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## Inside This Issue:

- *2004 Updated Fibrinolytic Practice Guidelines and Consensus Recommendations*
- *New Fibrinolytic Cost Calculator Facilitates Decision Making*
- *To Aliquot or Not: This Is the Question*

## 2004 Updated Fibrinolytic Practice Guidelines and Consensus Recommendations

Although practitioners embrace the concept of evidence-based medicine, how does one distill the volumes of published evidence into clinical practice? There are many definitions of evidence-based medicine, but it is unequivocal that, when there is evidence of benefit and value, do it; when there is evidence of no benefit, harm, or poor value, don't do it; when there is insufficient evidence to know for sure, be conservative.

The supporting clinical evidence associated with fibrinolytic agents is extensive and crosses several medical specialties. A number of pivotal efficacy and safety trials and key comparator studies have been conducted. Clinical decision-making is best guided by well-designed randomized controlled clinical trials (RCTs). Non-peer reviewed or observational reports are interesting, but these basically generate untested hypotheses. Drugs are frequently assessed for formulary inclusion across indications. Although an in-depth discussion of the supporting clinical evidence with fibrinolytics is beyond the scope of this summary, specific practice guidelines and consensus recommendations considering all fibrinolytic

*Continued on page 2*

## To Aliquot or Not: This Is the Question

When faced with a therapeutic situation which required a lower dose of a drug than was commercially available, pharmacists have prepared dosage aliquots. In terms of fibrinolytics, aliquotting was initially necessitated with t-PA for conditions such as central venous access device (CVAD) thrombosis since only 50 mg and 100 mg vials were initially available. Other fibrinolytics such as urokinase (UK) and r-PA must be aliquotted in order to use them in CVAD thrombosis. Procedures have been developed for aliquotting, freezing, storing, thawing, and determining beyond-use dating for these preparations. However, in

*Continued on page 4*

## New Fibrinolytic Cost Calculator Facilitates Decision Making

Pharmacy managers are increasingly being challenged to identify methods to maximize the value from their cardiovascular formulary of medications. Fibrinolytics are frequently scrutinized because of their cost and breadth of use. In contemporary practice, fibrinolytics are still a critically important pharmacologic management option for many thromboembolic disorders including ST-segment elevation myocardial infarction (STEMI), acute ischemic stroke (AIS), peripheral arterial occlusion (PAO), central venous access device (CVAD) occlusion, and pulmonary embolism (PE). They represent an excellent prototype for clinically and economically evaluating a formulary class across indications. Currently, four fibrinolytics are available: alteplase (Activase® and Cathflo™ Activase®), reteplase (Retevase®), streptokinase (Streptase®), and tenecteplase (TNKase™). It should be noted that effective December 2004 Abbott ceased marketing and manufacturing operations for urokinase. The existing supply of urokinase will still be available into 2005.

The comparative economics of fibrinolytics is a primary consideration in formulary decision-making. In order to comprehensively assess the economics of fibrinolytics across all indications, the comparative costs must be examined in detail. An evidence-based Fibrinolytic Economic Assessment Tool-Kit was developed and recently revised as a tool in assessing the economics of fibrinolytics.<sup>10</sup> The calculator is simple to use, comprehensive across fibrinolytic agents and indications, and able to be individualized to a health system's specific patient-base and purchasing agreements.

The calculator is displayed in detail as a spreadsheet in Figure 1. Since urokinase is no longer available, it is not included in the calculator. The specifics of the calculator are as follows:

The fibrinolytics are displayed across the top of the spreadsheet. Note that they are also color-coded (i.e., t-PA-red, r-PA-green, and TNK-gold). There are two columns for t-PA corresponding to the 100 mg (Activase®) and 2 mg vials (Cathflo™ Activase®). The vial sizes and the wholesale acquisition cost (WAC) per vial are listed under each drug.

*Continued on page 3*



## 2004 Updated Fibrinolytic Practice Guidelines and Consensus Recommendations

continued from page 1

Indications are presented below. Notably, the American College of Chest Physician Conference on Antithrombotic Therapy and American College of Cardiology/American Heart Association (ACC/AHA) Practice Guidelines were revised in 2004 and are reflected in this summary.

### ST-Segment Elevation Myocardial Infarction (STEMI): Choices Narrowed

- The 7th American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy Guidelines recommend alteplase, tenecteplase, reteplase, or streptokinase for patients with acute (STEMI) symptom duration of  $\leq 12$  hours. They specifically recommend the use of alteplase or tenecteplase over streptokinase in patients with a symptom duration of  $< 6$  hours.<sup>1</sup>
- The 2004 American Heart Association/American College of Cardiology (AHA/ACC) Practice Guidelines for the Management of Patients With Acute Myocardial Infarction address the use of fibrinolytics vs. percutaneous coronary intervention (PCI). They recommend that if the symptom duration is  $< 3$  hours and the expected door-to-balloon time minus the expected door-to-needle is:
  - within 1 hour, primary PCI is generally preferred;
  - $> 1$  hour, fibrinolytic therapy (fibrin-specific agent) is preferred

The guidelines further comment that there is serious and legitimate concern that a routine policy of primary PCI will result in unacceptable delays in achieving reperfusion in a substantial number of cases.<sup>2</sup>

### Acute Ischemic Stroke (AIS): Alteplase Stands Alone

- The 7th American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy Guidelines continue to recommend the administration of alteplase within 3 hours of stroke-symptom onset in eligible patients.<sup>3</sup> The routine use of intra-arterially administered fibrinolytics for the treatment of ischemic stroke is not recommended.
- The Stroke Council of the American Stroke Association guidelines strongly recommend alteplase in carefully selected patients within 3 hours of onset of ischemic stroke.<sup>4</sup> No other agents are recommended as a safe and effective alternative to alteplase. Also, the availability of intra-arterial fibrinolysis should not preclude the administration of alteplase in otherwise eligible patients.

### Peripheral Arterial Occlusion (PAO): Evidence and Cost Must Be Considered

- The 7th ACCP Consensus Conference on Antithrombotic Therapy Guidelines recommend that intra-arterial (IA) fibrinolytic therapy be considered as a potential alternative to surgical revascularization in patients with acute ( $< 14$  days) thrombotic or embolic occlusive disease.<sup>5</sup> The guidelines cite that there is no significant difference in efficacy or safety between t-PA and UK and that r-PA and TNK have been investigated in a few small series, however, there are no published head-to-head comparisons with these drugs.
- The Working Party on Thrombolysis in the Management of Limb Ischemia recommends IA fibrinolytic therapy followed by correction of the causative lesion as a primary treatment of acute ( $< 14$  days) native artery occlusions.<sup>6</sup>

- The Society of Interventional Radiology (SIR) Advisory Panel recommendations include the following key points in acute limb ischemia:<sup>7</sup>
  - t-PA is an effective alternative to UK & possesses similar safety,
  - overall procedure times are shorter with t-PA,
  - dosing  $< 2$  mg/hr
    - median: 0.5 to 1.0 mg/hr
    - total:  $< 40$  mg per patient advised
  - concurrent heparin use: low dose (400-500 units/hour),
  - t-PA is significantly less expensive than UK.

### Central Venous Access Device (CVAD) Thrombosis: Focus on the Evidence

- The National Association of Vascular Access Networks (NAVAN) 2000 Consensus Conference Statement recommends the use of alteplase for CVAD thrombosis.<sup>8</sup> Alteplase is FDA-approved for CVAD thrombosis under the trade name Cathflo™ Activase®.

### Deep-Vein Thrombosis: An Option for Some

- The 7th ACCP Consensus Conference on Antithrombotic Therapy guidelines recommend that the use of fibrinolytics be highly individualized and limited to patients with massive iliofemoral thrombosis who are at low risk for bleeding.<sup>9</sup>

### Pulmonary Embolism: Use Reserved

- The 7th ACCP Consensus Conference on Antithrombotic Therapy guidelines recommend fibrinolytic therapy for patients with hemodynamically unstable PE.<sup>9</sup>

## New Fibrinolytic Cost Calculator Facilitates Decision Making

continued from page 1

There are *4 simple steps* in comparing the cost of treating fibrinolytic patients with a variety of preferred products across all indications. It should be noted that some of the fibrinolytics do not have adequate evidence supporting their use in certain indications, therefore, evidence-based alternatives have been identified and substituted in the column (using the color of the evidence-based alternative).

- **STEP 1.** WAC is the cost at which wholesalers purchase from the manufacturer and is also the cost of the drug product for the pharmacy that purchases directly from the manufacturer. It is sometimes referred to as the list price or acquisition cost. WAC is a suggested price, and is typically not what is paid. Buyers obtain lower prices through further discounts or rebates. In the case of fibrinolytics, the specific group purchasing organization (GPO) market share/fixed discount off of WAC and the GPO system/other discount off of WAC must be totaled and entered in the grey cells. On the spreadsheet within the actual calculator, there are red dots in the far right corner within some of the cells. If you position the cursor over one of these cells, a comment will appear which provides you with additional insight (e.g., GPO market share discounts, evidence-based dosing regimens). In the vials/patient (dosing) section, the number of vials required per patient is indicated based on usual evidence-based dosing ranges. However, these cells are unlocked to allow for entry of other dosing regimens.

- **STEP 2.** Enter the Number of Treated Patients/Indication/Agent (i.e., the number of patients treated with each fibrinolytic per indication) over a period of time (e.g. 12 months) in the grey cells.

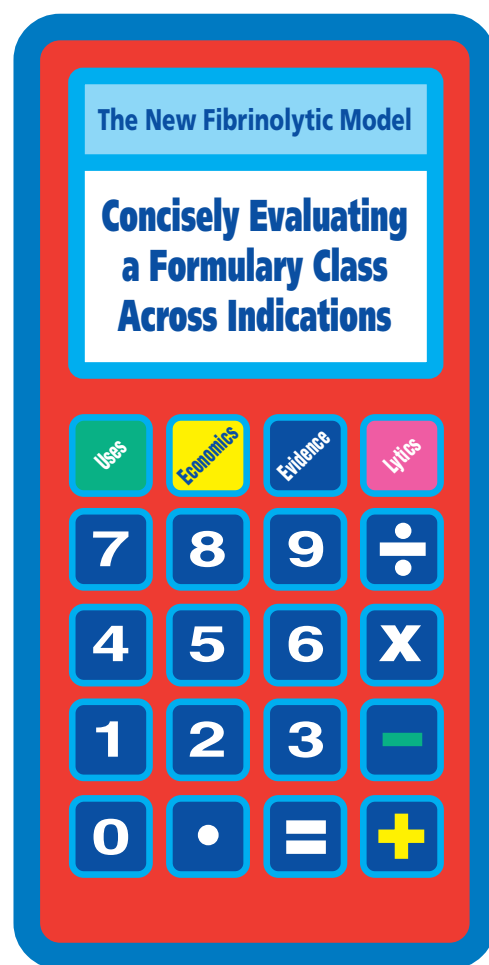
- Using an integrated health system example, some patient numbers have been entered in Figure 2. for each of the fibrinolytics. Note, the total number of patients treated with all fibrinolytics (*Total Pts.*) has been calculated for you and multiplied by the *Net Cost/Patient* for each preferred product(s) to calculate the *Total Spends with each of the Preferred Agents.*

- **STEP 3.** Enter the Maximum Combined Discounts/Rebates off of WAC in the grey cells. This provides the best possible (and worst) pricing for each product, assuming extremes in market share. Note that with best pricing for preferred products, this generally results in suboptimal pricing for non-preferred products due to unrealized market share attainment.

- **STEP 4.** Identify the Cost Difference from your *Total Current Spend* for each fibrinolytic agent. Again, if an agent has inadequate clinical evidence for a particular indication, an agent with well-documented evidence is substituted under that indication. For example, if r-PA is the preferred agent identified, an agent and its cost must be substituted for AIS (t-PA) and PE (t-PA) because of the lack of r-PA evidence for these indications. Because r-PA does have some evidence for PAO, CVAD, and STEMI, the yearly cost for those indications are displayed. *The Total Spends With Preferred Agents* are then calculated and subtracted from the *Total Current Spend (of all agents)* to Identify the Cost Difference. Note that if a cost

difference value is in parenthesis, this indicates cost savings for that drug. Go to the comparison graph tab at the bottom left of the screen for an easy visual assessment.

In summary, the cost calculator is a user-friendly evidence-based tool which enables a comprehensive fibrinolytic economic assessment. The economic comparisons are health system-specific based on a system's actual discounts, patient numbers, and fibrinolytic usage. A current copy of the Fibrinolytic Economic Assessment Tool-Kit is available for downloading on the UPA website (UPA-LLC.COM) under the publication section.



See page 5 for a useful Cost Comparison Calculator.

## To Aliquot or Not: That Is the Question

continued from page 1

answering the question: to aliquot or not, the following issues or concerns should be considered:

- No longer necessary
- Sterility/validation of aseptic procedures
- Stability/freezing
- Labeling/regulations
- Medication errors
- USP Chapter <797>
- JCAHO
- Wastage
- Time, labor, economics
- Evidence-based?

t-PA has been commercially available in a 2 mg unit-of-use vial (Cathflo™ Activase®). It is no longer necessary to aliquot t-PA. If aliquotting of r-PA or UK is considered, the need to ensure sterility and validate aseptic procedures, the question of stability with freezing, and the need for appropriate labeling and compliance with regulations remain important issues.

## Units of Use Recommended

The USP has recently published medication error-avoidance recommendations. Specifically, they state that commercially available formulations should be used whenever possible and feasible, rather than preparing medications through extemporaneous compounding, thus minimizing the opportunity for error and enhancing standardization.<sup>11</sup> Also, on January 1, 2004, USP Chapter 797; Pharmaceutical Compounding: Sterile Preparations came into effect.<sup>12</sup> This publication details the procedures and requirements for compounding sterile

preparations and sets standards which are applicable to all practice settings in which sterile preparations are compounded. Since USP Chapter 797 is considered a requirement, pharmacies may be subject to inspection against these standards by boards of pharmacy, the FDA, and accreditation organizations such as JCAHO. As outlined in USP Chapter 797, batch aliquotting of fibrinolytics would be considered a medium-risk level compounding activity.

Other important concerns relating to aliquotting include the potential for wastage, and the time, labor, and cost implications. The acquisition cost of a fibrinolytic as well as the time and labor cost which must be invested to perform aliquotting must be considered in determining overall comparative cost. Finally, the use of any fibrinolytic, whether it is aliquotted or not, should be evidence-based. For example, in CVAD thrombosis, the use of t-PA is supported by randomized controlled trials and has been shown

to be superior to urokinase in dissolving thrombotic occlusions.<sup>13-15</sup> Thus, formulary decisions relating to the clinical use of fibrinolytics should be based on both clinical and economic evidence. Anecdotal or observational reports on the use of fibrinolytic drugs do not provide adequate support for a drug to be used as a preferred agent. For example, what dose of r-PA should be used in CVAD thrombosis? There are anecdotal reports which identify doses ranging between 0.4-1.0 units per dose, but no evidence-based dose. While administrative and clinical decision makers are under intense pressure to control costs today, sound clinical evidence should guide practice.

Finally, with continuing staffing challenges, the time and labor which would be consumed by aliquotting is an opportunity cost which should be directed at other initiatives which significantly impact costs and are clinically sound. To aliquot or not; in this situation there really is no question.

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**Figure 1**

<b>Fibrinolytic Formulary Cost Comparison Calculator</b>				
Vial Size WAC/Vial	<b>t-PA</b>		<b>r-PA</b>	<b>TNK</b>
	<b>Activase®</b> 100 mg	<b>Cathflo™ Activase®</b> 2 mg	<b>Retavase®</b> 10 U	<b>TNKase®</b> 50 mg
<b>1. Enter Current Discounts/Rebates off WAC.</b>	0%	0%	0%	0%
<b>NET COST/VIAL (CURRENT)</b>	<b>\$2,723</b>	<b>\$65</b>	<b>\$1,149</b>	<b>\$2,334</b>
<b>Vials/Patient (e.g. dosing)</b>				
ST-Segment Elevation MI (STEMI)	1		2	1
Acute Ischemic Stroke (AIS)	1		t-PA	t-PA
Peripheral Arterial Occlusion (PAO)		12	3	t-PA 2mg
Central Venous Access Device Thrombosis (CVAD)		1.5	0.15	t-PA 2mg
Venous Thromboembolism (PE)	1		t-PA	t-PA
<b>2. Enter Treated Patients/Indication/Agent.</b>				
ST-Segment Elevation MI (STEMI)	0		0	90
Acute Ischemic Stroke (AIS)	19			
Peripheral Arterial Occlusion (PAO)		260		
Central Venous Access Device Thrombosis (CVAD)		5850		
Venous Thromboembolism (PE)	4			
<b>TOTAL CURRENT SPEND/AGENT</b>	<b>\$62,635</b>	<b>\$771,867</b>	<b>\$0</b>	<b>\$210,058</b>
<b>3. Enter Max Discounts/Rebates off WAC</b>				
<b>Best Possible Cost/Vial</b>	<b>30%</b>	<b>30%</b>	<b>47%</b>	<b>35%</b>
Min Discounts/Rebates off WAC	0%	0%	5%	0%
<b>Worst Possible Cost/Vial</b>	<b>\$2,723</b>	<b>\$65</b>	<b>\$1,092</b>	<b>\$2,334</b>
<b>Best Cost/Indication/Preferred Agent</b>				
ST-Segment Elevation MI (STEMI)	\$343,133		\$219,229	\$273,076
Acute Ischemic Stroke (AIS)	\$36,220		\$51,742	\$36,220
Peripheral Arterial Occlusion (PAO)		\$141,720	\$474,997	\$141,720
Central Venous Access Device Thrombosis (CVAD)		\$398,587	\$534,371	\$398,587
Venous Thromboembolism (PE)	\$7,625		\$10,893	\$7,625
<b>TOTAL SPEND WITH PREFERRED AGENT(S)</b>	<b>\$927,285</b>		<b>\$1,291,232</b>	<b>\$857,227</b>
<b>4. Identify the Cost Difference.</b>	<b>(\$117,276)</b>		<b>\$246,672</b>	<b>(\$187,333)</b>

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