

In diabetes, no added heart benefit from tighter sugar control

Major VA trial included nearly 1,800 veterans at 20 sites; largest study of its kind

Two in three people with diabetes die of heart attack, stroke or other cardiovascular events. But doctors have been unsure whether there is a direct cause-and-effect link between high blood sugar and cardiovascular disease.

Now, a major VA study has provided key evidence to help answer the question. The seven-year VA Diabetes Trial, which included nearly 1,800 veterans at 20 VA medical centers, found that intensive control of blood glucose in type 2 diabetes does little to cut the risk of heart disease, compared to standard treatment. The results were presented at last month's annual scientific meeting of the American Diabetes Association and could have a significant impact in VA's health system, where nearly a fifth of patients—some one million veterans—have type 2 diabetes.

“While we found that intensive treatment of patients with type 2 diabetes suggested some benefits from glucose control, it

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Photo by Larry Glick

Glucose in check—Carlos Abaira, MD, co-chair of the VA Diabetes Trial, discusses the use of a glucometer—a device that measures blood sugar—with patient Fulgencio Rodriguez at the Miami VA.

Nanotechnology team aims to build a better electrode

Implanted brain electrodes may one day play an important role in restoring independence to those with spinal cord injury, ALS, limb loss or other conditions. As part of technology being developed by

VA researchers and colleagues, the electrodes would pick up brain signals and send them to a decoder that would convert them to signals to control computer cursors, artificial arms or other devices.

One challenge, though, is that the electrodes appear to lose their effectiveness over time. This may be due to a “mechanical mismatch” between the rigid electrode and the surrounding soft tissue, says polymer scientist Christoph Weder, PhD. “The working hypothesis is that initially the electrode needs to be stiff, or you would not be able to implant it. But once it's in, the brain is soft, like Jell-O, and then you have this stiff electrode. What you really want is an electrode that uses as a substrate a ‘smart’ material—

Inspired by nature—The sea cucumber (left), seen here nested among corals in a home aquarium, can change its skin from hard to soft. A nanotechnology team with VA and Case Western Reserve University has engineered a material (microscope view, right) that mimics this quality.

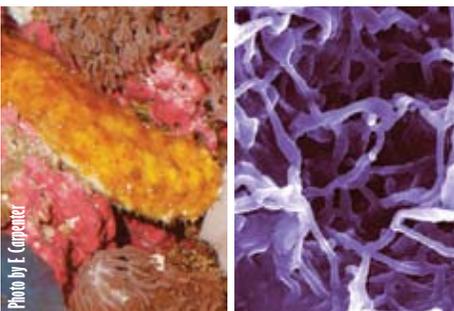


Photo by E. Comper

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did not reach significance for a reduction in the primary endpoint—a composite of specified cardiovascular disease events—in this population,” said study co-chair William C. Duckworth, MD, director of diabetes research at the Carl T. Hayden VA Medical Center in Phoenix and a professor of clinical medicine at the University of Arizona.

Past studies inconclusive

Past research had yielded mixed findings, with most clinical trials failing to show a significant drop in heart attacks, strokes or other cardiovascular events when blood sugar levels were well-controlled.

One aim in the VA trial was to reduce, as much as possible, other cardiovascular risk factors, such as hypertension, so the researchers could hone in on the effects of blood sugar alone. According to study co-chair Carlos Abaira, MD, of the Miami VA and the University of Miami, the trial was a huge success in this regard.

“This was a complicated study in which all of the patients had multiple health problems, including 40 percent with prior

cardiovascular events,” Abaira said. “Our first goal was to reduce all other cardiovascular risk factors in order to compare outcomes between standard and intensive blood glucose treatment groups—and we achieved that goal superbly.” On average, participants in both groups were at or below targets for lipids and blood pressure within the first two years and maintained these levels throughout the study.

While the average A1C—a measure of blood glucose control over the prior two to three months—was 9.5 percent upon entry into the trial, the standard group reached 8.4 percent and the intensive group reached 6.9 percent within six months. Below 7 percent is considered normal. Most participants in both groups received two to three oral drugs, such as rosiglitazone or metformin, plus insulin. The intensive-treatment group received higher doses as needed to further draw down their blood sugar. There were no increased deaths associated with any of the drugs used.

Outcomes better than expected

Duckworth explained that the study included only patients who had already failed what he called “simple therapy”: They had unacceptable blood-sugar levels even on maximum doses of at least one oral diabetes drug or insulin—or both treatments combined. The study population was also high-risk in that some 40 percent had experienced prior cardiovascular events, 80 percent had high blood pressure, more than half had high cholesterol or other lipid abnormalities, and most were obese. The average age of the volunteers at the study’s outset was 60. Even so, there were significantly fewer cardiovascular events in both study groups than predicted. The predicted event total for both groups was between 650 and 700, whereas the actual number of events that occurred was 494—

The study included a high-risk population, 40 percent of whom had prior cardiovascular events.

263 in the standard group and 231 in the intensive group. The difference between the two study arms was not statistically significant.

“We believe this was largely due to the excellent blood pressure control, lipid control, improved diet and exercise, and treatment with aspirin,” said Duckworth. “Both our intensive and control groups reduced their blood pressure levels to a mean of 127 over 70, and both improved lipid control to near or at American Diabetes Association guidelines.”

The take-home message of the study, said Duckworth, is that high blood sugar by itself may be more related to diabetes complications such as nerve, eye and kidney problems than to so-called “macrovascular” complications such as heart attack and stroke. Retinal and kidney problems are caused by damage to small blood vessels, which can result from excess blood sugar.

Duckworth noted another lesson from the trial: “For intensive glucose control to yield a significant benefit on cardiovascular risk reduction, you may have to do it early. If you go into a population that already has multiple risk factors—or prior cardiovascular disease—and longstanding poor glucose control, you cannot expect benefits from glucose control in the short term. You can’t expect miracles.”

Secondary results from the trial—including findings on retinal, kidney and nerve complications—will be presented in September at the European Association for the Study of Diabetes meeting in Rome. 

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Grape-derived compounds shine in lab studies

Resveratrol, even in small doses, found to protect heart in mice

Health enthusiasts have been buzzing for some years about resveratrol, an antioxidant found in the skin of grapes. Lab studies suggest it can fight cancer, help the heart and extend life, and it is reputed to be part of the answer to the so-called French Paradox: The French, who typically drink wine with their meals, have remarkably low rates of heart disease despite their high intake of butter, cheese, eggs, and other dietary sources of cholesterol and saturated fat.

In some studies, though, the resveratrol dose given to mice was very high—equivalent to what a person would get by drinking hundreds of bottles of wine a day. The results were met with some skepticism and even made it into Jay Leno’s monologue on the “Tonight Show.”

Recently, however, a team of researchers with VA, academia and industry found in lab experiments that far smaller amounts of resveratrol than previously thought may help protect the heart against aging and offer other wide-ranging health benefits.

Writing in the June 4 issue of the online, public-access journal *Public Library of Science One*, the scientists reported that low doses of resveratrol in the diet of middle-aged mice had effects similar to those of caloric restriction, which in many studies has been shown to blunt the effects of aging. In the study, a group of mice fed small doses of resveratrol and another fed a calorie-restricted diet showed strikingly similar changes in genetic activity: “Both dietary interventions inhibit gene expression profiles associated with cardiac and skeletal-muscle aging and prevent age-related cardiac dysfunction,” wrote the authors.



“This brings down the dose of resveratrol toward the consumption reality mode,” said senior author Richard Weindruch, MD, a University of Wisconsin-Madison professor of medicine and researcher at the

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Photo by Lynne Kantor

Research on the vine—Giulio Pasinetti, MD, PhD, of the Bronx VA, is funded by the National Center for Complementary and Alternative Medicine to study how grape-derived polyphenols may help against dementia.

Grape seed extract shows promise for Alzheimer’s disease

Anatural product called grape seed extract may hold promise as a treatment for Alzheimer’s disease and as a general brain tonic, according to an animal study published June 18 in the *Journal of Neuroscience*.

Using mice genetically engineered to develop Alzheimer’s disease, a team led by Giulio Pasinetti, MD, PhD, of the Bronx VA Medical Center and Mount Sinai School of Medicine found that grape seed extract prevents the build-up in brain cells of a protein called amyloid beta. In Alzheimer’s, this sticky protein forms toxic plaques that disrupt brain function.

The researchers tested a grape seed extract made by Polyphenolics, a California company whose motto is “Realizing the Health Benefits of the Grape.” Polyphenols are antioxidants naturally found in red wine, tea, chocolate, and a variety of fruits and vegetables. Red wine is an especially potent source of polyphenols—more so than grapes, grape juice, or white wine—because of how it is fermented.

To determine the effects of the grape seed extract on Alzheimer’s disease, the researchers exposed presymptomatic “Alzheimer’s mice” to the extract or placebo daily for five

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Study highlights new way to clear arteries

Jokes abound about doctors on the golf course. But it is “fishing” that is making a name for one VA physician.

Raed Aqel, MD, an interventional cardiologist and researcher with VA and the University of Alabama at Birmingham, has developed an innovative technique for “fishing” blood clots out of clogged arteries using a tiny surgical filter.

The device is normally used to catch blood clots that break free when doctors open plaque-clogged arteries with balloon catheters. The filter, attached to a long thin wire, is threaded up into the bloodstream past where a balloon will be inserted. It snares clots—or pieces of clots—that float into it, much like a net placed in a stream to catch fish. Particles that miss the filter, though, can lodge in the arteries and block blood flow to the heart or brain. The result can be a heart attack or stroke.

Aqel has learned how to use the filter more proactively. Before beginning the balloon procedure, he catches clots that might otherwise slip by the filter later on. He gingerly maneuvers the tiny basket into place directly behind a clot, snags it intact, and gently hauls it out of the artery. The clots he pulls in look like stringy worms, about a half-inch long.

Method used with nearly 50 patients so far

Aqel described the novel technique last year in the *Journal of Invasive Cardiology* and just last month published a study in *Catheterization and Cardiovascular Interventions*, an international journal, in which the method proved successful in 15 heart attack patients. Since completing that study, he has gone on to use the method in more than 30 additional patients.

The FilterWire EZ is used during angioplasty to trap blood clots.



Grateful patient—Raed Aqel, MD, and radiology technologist Earl Moore meet with 58-year-old Vietnam veteran Edward Peters, who suffered a heart attack in June and benefited from Aqel’s innovative clot-retrieval method.

VA’s Dr. Aqel first described his innovative technique in the *Journal of Invasive Cardiology*.

“We got bombarded by questions when we did our first case report last year,” recounts Aqel. “Will this injure the artery? Will it cause more clots to go and ‘run away’ from the basket? All of these are possible—but so far we have been using this procedure as our standard method and it has not caused any problems.”

The method had appeared only once in the medical literature before Aqel’s reports. It was used in that case to retrieve a clot inside a stent that had already been placed. Aqel believes he is the first to use it on “virgin” arteries—those that have never been catheterized and stented.

Is the technique catching on? “We get calls from other cardiologists asking about the technique,” says Aqel, “but to my knowledge there’s no one who has begun using it.” He points out that working on a patient with a heart attack is a high-stress time when even super-cool-headed doctors are wary about trying new techniques.

Aqel is hopeful, though, that VA or a private company will fund a multisite clinical trial in which he and other cardiologists can further explore the benefits of the technique for patients with coronary artery disease. 

At Palo Alto VA, physicians are ‘sharpening their image’

Marketing types are fond of saying that “image is everything.” The catchphrase is increasingly appropriate in medicine as well, especially with the advent of 3-D imaging software that gives physicians a virtual road map of a patient’s anatomy.

Roy Soetikno, MD, a gastroenterologist and researcher at the VA Palo Alto Health Care System and Stanford University School of Medicine, is looking to greatly expand the use of this technology. His vision is to make it easier than ever before for doctors to access and use 3-D imaging for diagnosis and treatment. He has helped spearhead a new program at the Palo Alto VA—called the Collaborative Imaging Initiative—that may serve as a model for other VA sites and possibly also for medical practices outside VA.

A ‘GPS’ map for doctors

Currently, doctors typically rely on radiology specialists to create and show them 3-D images—based on CT or other scans—on high-end imaging workstations. The doctors are unable to view the images on their own computers, so they have to study and essentially memorize them. During a surgery to take out a liver tumor, for example, they would have to rely on their mental image of the tumor’s exact location relative to the veins, arteries and other structures surrounding it.

“What we’re doing is empowering the treating physicians to have highly capable imaging viewers on their desktops. Soon this capacity will be in the operating room,” says Soetikno. “What that means is that rather than having to memorize the map, we will be



A new dimension— “Imaging is critical in patient care nowadays,” says physician-researcher Roy Soetikno, MD, who is promoting new ways of sharing and using 3-D and other advanced medical images among doctors.

able to use it during the procedure. It’ll work like a futuristic, 3-D GPS map.”

The system at Palo Alto relies on low-cost software and hardware. Computers are linked together via an existing data network. The power users who create the 3-D images still require special imaging workstations, but now referring physicians can handily view the images on any computer via the secure VA network.

The software also allows for real-time, Web-based videoconferences in which a medical team, the patient, and family members can all look together at the same 3-D image—of the patient’s colon or aorta, say—and manipulate the view in any number of ways as they discuss treatment options.

3-D images a click away

Another advantage of the system is that any physician, provided he or she has an Apple computer, can not only view 3-D images but also easily learn how to create or customize them independently. One click could render a set of two-dimensional images into a 3-D image.

The system sounds easy enough in this digital millennium, but it challenges some conventional ways of doing things. It’s a new paradigm, says Soetikno. “In five or 10 years, everyone will wonder why we weren’t doing this earlier.”

A practical, tech-savvy visionary, Soetikno hopes the system now in place at the Palo Alto VA to share 3-D images can eventually be replicated through the VA system and even meshed with VA’s electronic medical record system, which allows a patient’s chart to be easily accessed anywhere nationwide.

“In VA, this would be an incredible opportunity, because we are all connected to the same secure network,” he says.

He points out that the system could be particularly valuable in improving care for rural veterans, who might be four or five hours away from a major medical center with 3-D imaging capability and expertise.

Soetikno describes how the scenario would unfold: “The patient undergoes a CT scan of his colon, hundreds of miles away, and the images are transported via the Web

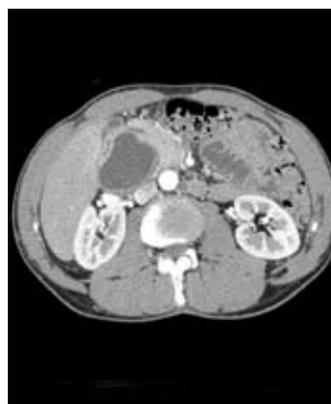
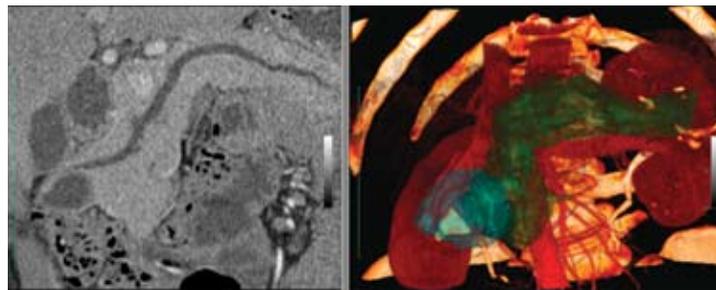
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to our imaging workstations. We create a virtual colonoscopy and identify the exact location of the polyp. We also open up Vista [VA's electronic medical record system] and look at the blood work and the other history. Using videoconferencing tools, an expert team including a gastroenterologist, radiologist and surgeon collaborate to determine the best way to manage this patient. Then we could either give a treatment recommendation to the patient's local physician or recommend that the patient come to Palo Alto. If the local surgeon is going to operate, he could get the 'GPS' map we have created to help him get precisely to the problem area."

Soetikno is quick to credit his colleagues at Palo Alto, including local and regional management and the information-technology group, for enabling the new imaging system to move forward.

"We have people and an environment here that are conducive to translating innovations into practice, in order to improve the medical care of our nation's veterans." —



Enhanced view—At the left is a conventional view of a CT scan of the pancreas. On top are two reformatted views, made possible by special imaging software, based on the same CT data—one a highly detailed black-and-white image, the other a colorized 3-D image, with the pancreas shown in green. The enhanced visualization improves diagnosis and treatment planning.

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months. The daily dose of polyphenols was equivalent to a human intake of about one gram—the amount in a typical daily diet of 2,500 calories.

At five months of age, the Alzheimer's mice normally start showing signs of disease. However, the mice given the extract had less amyloid beta accumulation and plaque formation. They also performed better on maze tests than mice that received placebo. The findings suggest that before symptoms begin, grape seed extract may prevent or postpone plaque formation and slow cognitive decline.

According to Pasinetti, the results may have implications not only for treating or preventing Alzheimer's disease, but also for forestalling even mild memory loss. "Amyloid is present in everyone's brain, and whenever it comes together in a more complex structure, it makes the brain function less efficiently. The ability of the compounds found in the product we tested to inhibit the formation of the more complex amyloid structures suggests that it

might even help memory loss in those who have not yet developed Alzheimer's disease."

Pasinetti emphasized that effective and safe natural compounds would be a vital addition to physicians' toolbox for treating Alzheimer's. "So far, the only treatments available for Alzheimer's only alleviate symptoms. We are trying to identify molecules that will interfere with the progression of the disease."

Pasinetti and colleagues previously found that red wine—specifically, Cabernet Sauvignon—reduced cognitive decline in Alzheimer's mice. In subsequent studies, Pasinetti's team has tried to isolate which of the nearly 5,000 molecules contained in red wine are important in disease prevention. Chemical analysis on the grape seed extract used in the new study showed that its major polyphenols are catechin and epicatechin, which are also abundant in tea and cocoa.

The research was performed at the Center of Excellence for Research in Complementary and Alternative Medicine in Alzheimer's Disease at Mount Sinai

School of Medicine and the Bronx VA. It was supported by the National Center for Complementary and Alternative Medicine, part of the National Institutes of Health; VA; Polyphenolics, which makes the extract used in the study; the Japan Human Science Foundation; and the Alzheimer's Association. —

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something that is stiff when it goes in and then becomes soft."

Weder and colleagues are designing just that. His group at Case Western Reserve University and VA's Advanced Platform Technology Center, based at the Louis Stokes Cleveland VA Medical Center, have created a "nanocomposite" that changes from hard to soft. They described their invention in the journal *Science* earlier this year.

"The materials on which we reported in *Science* were designed to change from a hard plastic—think CD case—to a soft

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Leslie Gonzalez Rothi, PhD, program director of VA's Brain Rehabilitation Research Center in Gainesville, Fla., was appointed to the National Medical Rehabilitation Research Advisory Board. The 18-member group provides guidance for rehabilitation-related programs and policies within the National Institutes of Health.



Richard Owen, MD, director of the Center for Mental Healthcare and Outcomes Research at the Central Arkansas Veterans Healthcare System (CAVHS), was elected president of the board of directors of the Arkansas chapter of the National Alliance for Mental Illness. Owens is also deputy associate chief of staff for research at the CAVHS.



Eugene Oddone, MD, MHSc, director of VA's Durham-based Center for Health Services Research in Primary Care, received the Chief's Recognition Award from the Association of Chiefs of General Internal Medicine, a subgroup of the Society of General Internal Medicine. The honor is given for criteria such as mentorship of young physicians in research or other areas; faculty development; and advocacy for general internal medicine.



Kevin G. Volpp, MD, PhD, an investigator with VA's Center for Health Equity Research and Promotion and associate professor at the University of Pennsylvania School of Medicine and the Wharton School, was one of 61 researchers elected to the American Society for Clinical Investigation in 2008. The group promotes research that improves knowledge and treatment of human diseases and provides mentorship to young physician-scientists. Volpp's research focuses on the impact of financial and organizational incentives on health outcomes. —

VA seeking more proposals for brain-injury research

VA's Office of Research and Development is looking to fund additional studies on traumatic brain injury (TBI). A solicitation issued last month calls for new proposals from VA investigators on topics relating to TBI and its associated conditions, such as cognitive impairment, mood and anxiety disorders, vision and hearing loss, chronic pain, substance abuse, and sleep disturbance. Prospective studies may be funded by any of the four divisions of VA research, representing the full spectrum of biomedical, clinical, rehabilitation and health-services research.

VA investigators already conduct a wide range of TBI research, from genetic and biochemical studies, to clinical trials of pharmacological, psychological and other treatments, to evaluations of vocational and community reintegration programs. The new funding announcement is partly based on the results of a VA conference on TBI held this past spring that included researchers and clinicians representing VA, academia, the Department of Defense and the National Institutes of Health.

More information on the new TBI program announcement can be found on the VA Research website at <http://www.research.va.gov/funding/solicitations/docs/TBI.pdf>.

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rubber when brought into contact with water," said coauthor Stuart Rowan, PhD.

The new material is inspired by the sea cucumber, explains Jeffrey Capadona, PhD, lead author on the *Science* article. "These creatures can reversibly and quickly change the stiffness of their skin. Normally is it very soft, but—for example, in response to a threat—the animal can activate its 'body armor' by hardening its dermis." Capadona keeps one of the creatures in an aquarium at home.

The theory is that an electrode that could morph from hard to soft in response to water would work well in the aqueous environment of the brain. The researchers, funded by VA and the National Institutes of Health, are preparing to test the theory in animals. An alternative route they are taking is to create similar electrodes that would change their stiffness in response to an electrical or light signal, instead of water. That could be useful, for example, if clinicians needed to remove the electrode from the brain of a patient and wanted to re-stiffen it. —

RESVERATROL *(from page 3)*

William S. Middleton Memorial Veterans Hospital. “At the same time, it plugs into the biology of caloric restriction.” Caloric restriction—diets with up to 40 percent fewer calories than a typical diet—has been shown to boost longevity in countless animal studies but has never emerged as a practical strategy for people.

Based on their findings, the researchers suggest that a glass of wine—preferably red—or food or supplements that contain even small doses of resveratrol are likely to represent “a robust intervention in the retardation of cardiac aging.” Besides wine, the substance is also found in varying amounts in red or purple grape juice, peanuts, and some berries. Taking the nutrient in supplement form may be one way to get a therapeutic dose while avoiding the alcohol or sugar content of wine or grape juice. Some experts caution, though, that more research is needed on its long-term effects and that commercially available supplements may vary in quality and actual resveratrol content, despite what the label says. Weindruch agrees that further studies are needed to learn whether resveratrol can really protect the heart and extend the lifespan in humans. ➔

INVESTIGATOR SNAPSHOT



Unlocking obesity’s mysteries—Neuroscientist Catherine Kotz, PhD, studies obesity at the Minneapolis VA Medical Center and University of Minnesota. She is seen here with specially bred obesity-prone rats, which she says provide an excellent model of the condition in humans. Her recent focus has been the genetic and biochemical factors that cause spontaneous, unconscious movement throughout the day. Kotz’s studies suggest such “fidgeting” plays a surprisingly large role in calorie-burning and weight control. Her findings on orexin—a brain hormone central to this process—have been featured in the news with headlines such as “Some Brains Wired to Encourage Fidgeting.”

Kotz: “The ‘calories in, calories out’ model of weight loss is simple in theory. But it’s not easy to lose weight, especially for those who may have a genetic predisposition to obesity. In these cases, having some pharmaceutical help can be a good thing. One goal of our research is to create new therapies for people who need to lose weight but have difficulty doing so.” ➔