damage that can lead to scarring.

The new magnet-driven device makes the surgery less invasive by obviating the need for an incision through which an instrument is inserted to retract the gallbladder. Instead, an external magnet does that job.

In a paper published online Oct. 24 in Annals of Surgery, the researchers shared the results of a 50-patient clinical trial in which they demonstrated the safety of the device. Homero Rivas, MD, assistant professor of surgery at Stanford and director of innovative surgery at Stanford Health Care, is lead author of the paper. The senior author is Mario Uribe, MD, of the Hospital Salvador in Santiago, Chile.

Nationwide, the device, which has received clearance from the Food and Drug Administration, is in use at Stanford Medicine and two other medical centers.

“Laparoscopy has truly revolutionized surgery over the past 30 years or so, and with very good results, but it still relies on a given number of incisions and instruments,” Rivas said. “Surgeons and patients continuously search for painless, scarless operations. This device takes a step toward that goal by reducing the need for fixed, transabdominal instruments.”

How it works

The device has two parts: an external magnet and a slender rod with a detachable clip that includes a magnet. The rod, with the clip at its far end, looks much like the reaching devices that people can use to grab objects from high shelves. A surgeon inserts the rod through the belly button and manipulates its clip to grasp the gallbladder. The clip is then released from the rod but remains connected to the gallbladder. The external magnet is placed on the abdomen to control the movement of the clip attached to the gallbladder. A rod with a camera attached to it sends video to a monitor in the operating room, giving the surgeon an inside view of the area near the gallbladder. Other instruments are inserted through incisions to detach the organ, after which the rod that was earlier unhitched from the clip is reconnected to it and used to remove the organ from the patient.

The study documented an average hospital stay for patients of 22 hours, and an average pain score of 0.6 on a scale of 0 to 10 seven days after surgery. The average time for patients to return to work was five days.

The device was the idea of Alberto Rodriguez-Navarro, MD, who specialized in minimally invasive surgery in his native Chile and is now CEO of Levita Magnetics, the San Mateo-based company he founded to develop the magnetic surgical system.

Rivas said he has used the device primarily for cholecystectomies, but he believes it is versatile enough to be applied to bowel resections, appendectomies, hysterectomies, gastrectomies and other abdominal surgeries.

“I hope that greater availability of the device will allow other innovators to propose other uses that even its pioneers have not thought of,” Rivas said.

Surgeons at three Santiago hospitals — the Hospital Salvador, the Hospital Luis Tisne and the Hospital Padre Hurtado — are co-authors of the study. The research was supported by a grant from the Chilean Economic Development Agency and sponsored by Levita Magnetics.

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“It is difficult for me to do a bowel resection that many times greater than current methods, an ultrasound camera-in-a-pill that can see through the walls of intestines, and a software program for analyzing tumor tissue samples that determines a prognosis more accurately than people can,” Rivas said.

An article on the stethoscope, asking whether the 200-year-old device is still relevant. A video about the stethoscope, featuring Stanford clinicians, including professor of medicine and best-selling author Abraham Verghese, MD, is available in the magazine online.

• A story about a family seeking an explanation for a mysterious seizure disorder striking two of their children, and how using computers to mine genetic data can secure answers more quickly.

The issue also includes an essay by physician-journalist Nancy Snyderman, MD, a consulting professor with Stanford’s Center for Innovation in Global Health, on the collision of science and politics, and an excerpt from Drug Dealer, MD, a new book by Stanford assistant professor of psychiatry Anna Lembke, MD, on how doctors are fueling the opioid epidemic.

The magazine is available online. Print copies are being sent to subscribers. Others can request a copy by calling 723-6911 or by sending an email to medmag@stanford.edu.
The U.S. Preventive Services Task Force now recommends adults ages 40 to 75 with no history of heart disease — but who nevertheless have at least one risk factor and an elevated risk of cardiovascular disease — take a low-to-moderate-dose statin.

The independent panel of experts in prevention and evidence-based medicine issued the recommendation in the Nov. 13 issue of JAMA. An estimated 505,000 adults died of coronary heart and coronary vascular disease in 2011. The prevalence of heart disease increases with age, ranging from about 7 percent in adults ages 45-64 to 20 percent in those 65 and older. It is somewhat higher in men than in women.

Douglas Owens, MD, was a member of the task force when the guideline was developed. He is a professor of medicine at the Stanford U.S. Preventive Services Task Force of the Center for Health Policy and Center for Primary Care and Outcomes Research. The centers are part of Stanford Health Policy. He is also a physician with the Veterans Affairs Palo Alto Health Care System.

Douglas Owens on new statin recommendation

Continued from page 1

1 What prompted this new recommendation by the task force?

Owens: Cardiovascular disease is the leading cause of death in the United States, accounting for 1 in 3 deaths among adults due to heart attack and stroke. As statins can provide an important benefit to people at elevated risk of cardiovascular disease, but in order to know whether statins are going to be beneficial, it’s important to know something about the patient’s cardiovascular risk.

We reviewed the literature comprehensively — including 19 randomized clinical trials involving more than 73,340 patients, as well as additional observational studies — to understand both the benefits and the harms of statins. We concluded that the benefits outweigh the harms in appropriately treated patients at increased risk of cardiovascular disease. The primary benefit of statins is a reduction in your chance of having a heart attack or stroke.

2 What are statins and why do they offer such benefit?

Owens: A statin is a drug that reduces the production of cholesterol by the liver. High cholesterol is a significant risk factor for cardiovascular disease and stroke, and statins help prevent the formation of the so-called bad cholesterol. Statin drugs also help lower triglycerides, or blood fats, and raise the so-called good cholesterol, HDL.

While there are some reported side effects from the use of statins, such as muscle and joint aches, most people tolerate statins fairly well. There is mixed evidence about whether statins may result in a modest increase in the chance of diabetes, but the task force assessed the benefits to clearly outweigh harms in patients at increased risk of cardiovascular disease.

3 Who should be taking low- to moderate-dose statins?

Owens: The task force recommends that clinicians offer statins to adults who are 40 to 75 years old and have at least one existing cardiovascular disease risk, such as diabetes, hypertension, high cholesterol or smoking. They also have a calculated risk of 10 percent or more that they will experience a heart attack or stroke in the next decade.

The task force recommends clinicians use the American College of Cardiology/American Heart Association risk calculator to estimate cardiovascular risk because it provides gender- and race-specific estimates of heart disease and stroke.

For people with a risk of 7.5 to 10 percent of heart attack or stroke over the next decade, the task force recommends individual decision-making, as the benefits of statins are less in this age group because these people have a lower baseline risk of having a cardiovascular event.

The task force also looked at initiation of statins in people 75 or older and found there wasn’t enough evidence to determine whether people in this age group who have not previously been on a statin would benefit from starting a statin. So the task force suggests people in this age group consult their physicians about whether a statin may be beneficial.

4 Do these new statin guidelines override the 2008 task force recommendation in 2008 that adults be screened for lipid disorders due to high cholesterol?

Owens: Yes, this recommendation replaces the 2008 recommendation on screening for lipid disorders in adults.

The accumulating evidence on the role of statins in preventing heart disease has now led the task force to reframe its main clinical question from “Who should be screened for dyslipidemia?” to “Which population should be prescribed statin therapy?”

We recommend that physicians go beyond screening for elevated lipid levels, and assess overall cardiovascular risk to identify adults ages 40 to 75 who will benefit most from statin use.

5 What does the task force hope to accomplish with the new recommendation?

Owens: This guideline will help both clinicians and patients decide what their cardiovascular risk is and what steps they can take to reduce those risks, which include a healthy lifestyle, a healthy diet and exercise. We hope to highlight areas that would benefit from additional research. Further research on the long-term harms of statin therapy, and on the balance of benefits and harms of statin use in adults 76 years and older, would be helpful in informing clinicians and patients.

The work is an example of Stanford Medicine’s focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Other Stanford affiliated co-authors are David Maron, MD, clinical professor of medicine and U.S. Preventive Services Task Force co-chair; and David S. Halperin, MD, assistant professor of medicine.

Stanford’s Department of Medicine supported this study.

Paul Heidenreich

“The greatest strength of this study is that we used a very large, well-defined clinical cohort.”

Settling the debate

The next step, researchers said, is to find out why some patients who should be on high-intensity statins may not be and whether individuals may be responding to the screening guidelines differently than the general population.

“Maybe hospitals can employ a clinical reminder that asks why a cardiovascular patient isn’t on the maximum dose of statin,” said Heidenreich, adding that he hopes this will help to settle the debate on which guidelines doctors should use when prescribing statins to patients.

The researchers also hope to follow up on longer-term data from these patient populations. “Not only do we hope to continue studying this population, but we also hope to study patients without prior cardiovascular disease but who are at high risk for it,” said Rodriguez.

Finally, they hope these results will help to settle the debate on which guidelines doctors should use when prescribing statins to patients. Heidenreich said, “This is the first study to control for differences in patient and physician behavior.”

The work was supported by the National Heart, Lung, and Blood Institute and the National Institute of Aging.

Conclusion

- This is the largest long-term clinical trial of statins in the world.
- It provides more evidence for the benefits of low- to moderate-dose statins than we have had in the past.
- It suggests that people aged 40 to 75 years old who have cardiovascular disease risk factors should be offered statins.
PTSD
continued from page 1

The findings were published online November 11 in Depression and Anxiety. The study is the first to show differences between male and female PTSD patients in a part of the brain involved in emotion and empathy.

“The insula appears to play a key role in the processing of PTSD,” said the study’s senior author, Victor Carrion, MD, professor of psychiatry and behavioral sciences at Stanford. “The differences we saw between the brains of boys and girls who have experienced trauma are more likely to develop PTSD than boys who experience trauma, but scientists have been unable to explain why.

The research team conducted MRI scans of the brains of 59 study participants ages 9-18. Of the 35 girls and 14 boys — 17 trauma and 18 non-traumatized participants — similar ages and IQs, five had experienced one episode of trauma, while the remaining 25 had experienced two or more episodes or had been exposed to chronic trauma. The researchers saw no differences in brain structure between boys and girls in those groups. However, whatever trauma boys and girls saw, they saw differences in a portion of the insula called insula’s central and distal subregions. This brain region had larger volume and surface area in traumatized boys than in boys in the control group. In addition, the region’s volume and surface area were smaller in girls with trauma than among girls in the control group.

**Findings could help clinicians**

“It is important that people who work with traumatized youth consider the sex differences,” said Megan Klabunde, PhD, the study’s lead author and an instructor in the Department of Psychiatry and Behavioral Sciences at Stanford; and a researcher from Stanford’s Department of Psychology and Behavioral Sciences. “Our findings suggest that it is possible that boys and girls could exhibit different trauma symptoms and that they might benefit from different approaches to treatment.

The insula normally changes during childhood and adolescence. In a study of 15 girls and 10 boys, a small insula volume typically seen as children and teenagers grows older. Thus, the findings imply that traumatic stress could contribute to accelerated cortical aging of the insula in girls who develop PTSD.

“There are some studies suggesting that high levels of stress could contribute to early puberty in girls,” she said. The researchers also noted that their study may help scientists understand how experiencing trauma could play into differences between the sexes in regulating emotions.

By better understanding sex differences in a region of the brain involved in emotion processing, clinicians and scientists may be able to develop sex-specific trauma and emotion dysregulation treatments,” the authors write in the study.

To better understand the findings, the researchers say what’s needed next is looking at sex differences in lowering traumatized young people of both sexes over time. They also say studies that further explore how PTSD might manifest itself differently in boys and girls, as well as tests of whether sex-specific treatments are beneficial.

The work is an example of Stanford Medicine’s focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill. A group of authors of the paper were Mira Ramam, a scientific program at Stanford; and a researcher from the American Foundation for Suicide Prevention.

Stanford’s Department of Psychiatry and Behavioral Sciences also supported the project. **work.**

Ebola
continued from page 1

country where Richardson and his colleagues cared for hundreds of patients in Ebola treatment units managed by Partners In Health.

In 2014, with about 900 residents, had been one of three major hot spots in the Kono District, in the eastern part of the country, during the height of the Ebola crisis between November 2014 and February 2015. The village had the largest and longest in history. More than 11,000 people are estimated to have died because of the disease.

In the aftermath, Richardson and his colleagues decided to go back to the village to try to determine whether the Ebola infection could be minimally symptomatic, as previous studies have suggested. He worked with a local physician and two community health workers in gathering data for the study, a process that was approved by the local village chief.

They used a test known as the ELISA assay, a technique that can detect the presence of an antibody. They first made sure the test was accurate by comparing results on 30 Ebola survivors in Sukuta with those of 132 people in other villages where the virus had not been reported.

Richardson said the test proved to be a reasonable measure of viral antibodies. The researchers then recruited 187 men, women and children from Sukuta who had likely been exposed to Ebola, either because they were living in the same household or had shared public facilities with people who had had the disease.

Of these, 14 were found to be carrying antibodies to Ebola, indicating they had been infected at some point, but had not had symptoms and been included in the official count. Twelve of them said they had had no symptoms of the disease, whereas two, however, had unexplained bleeding, headache, muscle pain, rash, vomiting, diarrhea, breathing problems and difficulty swallowing. When they had had symptoms at the time of the outbreak, the scientists reported.

In combining the initial reports of 34 infections with the newly identified cases, the researchers calculated the prevalence of minimally symptomatic infection in the village to have been 25 percent.

Richardson said it is unknown if an asymptomatic individual is capable of transmitting the virus. Because these individuals did not have an active case of the disease, “They were not passing it along in the usual way,” through vomiting or diarrhea, “he said. “It’s unclear if they can pass it along it sexually.”

**Working in other Sierra Leone villages**

The virus has been known to hide out for months in semen, even after symptoms have subsided, with some published cases of survivors transmitting the virus through sexual contact. Richardson said the study indicates that public health efforts to prevent infection and contain the virus should not be discontinued with the disease.

“It reminds us that we need to do a much, much better job in future epidemics,” Richardson said. He and his colleagues are now working in other villages in Sierra Leone where public health surveillance was poor during the epidemic, and in two other villages in Sierra Leone.

“Where the virus petered out, and it’s a much more undocu- mented survivors, so we can begin to answer the question of what was the true burden of disease,” he said.

Other Stanford co-authors of the paper are Michele Barry, MD, director of the Stanford Center for Health Policy and Implementation Research; and James Bond, PhD, associate professor of Earth systems science and a senior fellow at the Woods Institute for the Environment.

Researchers from Partners in Health, Brigham and Women’s Hospital, UC-San Francisco, the Kono District Ebola Response Centre and the Kono District Health Management Team in Sierra Leone also co-authored the study.

The study was funded by the Stanford Center for Innovation in Global Health.

GABA
continued from page 2

The DLPCF, a broad swath of neural tissue on the forebrain surface, has been involved in a complex process, the observations of brain-damaged patients to be integral to high-level executive functions such as planning, prioritizing and avoiding distractions. It has likewise been strongly implicated in working memory. The DLPCF orchestrates working memory and is active in neurons throughout the brain, including the visual cortex, which is located near the brain’s frontal pole.

**To better understand the findings, the researchers say what’s needed next is looking at sex differences in lowering traumatized young people of both sexes over time.**

**Tie to working-memory capacity**

“No previous study has ever pinpointed GABA’s link with working memory in humans,” said Yoon. “Working memory is a complex process, requiring coordinated activity in centers throughout the brain. Yet, remarkably, the amount of this one chemical in a single slice of the brain accounts for close to one-third of the variance in individuals’ load capacity.”

He worked with 25 healthy participants ages 19-32 were subjected to batteries of related memory tasks. In the simplest, they were shown two faces, some years apart, and asked to determine which face had been judged to be.

Participants repeated several related task within different scans. GABA, they were showed a drawing of a face and then, after a two-second delay, shown a second face and asked to determine which face had been different from the first. Variations of this task — initially presenting two faces instead of just one, lengthening the intervening delay, or displaying a different, irrelevant face between the two faces — lengthened measurement of load, maintenance and distraction resistance.

The scientists saw no differences in brain structure between boys and girls in those groups. However, whatever trauma boys and girls saw, they saw differences in a portion of the insula called insula’s central and distal subregions. This brain region had larger volume and surface area in traumatized boys than in boys in the control group. In addition, the region’s volume and surface area were smaller in girls with trauma than among girls in the control group.

**Findings could help clinicians**

“It is important that people who work with traumatized youth consider the sex differences,” said Megan Klabunde, PhD, the study’s lead author and an instructor in the Department of Psychiatry and Behavioral Sciences at Stanford; and a researcher from Stanford’s Department of Psychology and Behavioral Sciences. “Our findings suggest that it is possible that boys and girls could exhibit different trauma symptoms and that they might benefit from different approaches to treatment.

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Stanford’s Department of Psychiatry and Behavioral Sciences also supported the project. **work.**

Innovation in Global Health.
Cyberknife used to treat rare condition in pediatric patient

By Joe Molica

In October 2014, Kendall Kemm’s parents received devastating news: Their then-10-year-old daughter had suffered a hemorrhagic stroke.

Kendall’s stroke was a result of an arteriovenous malformation, or AVM, a rare defect that results in a tangle of abnormal blood vessels that disrupts the normal flow of blood. AVMs are most often found in the brain or spinal cord and affect less than 1 percent of the population.

Kendall survived, and is being treated at Stanford Health Care through stereotactic radiosurgery, which uses radiation to shrink and ultimately destroy the AVM in her brain.

Kendall travels from Pennsylvania to Stanford for treatment because Stanford Health Care offers a unique approach using CyberKnife technology, which delivers radiation with unprecedented precision. The CyberKnife was invented at Stanford, and is used to treat a variety of conditions. Steven Chang, MD, professor of neurosurgery, and Scott Seltys, MD, assistant professor of radiation oncology, oversee Kendall’s treatment.

“When Kendall had her stroke, it was devastating,” said Kendall’s mother, journalist Leslie Gudel Kemm. “We spent the better part of the first month crying, and then doing research. So few doctors want to treat kids with this condition, but when we connected with Dr. Chang, he said, ‘We can treat this.’”

Kendall’s Crusade

Grateful for the care she received at Stanford Health Care and Lucile Packard Children’s Hospital Stanford, Kendall brainstormed ways to help others with the same condition. Together with her family, she formed Kendall’s Crusade. The nonprofit aims to provide financial assistance to families affected by AVM, raise overall awareness of the condition and support neurosurgery research.

Kendall returned to Stanford in October to continue her treatment. With funds raised through Kendall’s Crusade, she presented a check to Chang to help fund his research on treatment and support a patient travel fund for AVM patients.

“When I first met Kendall and her family, they were so determined to learn all they could about AVMs,” Chang said. “Although some AVMs are inoperable, the CyberKnife opens up additional treatment options that other technology doesn’t allow.”

Kendall’s AVM is now approximately 90 percent gone, with her next MRI scheduled for next year. Additional treatments will be considered as her progress is monitored. Kendall has remained positive and devoted to her mission to help fellow AVM patients.

“I’m grateful for what we’ve been able to do for the other kids that are going through the same thing as me,” she said. “But I want us to get to a point where the research will help to develop a cure, so no other kids have to go through this.”

Top: Accompanied by research associate Lorello Shoshanker (left), Kendall Kemm visits a neuroscience lab, where she gets a close look at a human brain. Below: Kendall helps Shoshanker with an experiment.

Ben Barres
Christopher Contag
Christina Curtis
James Dunn
James Jacobson
Prithvi Muthyunayaja
Lidia Schapira
Alex Sox-Harrington
Eric Sun

OF NOTE

reports on significant honors and awards for faculty, staff and students

CHRISTOPHER ALMOND, MD, was promoted to associate professor of pediatrics, effective Aug. 1.

BEN BARRES, MD, PhD, professor of neurobiology, of developmental biology and of neurology and neuroscientific sciences, has received the Society for Neuroscience’s Ralph W. Gerard Prize in Neurosciences, the society’s highest award. He will share the $25,000 prize with fellow recipient Thomas Jessell, PhD, of Columbia University. The prize honors outstanding scientists who have made significant contributions to neuroscience. Barres’ research focuses on the role of glial cells in development and synapse function and in diseases such as Alzheimer’s.

CHRISTOPHER CONTAG, PhD, professor of pediatrics and of microbiology and immunology, will receive the 2017 Britton Chance Biomedical Optics Award from SPIE, the international society for optics and photonics. The award recognizes outstanding lifetime contributions to biomedical optics. Contag develops and uses optics-based imaging tools to study biology in living animal models of human disease, and for early detection of cancer in patients.

CHRISTINA CURTIS, PhD, assistant professor of medicine and of genetics, was named a 2016 Kavli Frontiers of Science Fellow by the National Academy of Sciences. The program selects outstanding young scientists to attend symposia, thereby promoting communication and collaboration. In her research, Curtis uses experimental and analytical approaches to improve the diagnosis and treatment of cancer.

JAMES DUNN, MD, PhD, was appointed professor of surgery, as well as surgeon-in-chief at Lucile Packard Children’s Hospital Stanford and chief of pediatric surgery, as well as surgeon-in-chief at Lucile Packard Children’s Hospital Stanford and chief of pediatric surgery. Dunn will also serve as the director of clinical research for the Department of Surgery, and his research focuses on cancer survivorship and on improving communication between caregivers and patients.

RAPHAEL MONTAGU, MD, PhD, was promoted to associate professor of anesthesiology, perioperative and pain medicine, effective Sept. 1. His research combines high-dimensional mass cytometry analysis with machine-learning-based biocomputation to study the human immune system’s response to perturbations, such as pregnancy. His clinical interests include surgical trauma, ischemic stroke, pregnancy and preterm labor.

JAMES JACOBS, MD, PhD, was appointed associate professor of psychiatry and behavioral sciences, effective Sept. 1. He is the executive director of Vaden Health Center and associate vice provost for student affairs. DAVID MAIKS, MD, PhD, was appointed professor of pediatrics, effective Sept. 1. He is chief of the division of pediatric endocrinology. His research and clinical focus is on improving care for children with type 1 diabetes.

ROBERT MULENKA, MD, PhD, professor of psychiatry and behavioral sciences and the Nancy Friend Pritzker Professor in Psychiatry and Behavioral Sciences, has been awarded the Julius Axelrod Prize by the Society for Neuroscience. The $25,000 prize recognizes exceptional achievements in neuropharmacology and an exemplary commitment to mentoring young researchers. Mulenk’s interests include translating research on synaptic transmission into clinically useful therapies.

ARASH MOMENI, MD, was appointed assistant professor of surgery, effective Sept. 1. He is the co-director of the hand transplant program. He specializes in microsurgical reconstruction of the breast, head and neck, trunk and extremities.

PRITHVI MUTHYUNAYAJA, MD, was appointed associate professor of ophthalmology, effective Sept. 1. He is the director of ocular oncology. He specializes in the treatment of pediatric and adult ocular cancers and conditions affecting the retina. His research interests include ocular cancer imaging, genetics and tumor biology.

LIDIA SCHAPIRA, MD, was appointed associate professor of medicine, effective Sept. 1. Her research focuses on cancer survivorship and on improving communication between caregivers and patients.

ALEX SOX-HARRINGTON, MD, was appointed associate professor of surgery, effective Sept. 1. He is the director of clinical research for the Department of Surgery, and his research focuses on the evaluation of health-care quality and efficacy.

ERIC SUN, MD, PhD, was appointed assistant professor of anesthesia, perioperative and pain medicine, effective Sept. 1. His research interests include health economics and policy, with a focus on economics and policy in the perioperative setting.