5 Minute JournalClub

Key ASH Presentations
Issue 5, 2012

CaVenT Study of Additional Catheter-Directed Thrombolysis versus Standard Treatment for Acute Iliofemoral Deep Vein Thrombosis

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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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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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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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CaVenT Study of Additional Catheter-Directed Thrombolysis versus Standard Treatment for Acute Iliofemoral Deep Vein Thrombosis

Presentations discussed in this issue

Enden T et al. **Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): A randomised controlled trial.** *Lancet* 2012;379(9810):31-8. **Abstract**

Enden TR et al. **Improved functional outcome after additional catheter-directed thrombolysis for acute iliofemoral deep vein thrombosis: Results of a randomized controlled clinical trial (the CaVenT study).** *Proc ASH* 2011;**Abstract LBA-1**.

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

Background

- Conventional anticoagulant treatment of acute deep vein thrombosis (DVT) effectively prevents thrombus extension and recurrence.
- However, such treatment of DVT does not dissolve the clot leading to the development of post-thrombotic syndrome (PTS) in many patients.
- Catheter-directed thrombolysis (CDT) is a novel and promising modality whereby multiple side holes enable delivery of reduced doses of the thrombolytic agent into the clot.
- **Objective:**
  - Examine whether additional therapy with CDT with alteplase for acute iliofemoral vein thrombosis (VT) improves long-term outcomes by reducing the risk of PTS.

Enden T et al. *Lancet* 2012;379(9810):31-8.

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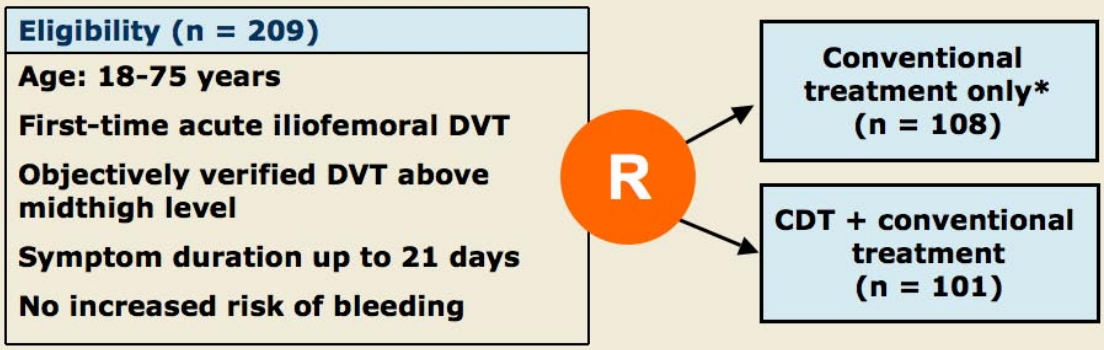
CaVenT Trial: Study Design



* Initial low molecular weight heparin (LMWH) and warfarin followed by warfarin alone with target intensity international normalized ratio (INR) of 2.0-3.0

- Randomization was stratified for involvement of the pelvic veins.
- **Primary outcomes:**
  - Frequency of PTS at 24 months, assessed by the Villalta score
  - Iliofemoral patency after 6 months

Enden T et al. *Lancet* 2012;379(9810):31-8.

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Villalta Scoring Scale

Five patient-related venous symptoms	Six clinician-rated signs
Pain	Pretibial edema
Cramps	Skin induration
Heaviness	Hyperpigmentation
Paraesthesia	Pain during calf compression
Pruritus	Venous ectasia
	Redness

Scoring — Each sign or symptom is rated as:
0 = None
1 = Mild
2 = Moderate
3 = Severe

Summed-up ratings = total score:
- <5 = no PTS
- 5-14 = mild/moderate PTS
- ≥15/venous ulcer = severe PTS

Enden T et al. *Lancet* 2012;379(9810):31-8.

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Outcomes: Additional CDT versus Standard Therapy

Outcome	Additional CDT (n = 90)		Standard therapy only (n = 99)		*p*-value
	n	% (95% CI)	n	% (95% CI)	
PTS after 6 mo	27	30.3 (21.8-40.5)	32	32.2 (23.9-42.1)	0.77
PTS after 24 mo	37	**41.1** (31.5-51.4)	55	**55.6** (45.7-65.0)	0.047
Iliofemoral patency after 6 mo*	58	**65.9** (55.5-75.0)	45	**47.4** (37.6-57.3)	0.012

* Five patients had inconclusive patency assessments, and 1 was lost to follow-up. At completion of 24 months of follow-up, 189 patients were available for analysis.

- PTS is defined as a Villalta score ≥5.
- *p*-values stated are from an unadjusted Chi-square test.
- Absolute risk reduction of long-term endpoint PTS at 24 months of follow-up in CDT versus standard therapy: 14.4% (95% CI 4-502).

Enden T et al. *Lancet* 2012;379(9810):31-8.

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PTS After 24 Months in Patients with Iliofemoral Patency or Insufficient Recanalization After 6 Months

Outcome	Regained iliofemoral patency (n = 103)		Insufficient recanalization (n = 80)		*p*-value
	n	% (95% CI)	n	% (95% CI)	
PTS after 24 mo	38	**36.9** (28.2-46.5)	49	**61.3** (50.3-71.2)	0.001

- Absolute gain in short-term endpoint iliofemoral patency after 6 months in CDT versus standard therapy group: 18.5% (95% CI 4.2–31.8).
- Absolute risk reduction in the frequency of PTS after 24 months in patency versus insufficient recanalization: 24.4% (95% CI 9.8–37.6).

Enden T et al. *Lancet* 2012;379(9810):31-8.

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Adverse Events (AEs)

AEs	Additional CDT (n = 101)	Standard treatment (n = 108)
Bleeding complications	20	0
Major bleeding complications	3	0
Clinically relevant bleeding complications	5	0
Deaths	0	NR
Pulmonary embolisms	0	NR
Cerebral hemorrhages	0	NR
Nonbleeding complications	4	NR
Recurrent VTE at 24 mo	10	18

NR = not reported

During follow-up, 28 patients had recurrent VTE and 11 had cancer; no significant difference between treatment groups ($p > 0.05$).

Enden T et al. *Lancet* 2012;379(9810):31-8.

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Author Conclusions

- Additional CDT improved the clinically relevant long-term outcome after iliofemoral DVT by decreasing PTS compared to conventional therapy.
- No significant difference was observed in PTS between additional CDT and conventional therapy after 6 months of follow-up (p = 0.77).
- The effect of CDT on severe PTS remains unclear for the following reason:
  - Despite the high frequency of PTS overall, severe PTS occurred in only 1 patient (data not shown).
- The CaVenT study demonstrates that additional CDT should be considered as treatment for patients with a high proximal DVT and low risk of bleeding.

Enden T et al. *Lancet* 2012;379(9810):31-8.

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Investigator Commentary: Long-Term Outcome After Additional Catheter-Directed Thrombolysis versus Standard Treatment for Acute Iliofemoral Deep Vein Thrombosis — CaVenT Study

For many years, one area of interest in the treatment of massive DVT has been the use of aggressive therapies, be it thrombolysis, modern-day catheter-directed thrombolysis or even mechanical types of thrombectomies conducted by interventional radiologists. However, the problem has always been the lack of clear evidence that the outcomes, in terms of post-thrombotic or postphlebitic syndrome, were better. This is the first of several methodologically well-conducted randomized trials asking if CDT or even other interventions are better than anticoagulation therapy alone. The finding of a 14% significant reduction in postphlebitic syndrome, as measured by the Villalta score at 2 years, is important. Though the p-value of 0.047 was just under 0.05, this is the first relatively methodologically sound trial to clearly show a benefit for aggressive therapies, at least thrombolysis, in postclot syndrome. Therefore, for a symptomatic patient with a bad leg and with no active cancer who has low risk factors for bleeding, additional CDT should be seriously considered because the morbidity of postclot syndrome is great.

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