

# Guidelines on CV Risk Assessment Go Low-Tech

BY BRUCE JANCIN

FROM THE ANNUAL SCIENTIFIC SESSIONS OF THE AMERICAN HEART ASSOCIATION

CHICAGO – New American College of Cardiology/American Heart Association guidelines on cardiovascular risk assessment in asymptomatic adults may be better remembered for the tests and procedures that received a thumbs-down rather than for those endorsed for routine use.

For example, genetic testing was among the newer, often glamorous tests that have captured intense public and physician interest, yet they were classified as class III – meaning they're deemed not useful and may be harmful. In other words, don't do them in people without symptoms of heart disease.

"Genetic testing is a sexy area right now, but we didn't see it as being ready or as having shown added value," Dr. Sidney C. Smith Jr. said in a press briefing on the new guidelines held during the meeting.

Other tests that were rated class III included advanced lipid testing with measurement of apolipoproteins and particle size and density, MRI for the detection of



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arterial plaque, measurement of natriuretic peptide levels, and coronary CT angiography.

"You'll hear a lot of discussion about the value of coronary CT angiography in people who come into the emergency department with chest pain, but that's a very different population," said Dr. Smith, a member of the risk assessment guideline writing committee and immediate past chair of the ACC/AHA task force on practice guidelines.

Stress echocardiography, measures of arterial stiffness, and assessment of flow-mediated dilation also received class III status, noted Dr. Smith, professor of medicine and director of the center for cardiovascular science and medicine at the University of North Carolina, Chapel Hill.

In his Ansel Keys Memorial Lecture delivered at the AHA conference, Dr. Philip Greenland, chair of the guideline writing committee, explained that new diagnostic tests have to clear a high bar: They must show evidence of added value beyond that provided by the Framingham Risk Score or another global cardiovascular risk score plus assessment of family history, which are the only class I recommendations in the new report, meaning they should be performed in all adults.

The family history is a new class I recommendation. A positive family history

under the Framingham definition is a first-generation male relative with a cardiovascular event at age 50 or younger, or by age 60 or younger in a female relative.

The new guidelines state that a global cardiovascular risk score and family history are essential for everyone, preferably starting at age 20, and should be repeated every 5 years.

For a new risk marker to be considered as useful for risk prediction, it must be

shown to be a statistically independent predictor after an accounting for established risk factors. Beyond that, it must also be shown to change predictive risk sufficiently to alter recommended therapy. And then it must be shown that using the novel marker to sort patients and treat them accordingly would actually yield better clinical outcomes than if the marker had not been used, said Dr. Greenland, professor of medicine and

preventive medicine at Northwestern University in Chicago.

"This is a big question for almost all of our biomarkers in cardiovascular medicine, where we can perhaps show improvement in prediction, but it's not quite so clear we can show improvement in clinical outcomes," he said. "Generally speaking, we haven't seen much evidence of improvement of risk prediction with the new markers when

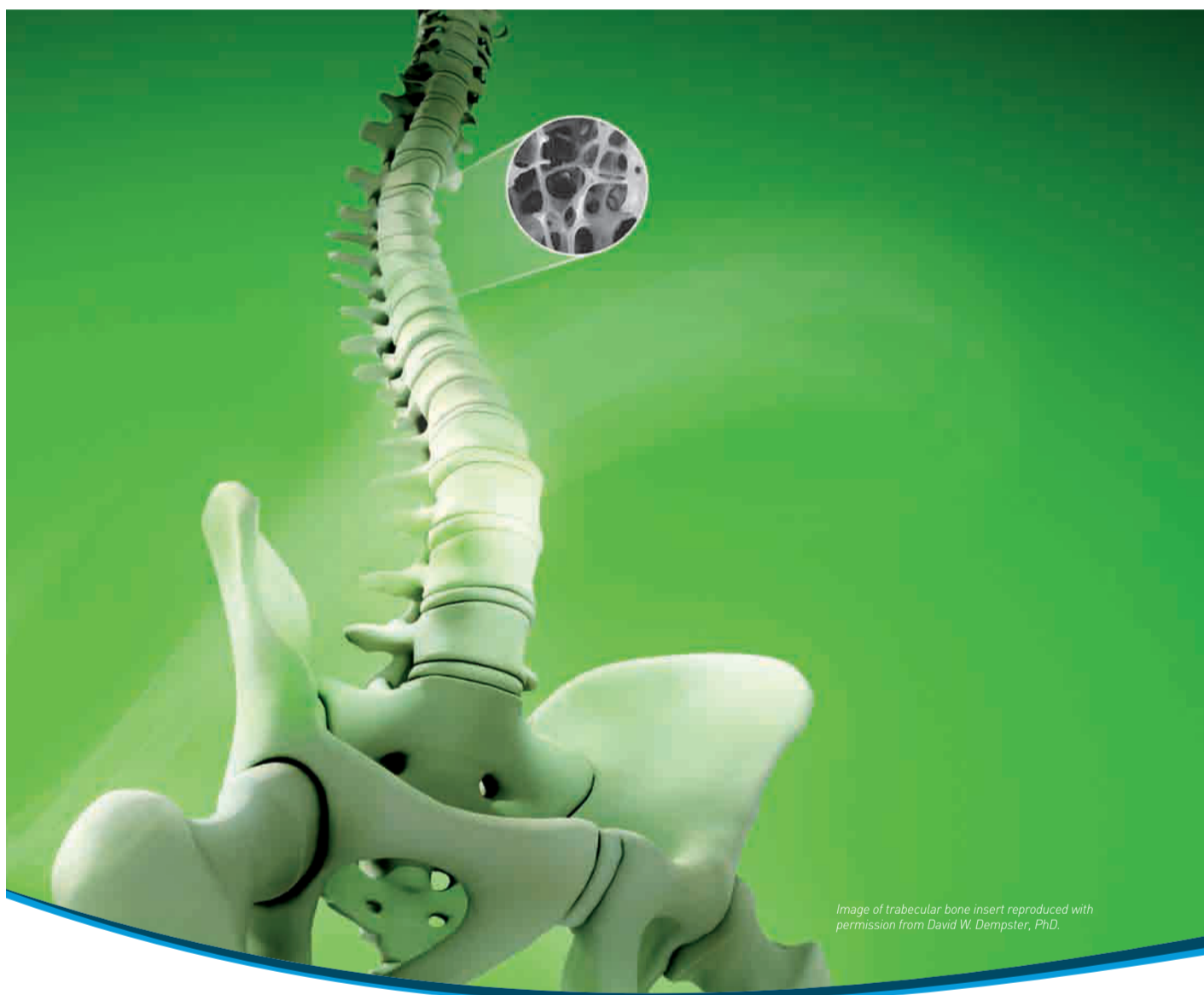


Image of trabecular bone insert reproduced with permission from David W. Dempster, PhD.

## INDICATION

**Prolia™ is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia™ reduces the incidence of vertebral, nonvertebral, and hip fractures.**

## IMPORTANT SAFETY INFORMATION

- ♥ **Hypocalcemia:** Prolia™ is contraindicated in patients with hypocalcemia. Pre-existing hypocalcemia must be corrected prior to initiating Prolia™. Hypocalcemia may worsen, especially in patients with severe renal impairment. In patients predisposed to hypocalcemia and disturbances of mineral metabolism, clinical monitoring of calcium and mineral levels is highly recommended. Adequately supplement all patients with calcium and vitamin D.
- ♥ **Serious Infections:** In a clinical trial (N = 7808), serious infections leading to hospitalization were reported more frequently in the Prolia™ group than in the placebo group. Serious skin infections, as well as infections of

the abdomen, urinary tract and ear, were more frequent in patients treated with Prolia™. Endocarditis was also reported more frequently in Prolia™-treated subjects. The incidence of opportunistic infections was balanced and the overall incidence of infections was similar between the treatment groups. Advise patients to seek prompt medical attention if they develop signs or symptoms of severe infection, including cellulitis.

Patients on concomitant immunosuppressant agents or with impaired immune systems may be at increased risk for serious infections. In patients who develop serious infections while on Prolia™, prescribers should assess the need for continued Prolia™ therapy.

- ♥ **Dermatologic Adverse Reactions:** Epidermal and dermal adverse events such as dermatitis, eczema and rashes occurred at a significantly higher rate in the Prolia™ group compared to the placebo group. Most of these events were not specific to the injection site. Consider discontinuing Prolia™ if severe symptoms develop.
- ♥ **Osteonecrosis of the Jaw (ONJ):** ONJ, which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients receiving Prolia™. An oral exam should

you look at the whole picture. The one exception, I would say, is measurement of coronary artery calcium. I came to this as a major skeptic about coronary calcium, and only after seeing some data did I come to believe that coronary calcium might actually have clinical impact. But even with coronary calcium, I think we're too early in the evaluation process to recommend routine use beyond standard risk measurement."

Indeed, coronary artery calcium scoring gets a class IIa recommendation (meaning it's reasonable for cardiovascular risk assessment) only in asymptomatic

adults who are at intermediate risk, as defined by their global Framingham-type risk assessment, with an estimated 10%-20% risk of a cardiovascular event in the next 10 years. Coronary calcium scoring gets a lesser IIb rating (meaning it 'may be considered appropriate') in patients who are at low to intermediate risk, as defined by an estimated 6%-10% risk of an event over 10 years. In patients with less than a 6% 10-year risk, it gets a class III rating.

Investigators in MESA (Multi-Ethnic Study of Atherosclerosis) found that adding coronary artery calcium scores to

standard cardiovascular risk factors improved risk discrimination from 77% to 82%, which the committee deemed clinically meaningful, Dr. Smith noted.

Measurement of C-reactive protein, another hot topic, is rated class III (no benefit) in asymptomatic adults who are defined as high-risk by the Adult Treatment Panel III standard of a greater than 20% 10-year risk. Similarly, CRP is class III in low-risk men younger than age 50 and in low-risk women younger than age 60.

However, CRP gets a class IIa recommendation as a guide to deciding on

statin therapy in men aged 50 or older and in women aged 60 and older with an LDL cholesterol level of less than 130 mg/dL. It gets a class IIb recommendation in asymptomatic men and women aged 50 and 60 years, respectively, or younger.

The full 54-page guideline was released online in *Circulation* during the conference, and it is available at <http://circ.ahajournals.org/cgi/reprint/CIR.0b013e3182051b4cv1>.

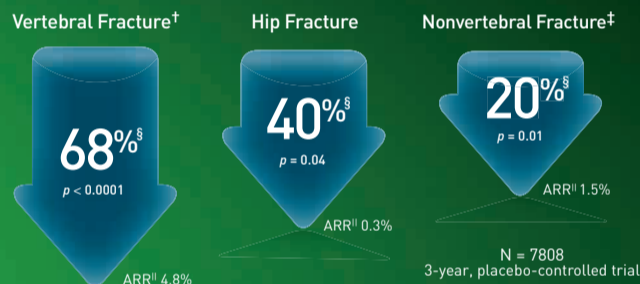
Dr. Smith declared having no relevant financial interests. Dr. Greenland disclosed serving as a consultant to Pfizer, General Electric, and Toshiba. ■

In Treating Your Postmenopausal Osteoporosis Patients at High Risk for Fracture, Help . . .

# BE A FORCE AGAINST FRACTURE

Prolia™ targets and binds to RANK Ligand, inhibiting osteoclast formation, function, and survival<sup>1</sup>

Prolia™ significantly reduced fracture risk at key sites\* in a phase 3 trial<sup>1,2</sup>



Prolia™ is a subcutaneous injection administered every 6 months in your office<sup>1</sup>



Please see Brief Summary of Prescribing Information on the following page.

be performed by the prescriber prior to initiation of Prolia™. A dental examination with appropriate preventive dentistry should be considered prior to treatment in patients with risk factors for ONJ. Good oral hygiene practices should be maintained during treatment with Prolia™.

For patients requiring invasive dental procedures, clinical judgment should guide the management plan of each patient. Patients who are suspected of having or who develop ONJ should receive care by a dentist or an oral surgeon. Extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of Prolia™ should be considered based on individual benefit-risk assessment.

**Suppression of Bone Turnover:** Prolia™ resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. The significance of these findings and the effect of long-term treatment are unknown. Monitor patients for consequences, including ONJ, atypical fractures, and delayed fracture healing.

**Adverse Reactions:** The most common adverse reactions (> 5% and more common than placebo) are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis. Pancreatitis has been reported with Prolia™.

The overall incidence of new malignancies was 4.3% in the placebo and 4.8% in the Prolia™ groups. A causal relationship to drug exposure has not been established. Denosumab is a human monoclonal antibody. As with all therapeutic proteins, there is potential for immunogenicity.

**Prolia™ Postmarketing Active Safety Surveillance Program:**

The Prolia™ Postmarketing Active Safety Surveillance Program is available to collect information from prescribers on specific adverse events. Please go to [www.proliasafety.com](http://www.proliasafety.com) or call 1-800-772-6436 for more information about this program.

\* Key sites: vertebral, hip, and nonvertebral.<sup>1,2</sup>  
<sup>†</sup> Includes 7393 patients with a baseline and at least one post-baseline radiograph.<sup>1,2</sup>  
<sup>‡</sup> Composite measurement excluding pathological fractures and those associated with severe trauma, fractures of the vertebrae, skull, face, mandible, metacarpals, fingers, and toes.<sup>1,2</sup>  
<sup>§</sup> RRR = relative risk reduction.  
<sup>||</sup> ARR = absolute risk reduction.

References: 1. Prolia™ (denosumab) prescribing information, Amgen. 2. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med.* 2009;361:756-765.

For more information, visit [www.ProliaHCP.com](http://www.ProliaHCP.com)

