

Appendix #437

Francis Collins, MD, Director, National Institutes of Health
Feb 18, 2012

NIH funded anticoagulant drug guidelines closed to scientific criticism

Dear Dr. Collins,

For the first time, the 9th set of “Antithrombotic Therapy and Prevention of Thrombosis Guidelines” (AT9) of the American College of Chest Physicians (ACCP) have been partially funded by the National Heart, Lung, and Blood Institute [R13 HL104758] rather than entirely by anticoagulant drug producing drug companies. Also for the first time, as explained in the [AT9 introduction](#), “conflicted experts, who often hold strong opinions about optimal management approaches...” did not vote on treatment or prophylaxis recommendations. Supposedly to avoid bias, non anticoagulation drug researchers were included as authors and voted on the recommendation decisions. How these generalist physician authors were selected and reimbursed was not explained in AT9.

My letter about Antithrombotic Therapy for VTE Disease (below) to the *CHEST* Chief Editor, Richard Irwin, MD, received the following reply:

CHEST - Decision on Manuscript ID CHEST-12-0442

DL-18

17-Feb-2012

CC: Cundiff, David

Dear Dr. David Cundiff:

We are writing in regards to your manuscript # CHEST-12-0442 entitled "Evidence lacking for antithrombotic therapy for venous thromboembolism" which you submitted to CHEST.

We receive far more Letters than we can publish, and difficult decisions must be made. Your report unfortunately did not receive a high enough priority score to be considered further for publication.

Sincerely,
Richard S. Irwin, MD, Master FCCP
Editor in Chief, CHEST

The excuse that *CHEST* receives more letters than it can publish about these extremely important anticoagulation guidelines is questionable. After the 8th set of ACCP anticoagulation guidelines were published in *CHEST* in 2008, only one letter to the editor was subsequently published in *CHEST* concerning one of the 22 anticoagulation guideline articles.

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Since the NIH now partially funds the development of these ACCP anticoagulation guidelines and the ACCP won't defend the guidelines publicly, please have NIH or FDA anticoagulation medicine experts address my criticisms in the letter below of the evidence basis of anticoagulant drugs for the treatment of VTE.

Thank you.

Best wishes,

David K. Cundiff, MD

CC: Richard Irwin, MD, Chief Editor of *Chest*
Ann Farrell, MD, Acting Director of CDER Hematology Section
Janet Woodcock, MD, Director FDA, CDER
Margaret Hamburg, FDA Commissioner
Kathleen Sebelius, HHS Secretary

Evidence lacking for antithrombotic therapy for venous thromboembolism

To the *Chest* Editor,

The 9th ACCP guideline for “Antithrombotic Therapy for VTE Disease” states, “The first and only randomized trial that compared anticoagulant therapy with no anticoagulant therapy in patients with symptomatic DVT or PE was published in 1960 by Barritt and Jordan.”¹ The Barritt and Jordan “randomized” trial² is too flawed to justify the use of anticoagulant drugs for the following reasons:

- The clinical PE diagnoses of the patients in the 1950s when this trial was conducted were not confirmed by pulmonary angiograms or lung scans as is now required because of the high false positive rate of clinical diagnoses;
- Autopsy descriptions of the patients in the Barritt and Jordan trial show that in 4 of the 5 deaths, severe underlying diseases caused the deaths (e.g., cerebral infarction and cavitory pneumonia with sepsis), with PE only appearing as a contributing factor;
- Doctors other than the investigators referred the patients into the trial, so the selection was not random;
- The trial was not double-blind; and
- The investigators provided no information about the comparability of the anticoagulated and un-anticoagulated patients.

After the Barritt and Jordan trial, the following three RCTs of VTE patients comparing anticoagulant drug treatment with no anticoagulation have been published:

- An abstract-only report by Kakkar and colleagues of DVT treatment compared heparin, Malayan pit viper venom (*Arvin*), streptokinase, and placebo, reporting deaths in 2 of 7 patients in the heparin group and 0 of 6 in the placebo group.

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- Ott and colleagues published a placebo-controlled trial in which 2 of 11 patients receiving heparin and warfarin died , and 1 of the 12 placebo-treated patients died.³
- Nielsen and colleagues randomized 90 ambulatory patients with DVT into standard heparin and phenprocoumon versus phenylbutazone (i.e., no anticoagulants). Two of 48 patients in the anticoagulated group died (one of PE), whereas 0 of 42 in the un-anticoagulated group died.⁴

I co-authored a Cochrane review of anticoagulant drug treatment of VTE published in 2006 that excluded the Barritt and Jordan RCT because of the flaws. The review based findings only on the Ott and Nielsen RCTs.⁵ The RCT evidence did not support the efficacy or safety of anticoagulant drugs for VTE. The practice of using anticoagulants must therefore be considered “opinion-based” rather than evidence-based (i.e., Grade “2C” instead of “1B”). The use of anticoagulant drugs for VTE should be reconsidered.

1. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic Therapy for VTE Disease. 10.1378/chest.11-2301. *Chest*. February 1, 2012 2012;141(2 suppl):e419S-e494S. Available at: http://chestjournal.chestpubs.org/content/141/2_suppl/e419S.abstract.
2. Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism -- A controlled trial. *Lancet*. 1960; 1:1309-1312.
3. Ott P, Eldrup E, Oxholm P. The value of anticoagulant therapy in deep venous thrombosis in the lower limbs in elderly, mobilized patients. A double-blind, placebo-controlled investigation with open therapeutic guidance. *Ugeskr Laeger*. 1988;150:218-221.
4. Nielsen HK, Husted SE, Krusell LR, Fasting H, Charles P, Hansen HH. Silent pulmonary embolism in patients with deep venous thrombosis. Incidence and fate in a randomized, controlled trial of anticoagulation versus no anticoagulation. *Journal of Internal Medicine*. 1994;235(5):457-461.
5. Cundiff D, Manyemba J, Pezzullo J. Anticoagulants versus non-steroidal anti-inflammatories or placebo for treatment of venous thromboembolism. *The Cochrane Database of Systematic Reviews*. 2006(Issue 1):Art. No.: CD003746. DOI: 003710.001002/14651858.CD14003746.pub14651852. Available at: <http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD003746/frame.html>.