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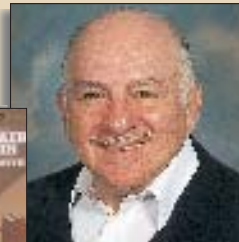


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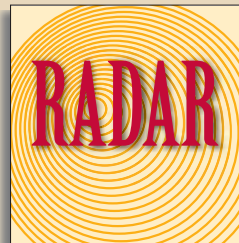
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# Routine Prophylaxis Not Recommended for Cancer Patients with Central Venous Catheters

By Alice Goodman

Two large, randomized, placebo-controlled, clinical trials found that prophylaxis with either warfarin or enoxaparin did not reduce the incidence of central venous catheter (CVC)-related thrombosis or

venous thromboembolism, respectively, in patients with cancer who required indwelling catheters.

Further, the incidence of CVC-associated thrombosis and thromboembolism was much lower in these trials than has been commonly assumed and than had been postulated by the

authors of both trials. Both trials were published in the June 20 issue of the *Journal of Clinical Oncology* and were posted online in March.

## Low-Dose Warfarin

The first study, led by Stephen Couban,

MD, Director of the Bone Marrow Transplant Program at Nova Scotia Cancer Centre, included 255 cancer patients who required a central venous catheter for at least seven days.

Patients were randomized to receive either warfarin at 1 mg or placebo daily within 72 hours of catheter insertion; treatment was continued until catheter removal, death, or the development of a symptomatic, radiographically confirmed, CVC-associated thrombosis.

Patients with different types of solid tumors and hematologic cancers were included in the study, which was conducted at three centers in Canada. Warfarin was chosen for the trial because it is a tried-and-true, relatively inexpensive oral drug, the researchers explained.

*Prophylaxis was initiated after catheter insertion, rather than before as is recommended in guidelines for orthopedic and general surgical procedures, and this may have affected the results, the researchers noted.*

In the study, which the researchers called one of the largest prospective trials of antithrombotic prophylaxis in cancer patients with central venous catheters, Dr. Couban and his coauthors found a clinically significant incidence of symptomatic CVC-associated thrombosis of 4.3%.

Previous studies in cancer patients not receiving prophylaxis found that anywhere from 3% to 37% of cancer patients experienced symptomatic CVC-associated thrombosis.

The second author, Michael Goodyear, MD, Assistant Professor at Dalhousie University in Halifax, said in an interview, "Many articles have recommended anticoagulant prophylaxis in cancer patients with a CVC. Based on our study, and the second study by Verso et al, we can now say there is no evidence to support routine prophylaxis.

"The good news from this study is that CVC-associated complications are not as common in cancer patients as people have claimed in the past."

Dr. Goodyear noted that the small number of primary events in both trials limits the statistical power to detect a clinically meaningful difference, and

that a much larger trial than either of the two trials would be needed to detect a difference with prophylaxis.

Overall, 11 (4.3%) symptomatic CVC-associated thromboses occurred, with no difference between treatment groups; six of 130 patients (4.6%) in the warfarin group and five of 125 patients in the placebo group (4.0%) developed symptomatic CVC-associated thromboses.

No difference between groups was seen in the duration of catheter insertion or in the number of catheter removals. The incidence of major bleeds was also similar in both groups: 2% for warfarin and 0% for placebo.

When the outcomes were assessed according to the type of cancer, no difference in CVC-associated thromboses was observed among different cancer types.

Dr. Goodyear noted that prophylaxis was initiated after catheter insertion, rather than before as is recommended in guidelines for orthopedic and general surgical procedures, and this may have affected the results.



**Michael Goodyear, MD:** "The good news from this study is that CVC-associated complications are not as common in cancer patients as people have claimed in the past."

### Low-Molecular-Weight Heparin

The second study—which the researchers, led by Melina Verso, MD, of the University of Perugia in Italy, noted was the largest prospective trial of antithrombotic prophylaxis in cancer patients—utilized enoxaparin, a newer, more expensive antithrombotic agent than warfarin. Venography was also used to evaluate the presence of venous thromboembolism.

The results showed that enoxaparin was safe, but did not affect the rate of CVC-related venous thromboembolism.

As in the other study, there was a lower than expected rate of CVC-related deep vein thrombosis. Also, enoxaparin achieved disappointing results, with a lower than anticipated risk reduction than has been observed in other trials, noted one of the authors, Giancarlo Agnelli, MD, Professor of Internal Medicine.

"This study, along with the study by Couban et al and the accompanying editorial, challenges the idea that routine prophylaxis should be given to cancer patients with CVC," Prof. Agnelli said in a telephone interview.

The study enrolled 385 cancer patients and randomized them to either subcutaneous enoxaparin at 40 mg/day or

placebo. Treatment was initiated two hours prior to CVC insertion and was continued for six weeks.

The primary endpoints of the study were deep vein thrombosis confirmed by venography of the CVC limb performed six weeks after randomization or clinically overt pulmonary embolism, confirmed by testing.

Of the 385 patients, 321 (83.4%) underwent venography. Upper limb deep vein thrombosis was found in 50 of 310 patients (16.1%). Deep vein thrombosis (DVT) was found in 22 patients (14.1%) treated with enoxaparin and in 28 placebo patients (18%).

No major bleeding was observed in either group.

During the treatment period, there were five deaths (2.6%) in the enoxaparin group and two in the placebo group (1.0%), all of them due to cancer progression.

As in the study by Dr. Couban's group, the number of symptomatic thromboses was much lower (3.1% on placebo and 1% on enoxaparin).

"We found a lower than expected rate of DVT events," Dr. Agnelli said. "We planned the trial for an overall rate of 22%, but we actually found that the rate of DVT events in this trial was 16%. We based our estimates on historical trials, but perhaps those trials included sicker patients and/or different types of catheters."

He added that the treatment period in the study was limited to six weeks, and that perhaps extending the treatment period or using a higher dose of enoxaparin would have achieved different results.

"Although both of these trials were negative, perhaps there is a subgroup of patients who can benefit from prophylaxis—possibly high-risk patients with metastases. The story is not over, but we know more than we did before," Dr. Agnelli commented.

### Routine Prophylaxis?

In an accompanying editorial, Mark Levine, MD, of McMaster University's

*Enoxaparin was found to be safe, but it did not affect the rate of CVC-related venous thromboembolism.*

Juravinski Cancer Center in Hamilton, Ontario, commented that although the studies used different endpoints and evaluations, their similarities could allow some conclusions.

He noted that both prospective trials found a relatively low rate of catheter-associated thrombus, whether measured clinically or radiographically. On the basis of these and other trials, Dr. Levine said that routine antithrombotic prophylaxis in cancer patients with CVC cannot be routinely recommended, adding that larger trials with symptomatic thrombosis as an outcome measure are needed.



**Giancarlo Agnelli, MD:** "Although both of these trials were negative, perhaps there is a subgroup of patients who can benefit from prophylaxis—possibly high-risk patients with metastases. The story is not over, but we know more than we did before."

Previous studies have included both symptomatic and asymptomatic events in the primary endpoint. This study utilized symptomatic thrombosis as the primary outcome, because this leads to morbidity and increased utilization of resources, whereas asymptomatic thrombosis may not be clinically important in this population.

Dr. Goodyear said that oral anti-Xa (anti-activated factor X) inhibitors appear to be promising antithrombotic agents. "If they live up to their promise and have no new side effects and complications, then these agents may be worth studying in the context of CVC-associated complications in cancer patients," he commented.

*An accompanying editorial by Mark Levine, MD, noted that both prospective trials found a relatively low rate of catheter-associated thrombus, whether measured clinically or radiographically. He said that on the basis of these and other trials, routine antithrombotic prophylaxis in cancer patients with CVC cannot be routinely recommended and larger trials with symptomatic thrombosis as an outcome measure are needed.*



**Ajay K. Kakkar, MD:** "More research is needed in this area, but routine CVC prophylaxis is not warranted on the basis of these two studies."

Both trials were well-conducted, randomized, double-blind, and controlled and provided higher-quality evidence than previous trials, which were not double-blinded, Dr. Levine said.

The Verso et al trial used mandatory venography of the upper limb at 42 days, whether or not symptoms were present, while the Couban et al trial used clinical outcome as the primary measure.

Dr. Levine said that he considered symptomatic thrombosis to be a better endpoint because the natural history of an asymptomatic thrombus detected by screening venogram is unclear.

He suggested that the lower rates of CVC-associated complications in these trials compared with previous trials may have been related to the lack of a double-blind design in the previous trial or to improvements in insertion

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## AACR Public Forum Provides 'Cancer Biology 101' Review

By Eric T. Rosenthal

**A**NAHEIM, CA—The American Association for Cancer Research's Ninth Annual Public Forum Highlighting the Latest Discoveries, held here at the beginning of the Annual Meeting, discussed "Progress and New Hope in the Fight Against Cancer" in true translational style—taking the audience from the bench to the bedside and beyond.

AACR CEO Margaret Foti, PhD, opened the session with an overview of AACR and its role in preventing and curing cancer, explaining the unique educational opportunity the public forum provides.

She was followed by Anna D. Barker, PhD, Deputy Director for Advanced Technologies and Strategic Partnerships for the National Cancer Institute; NCI Director Andrew C. von Eschenbach, MD; AACR 2004-2005 President Lynn M. Matrisian, PhD, Professor and Chair of the Department of Cancer Biology at Vanderbilt School of Medicine; James L. Abbruzzese, MD, Professor and Chair of GI Medical Oncology at the University of Texas M. D. Anderson Cancer Center; Amy Dilbeck, Communications Coordinator of CureSearch National Childhood Cancer Foundation; and Thomas A. Sellers, PhD, Associate Center Director of Cancer Control at H. Lee Moffitt Cancer and Research Institute.

In addition, Dennis J. Slamon, MD, PhD, Director of the Revlon/UCLA Women's Cancer Research Program at UCLA's Jonsson Cancer Center, talked about the use of Herceptin as a targeted therapy for breast cancer.

### 'Mind-Numbing Statistics'

Dr. Barker described the "mind-numbing statistics" related to the cancer

problem in America, citing 1,372,000 new cases and 570,280 deaths in 2005—translating to 1,500 deaths a day; the lifetime probability of developing cancer as one in two for men, and one in three for women; age as the major risk factor for cancer; the fact that one quarter of the current population will die of cancer; and the costs of the disease reaching \$192 billion a year.

Cancer now exceeds heart disease as the number one killer of Americans younger than 85, she noted, and some 10,000,000 Americans are now designated as cancer survivors.

On a positive note, Dr. Barker said this nation's investments in biomedical and cancer research are paying off as "we stand on the threshold of unimagined progress against cancer.

"This new era of progress," she said, includes the sequencing of the human genome; the unprecedented information explosion from science and advanced technologies; the enabling of "breakthrough" detection, therapy, and prevention through knowledge of changes in cancer genes and proteins; the production of thousands of new specific targets from genomics and proteomics; and development of evidence-based personalized diagnostics, prevention, and treatment.

### National Cancer Program's New Opportunities

Dr. von Eschenbach, a three-time survivor of cancer, told about the National Cancer Program's new opportunities for advancing progress against cancer through preventing or interrupting the cancer process before it becomes deadly.

Explaining that cancer is a "disease process," he discussed preempting this process through prevention, detection, modulation, and elimination, using his "3D Paradigm" of discovery, develop-

ment, and delivery, which requires collaboration among the many entities that make up the cancer establishment.

He also elaborated on the National Advanced Technology Initiative for cancer (NATIC) that hopes to accelerate the pace of progress through genomics, proteomics, nanotechnology, molecular imaging, and informatics projects such as the Cancer Biomedical Informatics Grid (caBIG).

Dr. von Eschenbach said that NCI and the FDA have an Interagency Oncology Task Force working on bioinformatics, process enhancement, markers of clinical benefit, and training and joint appointments, and reiterated again NCI's vision to reality as "a time as early as 2015 when no one will suffer or die as a result of cancer."

### 3 Components of Knowledge Pyramid

Dr. Matrisian provided the audience with a cancer biology 101 review, discussing "how understanding the biology of cancer can help you," and the three components of the knowledge pyramid—basic, translational, and clinical research.

The impact of basic research on cancer care was Dr. Abbruzzese's topic. "Cancer research can be no more divorced from oncology practice than can oncology practice from research," he said, with apologies to Dr. Abraham Flexner's *A Medical Education: a Comparative Study* report on medical education.

### Osteosarcoma Survivor's Story


The actual impact of research on patients was exemplified anecdotally by Amy Dilbeck, a 25-year-old 10-year survivor of osteosarcoma.

Ms. Dilbeck recalled that when she was a 15-year-old cheerleader and

swimmer, she had a pain in her right knee that didn't get better. After seeing a doctor and being diagnosed with cancer, she learned from her mother that 20 years earlier her mother's friend also had osteosarcoma, and eventually died from the disease.

*Amy Dilbeck, a 10-year survivor of osteosarcoma, explained that as a result of limb-salvage therapy, she proudly sports a two-and-a-half foot scar on her right leg, and enough stainless steel substituting for bone to trigger any airport metal detector.*

Ms. Dilbeck said 20 years of research helped explain the difference in outcomes, which in her case was "definitely life. Survivorship has been an incredible course," she added. "Cancer is a curse, but it also has benefits, such as giving me an incredible thankfulness for life."


Ms. Dilbeck explained that as a result of limb-salvage therapy, she proudly sports a two-and-a-half foot scar on her right leg, and enough stainless steel substituting for bone to trigger any airport metal detector, which, she said has caused airport screeners to scream out to their co-workers to come see the girl who had cancer...and survived. 

## CVC

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and maintenance techniques.

The coauthor of the editorial, Ajay K. Kakkar, MD, Professor of Surgical Sciences at Barts and the London School of Medicine and Dentistry, said that the results of these two studies raise interesting questions: Is it possible to identify the high-risk group of patients who will benefit from CVC prophylaxis? Will rates of CVC prophylaxis change with more aggressive biological interventions such as anti-VEGF bevacizumab?

"More research is needed in this area," he said, "but routine CVC prophylaxis is not warranted on the basis of these two studies." 

## Tool Gives Nurses Guidelines for Helping Patients to Stop Smoking

**T**he US Department of Health and Human Services has released a pocket guide that provides nurses with evidence-based information for helping their patients quit smoking.

Studies have shown that the country's three million nurses can effectively help people quit smoking, largely because of their number and the public trust, a news release notes.

"Nurses are an invaluable resource in health care, and they have tremendous opportunities to help patients eliminate their dependence on tobacco," said Carolyn M. Clancy, MD, Director of the Agency for

Healthcare Research and Quality (AHRQ).

"Current evidence-based treatments for tobacco cessation offer nurses and other clinicians a great opportunity to improve health and reduce the deaths and economic burden caused by tobacco use."

AHRQ developed the tool, called *Helping Smokers Quit: A Guide for Nurses*, in collaboration with Tobacco Free Nurses, a national initiative funded by The Robert Wood Johnson Foundation.

The guide presents the "5 A's" approach to cessation intervention:

- Ask about tobacco use at every visit.

- Advise tobacco users to quit.
- Assess readiness to quit.
- Assist tobacco users with a quit plan.
- Arrange follow-up visits.

The tool also includes a listing of FDA-approved smoking-cessation medications and their dosage, duration, availability, precautions/contraindications, and side effects, as well as the phone number for the National Quitline, 1-800-QUIT NOW.

The free guide is available on the AHRQ Web site at [www.ahrq.gov/about/nursing/hlpsmksqt.htm](http://www.ahrq.gov/about/nursing/hlpsmksqt.htm).