5 Minute JournalClub

Key ASH Presentations
Issue 5, 2012

SAVE-ONCO Trial of Thromboprophylactic Treatment with Semuloparin for Venous Thromboembolism

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual American Society of Hematology (ASH) meeting is unmatched in its importance with regard to advancements in hematologic cancer and related disorders. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results and new information lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across virtually all malignant and benign hematologic disorders. As online access to posters and plenary presentations is not currently available, a need exists for additional resources to distill the information presented at the ASH annual meeting for those clinicians unable to attend but desiring to remain up to date on the new data released there. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists, hematologists and hematology-oncology fellows in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Assess the benefit-risk profile of the novel ultra-low-molecular-weight anticoagulant semuloparin for the treatment of venous thromboembolism in patients with locally advanced or metastatic cancer.
- Evaluate the efficacy and safety data with anticoagulant therapy for patients with deep vein thrombosis and venous thromboembolism, and incorporate this information into your personal therapeutic algorithm.
- Develop an understanding of the incidence and risk factors for venous thrombosis and venous thromboembolism, and be able to counsel patients with newly diagnosed or recurrent cancer about the appropriate prophylactic treatments available.

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Key ASH Presentations
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To go directly to slides and commentary for this issue, **click here**.

While a bunch of important ASH papers this year focused on prevention and treatment of venous thromboembolism (VTE), perhaps the most clinically relevant data set was a follow-up from the Phase III SAVE-ONCO study initially presented at ASCO and published on February 16th in the *New England Journal*. This landmark randomized trial involving more than 3,200 patients with advanced solid tumors receiving outpatient chemotherapy evaluated the role of the ultra-low-molecular-weight heparin semuloparin versus placebo in preventing VTE.

The editorial that accompanies the *NEJM* publication praises the high quality of this international effort that helped take VTE research in oncology to a new level and provides a much better quantitative understanding of the impact of anticoagulation in patients with cancer where the potential benefits are similar to many oncology interventions, including a number of common chemo regimens. The editorial authors also raise the hope, based on preliminary data, that heparins may have a direct antitumor effect.

To get the inside story on what happened at ASH in this field I chatted with Harvard's VTE maven Dr Ken Bauer, and the data sets listed below are the ones you should know about.

1. SAVE-ONCO

During our conversation, Dr Bauer reviewed the impressive hazard reduction in the risk of symptomatic VTE with semuloparin (0.36 — a 64% relative reduction), but he also pointed out that the absolute overall risk in the placebo group was 3.6%, resulting in only about a 2% absolute benefit. This led me to ring up Duke's Dr George, who responded that in unselected (ie, nontrial) populations VTE rates are much higher and since the treatment effect observed in SAVE-ONCO was consistent across risk groups, presumably these patients would benefit even more. Dr George also commented that VTE seems to be associated with significantly increased subsequent mortality in patients with cancer, and in that regard Dr Bauer believes that if we could better quantify risk, patients with greater projected absolute benefit could be identified and receive treatment.

Given that minimal excess bleeding was reported in SAVE-ONCO it's interesting to speculate how much benefit justifies treatment in patients who (as stated in the editorial) "are not bothered much by daily injections." Somewhat similarly, although a number of computer-based VTE risk models are out there, it would be extraordinary if someone could harness the massive quantity of data being generated in trials like SAVE-ONCO to create an Adjuvant! Online-like oncology/VTE model that might include tumor type, stage and specific chemo regimen. This would allow for more precise

estimates of the potential absolute effects of anticoagulation, help doctors and patients make more informed decisions and perhaps lead to a consensus about a level of risk that requires treatment, similar to the 20% bar for risk of neutropenic fever and the preemptive use of growth factors.

2. VTE in the inpatient versus outpatient oncology setting; risk assessment model (RAM) for medical inpatients

At ASH, Dr Alok Khorana presented an **observational retrospective study** based on insurance claims demonstrating that more than three quarters of VTE cases in patients with cancer occur in the outpatient setting. Interestingly, Dr Khorana previously published data suggesting that only about half of oncology patients are aware of their increased risk of VTE and when this is explained, many are interested in prevention. **A related ASH paper** reported on a RAM that identified 39% of a medical inpatient population as being at high risk for VTE.

3. Catheter-directed thrombolysis (CDT) for acute iliofemoral DVT

Dr Bauer commented that this impressive Phase III randomized trial is perhaps the most methodologically sound study to date to document a reduction in the risk of post-thrombotic syndrome and improved functional outcome with CDT.

4. Dabigatran versus warfarin in acute VTE (RE-COVER II study)

In this Phase II study, the efficacy of dabigatran, an oral anticoagulant from the class of direct thrombin inhibitors, was shown to be noninferior to warfarin with a slightly lower risk of bleeding but a slightly higher incidence rate of acute coronary syndrome. Dr Bauer noted that these findings further contribute to the current challenge associated with selecting from a plethora of new and older agents.

Next on this ASH series: Key data sets in non-Hodgkin lymphoma.

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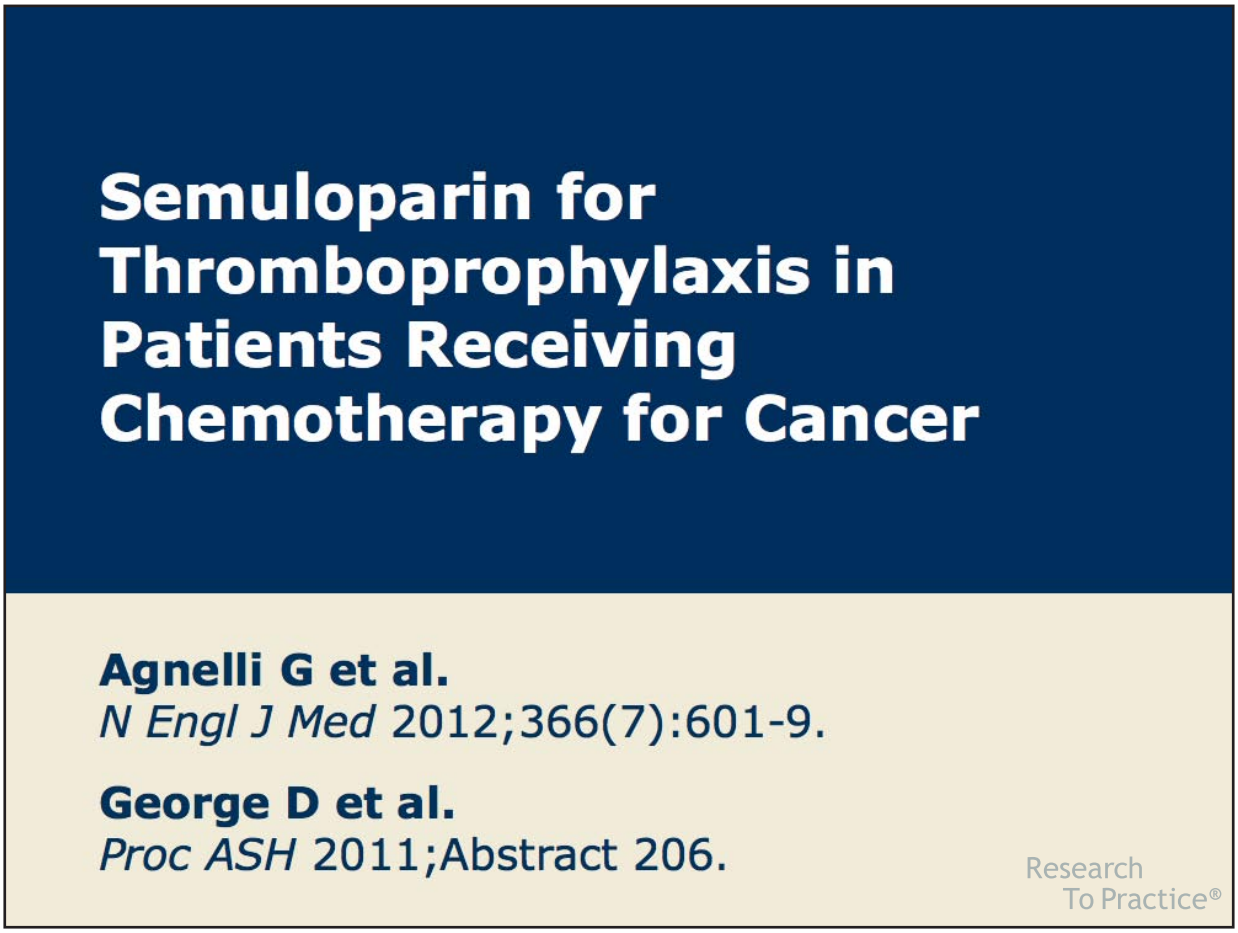
SAVE-ONCO Trial of Thromboprophylactic Treatment with Semuloparin for Venous Thromboembolism

Presentations discussed in this issue

Agnelli G et al. **Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer.** *N Engl J Med* 2012;366(7):601-9. **Abstract**

George DJ et al. **Venous thromboembolism (VTE) prevention with semuloparin in cancer patients initiating chemotherapy: Benefit-risk assessment by VTE risk in SAVE-ONCO.** *Proc ASH* 2011;**Abstract 206**.

Slides from a presentation at ASH 2011 and transcribed comments from a recent interview with Kenneth A Bauer, MD (1/26/12)



Background

- There is an increased risk of developing venous thrombo-embolism (VTE) in patients (pts) with cancer who are receiving chemotherapy due to multiple cancer- and patient-specific risk factors.
- Semuloparin is a new ultra-low molecular weight heparin (ULMWH) with high antifactor Xa and minimal antifactor IIa activity that may inhibit the development of VTE.
- **Objective:**
  - Assess semuloparin versus placebo for VTE prevention in pts with cancer who are receiving chemotherapy for a locally advanced or metastatic solid tumor.

Agnelli G et al. *N Engl J Med* 2012;366(7):601-9.

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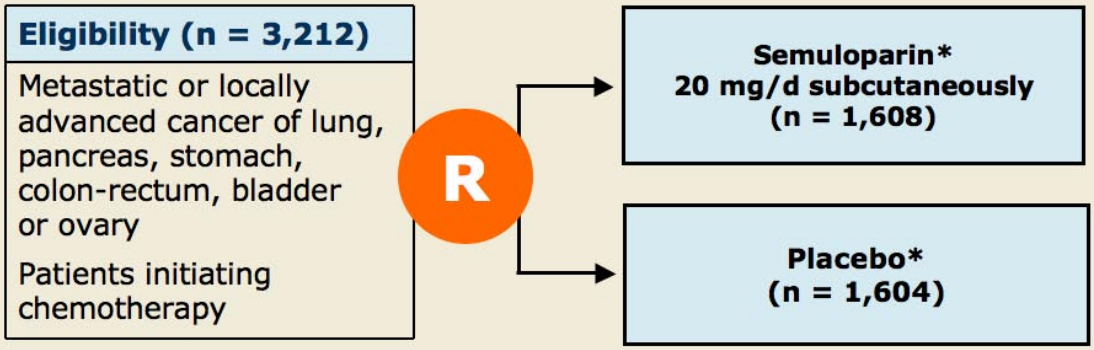
SAVE-ONCO Study Design



* Semuloparin and placebo were administered until change of chemotherapy.

- **Primary endpoints**:
  - Efficacy: VTE (symptomatic deep vein thrombosis or nonfatal pulmonary embolism) or VTE-related deaths
  - Safety: Any clinically relevant bleeding (major or nonmajor)
- **Baseline VTE risk**: Assessed by a score specifically developed and validated in patients receiving chemotherapy for cancer (*Blood* 2008;111:4902).

Agnelli G et al. *N Engl J Med* 2012;366(7):601-9.

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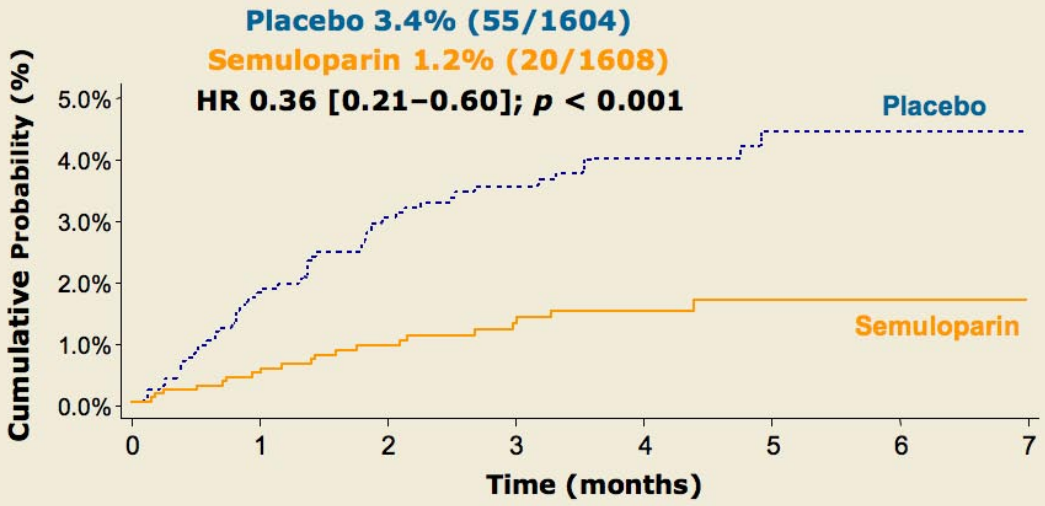
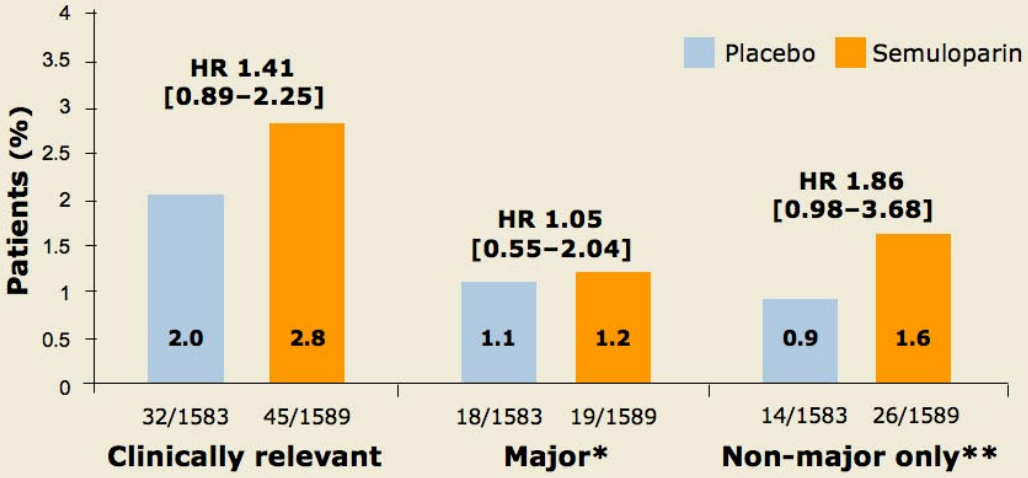
Primary Endpoint: Composite of VTE or VTE-Related Deaths



HR = hazard ratio
A 64% relative risk reduction was observed over median treatment duration of approximately 3.5 months.

Primary Endpoint: Bleeding

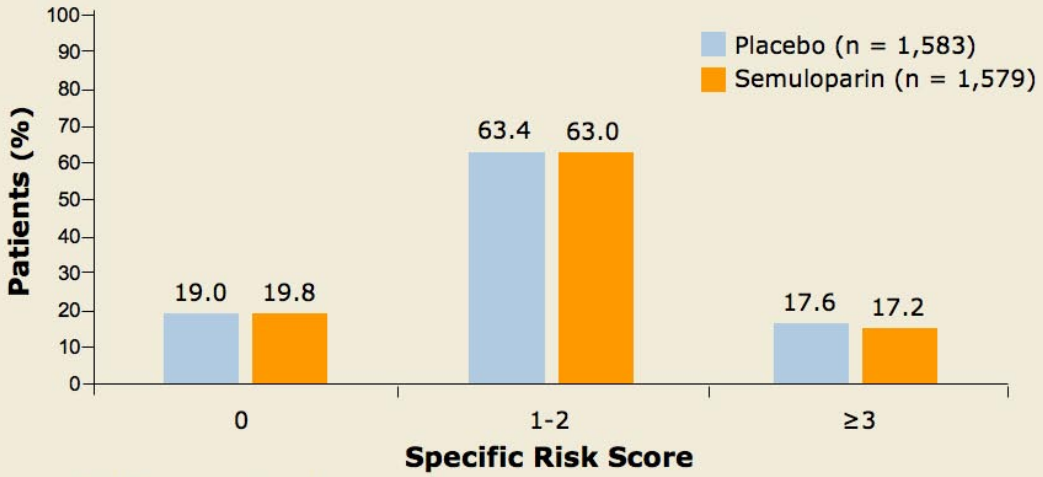


* Includes 6 pts with fatal bleedings: 4 (placebo) and 2 (semuloparin); 5 nonfatal bleedings (semuloparin)

** Treatment discontinuation: 7 pts (placebo) and 9 pts (semuloparin); serious events: 4 pts (placebo) and 9 pts (semuloparin); recovered: 14 pts (placebo) and 24 pts (semuloparin)

With permission from George D et al. *Proc ASH* 2011;Abstract 206.

Baseline VTE Risk According to Cancer Chemotherapy-Specific Risk Score



Khorana Risk Score assigned:
+2 = high-risk cancer sites (pancreas and stomach)
+1 = high-risk cancer sites (lung, lymphoma, gynecologic, bladder, testicular cancer)
+1 = platelet count: ≥350 x 10^9/L; hemoglobin (Hb): <10 g/dL and/or use of erythropoiesis-stimulating agents; white blood cell count: >11 x 10^9/L; body mass index: ≥35 kg/m^2

With permission from George D et al. *Proc ASH* 2011;Abstract 206.

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VTE or VTE-Related Death by Baseline VTE Risk Score (Abstract Only)

	Placebo	Semuloparin	HR (95% CI)
All pts	3.4%	1.2%	0.36 (0.21-0.60)
VTE risk score			
0 (n = 301, 313)	1.3%	1.0%	0.71 (0.16-3.15)
1-2 (n = 1,003, 995)	3.5%	1.3%	0.37 (0.20-0.70)
≥3 (n = 279, 271)	5.4%	1.5%	0.27 (0.09-0.82)

George D et al. *Proc ASH* 2011;Abstract 206.

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Major Bleeding by VTE Risk Score or Factors

	Placebo	Semuloparin	HR	*p*-value
All pts (n = 1,583, 1,589)	1.1%	1.2%	1.05	—
Cancer chemotherapy-specific VTE risk score				
0 (n = 297, 310)	0.7%	0.6%	1.13	
1-2 (n = 988, 987)	1.1%	1.2%	1.09	0.9845
≥3 (n = 277, 264)	1.8%	1.9%	1.01	
General VTE risk factors*				
None (n = 923, 914)	0.9%	1.0%	1.11	
1 or 2 (n = 620, 643)	1.3%	1.2%	0.97	0.9391
≥3 (n = 40, 32)	5.0%	6.3%	1.16	

* Includes any risk factor, history of pulmonary embolism, use of hormonal therapy, history of deep vein thrombosis, chronic heart failure, venous insufficiency/varicose veins, chronic respiratory failure, age ≥75, obesity and central venous line at baseline

George D et al. *Proc ASH* 2011;Abstract 206.

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Author Conclusions

- Semuloparin treatment at 20 mg/d produced a favorable benefit-risk profile for the prevention of VTE in patients with cancer initiating chemotherapy.
- The benefits of semuloparin were observed across different degrees of baseline VTE risk.
- The SAVE-ONCO study demonstrates that antithrombotic prophylaxis should be considered in patients with cancer initiating chemotherapy.

Agnelli G et al. *N Engl J Med* 2012;366(7):601-9.

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Investigator Commentary: The SAVE-ONCO Study

VTE is a significant complication of cancer. It is a risk that is dramatically seen with some of the newer agents, especially with lenalidomide and high-dose dexamethasone in myeloma. This is a study of ULMWH versus placebo in patients with locally advanced or metastatic cancer receiving initial chemotherapy. In the metastatic or locally advanced setting, semuloparin effectively reduced the risk of VTE from 3.4% to 1.2% within an approximate 3.5-month duration as patients were only on semuloparin during the first chemotherapy regimen. It is questionable whether the risk of 3.4% with placebo is enough for the use of any form of anticoagulant. Even though the Khorana Score incorporates high platelet counts or low Hb levels, with a high risk score of 3 or higher, the incidence of VTE was only 5.4%. This raises further questions about finding better ways of determining the patients with high-risk VTE and for clinicians in identifying the patients requiring VTE prevention. This is important because the standard treatment currently does not use anticoagulants unless the patient has a history of thrombosis.

Interview with Kenneth A Bauer, MD, January 26, 2012