Options to Restrict Hematoma Expansion After Spontaneous Intracerebral Hemorrhage

Thorsten Steiner, MD, PhD, MME; Julian Bösel, MD

Background and Purpose—Secondary expansion of hematoma after spontaneous intracerebral hemorrhage occurs frequently and early with the potential sequelae of functional deterioration or death. The aim of this topical review is to give a summary of current evidence- and experience-based options to avoid or attenuate hematoma expansion.

Method—we reviewed the literature of the past 10 years on efforts to restrict spontaneous intracerebral hemorrhage expansion by searching Medline and adding related articles known to us. Based on evidence, current guidelines, and our own clinical practice, we have collected consistent and inconsistent pieces of data. These were differentiated according to surgical versus medical approaches, weighed and discussed with regard to expectable benefit, potential risk, and practicability. Finally, we have outlined promising future approaches.

Results—Although consistent evidence on the topic is generally limited, some important studies have provided data on risk factors predicting spontaneous intracerebral hemorrhage expansion implying ways of directing therapy toward these risk factors. Large trials have shed light on 4 major efforts to avoid hematoma expansion: surgical hematoma treatment, reduction of hypertension, reversal of coagulopathies or anticoagulants, and hemostatic therapy. The results were largely disappointing but provide insights for new trials. Future strategies include the combination of surgical and medical treatment and the use of neuroprotectants.

Conclusions—Early restriction of intracerebral hemorrhage is of paramount importance because secondary volume expansion leads to outcome deterioration and death. Although there appear to be few indications for neurosurgical measures, nonsurgical measures such as reduction of hypertension and normalization of altered coagulation seem to be beneficial. However, the routine use of coagulation factors outside of warfarin-associated spontaneous intracerebral hemorrhage cannot generally be recommended at present. The same applies for future approaches such as combined medical–surgical approaches and neuroprotective therapies at this point. (Stroke. 2010;41:402-409.)

Key Words: hematoma expansion ■ ICH growth ■ intracerebral hemorrhage ■ rebleeding ■ outcome

Spontaneous intracerebral hemorrhage (SICH) accounts for approximately 15% of all strokes, and although mortality could be reduced during the last 10 years, it is still approximately 20% to 30% within 3 months. Hematoma volume at presentation, further increase of hematoma volume, and the development of intraventricular hemorrhage were shown to be independent predictors of poor outcome, and hematoma growth (as defined by Brott et al, see subsequently) was also found to be a predictor of early neurological deterioration. These findings indicate that early extension of the initial hematoma boundaries has substantial clinical implications. Increase of hematoma volume is a frequent complication in SICH and was observed in >70% of cases when defined as any increase in parenchymal volume or intraventricular invasion. Brott and coworkers found the majority of relevant growth, that is, 26% (defined as an increase of >33% of the hematoma volume on admission CT), to occur within 4 hours after symptom onset, whereas an additional 12% of patients developed growth within the next 21 hours. This suggests that growth occurs early in the course of SICH and early CT scan repetition is warranted to detect it. This is supported by other prospective studies that found lower frequencies of growth at later time points (Table 1). Although these studies used the same growth definition, they differ in several points, for example, inclusion time window, time of CT control, trial size, and blood pressure treatment.

The pathophysiology behind early hematoma expansion is not well understood. It is not clear whether it reflects leakage,
rebleeding, or both. Several mechanisms of brain injury after SICH have been investigated (for review, see Xi8), but most of these evolve too late to account for early hematoma expansion. In addition to disruption of supportive and protective functional tissue, elevated intracranial pressure, reduced oxygen supply, and mitochondrial dysfunction in the perihematomal zone,9 deleterious factors in the blood or brain barrier. Animal and human studies suggest an association of inflammatory activation (increased interleukin-6, tumor necrosis factor-α) and degradation of components of the blood–brain barrier basal membrane (eg, fibronectin) by matrix metalloproteinases with hematoma enlargement in SICH.10,11 Deleterious factors in the blood–brain barrier might act on vessels and the blood–brain barrier. Animal and human studies suggest an association of inflammatory activation (increased interleukin-6, tumor necrosis factor-α) and degradation of components of the blood–brain barrier basal membrane (eg, fibronectin) by matrix metalloproteinases with hematoma enlargement in SICH.10,11 Deleterious factors in the blood–brain barrier might act on vessels and the blood–brain barrier. Animal and human studies suggest an association of inflammatory activation (increased interleukin-6, tumor necrosis factor-α) and degradation of components of the blood–brain barrier basal membrane (eg, fibronectin) by matrix metalloproteinases with hematoma enlargement in SICH.10,11 Deleterious factors in the blood–brain barrier might act on vessels and the blood–brain barrier.

Table 1. Hematoma Expansion After SICH

<table>
<thead>
<tr>
<th>Author</th>
<th>Brott4</th>
<th>Brott4</th>
<th>Leira3</th>
<th>Mayer5</th>
<th>Anderson6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial acronym or abbreviation</td>
<td>GCNKSS</td>
<td>GCNKSS</td>
<td>ICH-FVII</td>
<td>INTERACT*</td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>103</td>
<td>103</td>
<td>266</td>
<td>120</td>
<td>200</td>
</tr>
<tr>
<td>Planned inclusion time window, hours</td>
<td>3</td>
<td>3</td>
<td>6±3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Mean onset to first CT time window; SD, hours</td>
<td>1.5; 0.5</td>
<td>1.5; 0.5</td>
<td>6.1; 3</td>
<td>2; 0.5</td>
<td>3; 0.5</td>
</tr>
<tr>
<td>Second CT at hour</td>
<td>4</td>
<td>24</td>
<td>48</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Growth definition</td>
<td>&gt;33%</td>
<td>&gt;33%</td>
<td>&gt;33%</td>
<td>&gt;33%</td>
<td>&gt;33% or 12.5 mL</td>
</tr>
<tr>
<td>Percent patients with growth</td>
<td>26</td>
<td>38</td>
<td>27</td>
<td>32</td>
<td>23</td>
</tr>
</tbody>
</table>

*Study arm: guideline therapy (National Institute of Neurological Disorders and Stroke Study).
GCNKSS indicates The Greater Cincinnati/Northern Kentucky Stroke Study.

Risk of Early Hematoma Expansion After SICH

Several smaller and larger trials have investigated various potential predictors of HE, resulting in consistent as well as inconsistent evidence on several parameters.4,17–20 Broderick and coworkers demonstrated in one trial that predictors of hematoma expansion can vary if assessment methods of change in hemorrhage volume are not identical.21 Therefore, we have summarized predictors that were only found in prospective trials or post hoc analyses of randomized controlled trials that used similar definitions of HE, that is, the dichotomized end point definition of growth as being >33% of admission volume or not (Table 2). Table 2 demonstrates the variety of factors that were considered to predict HE and reflects best current evidence from comparable trials. Of note, none of these predictors has been found positive in more than one of these trials. Predictors that neither have been disapproved of nor have been confirmed prospectively comprise patient and treatment characteristics (hematoma volume, intraventricular invasion, early neurological deterioration, treatment with recombinant coagulation factor VIIa, nonintensified blood pressure treatment), radiological characteristics (shorter time between onset and first CT, hematoma density heterogeneity on admission CT, occurrence of a “spot sign” in CT angiography), and laboratory characteristics (reduced platelet activity, elevated interleukin-6, elevated cellular fibronectin). Contradictory results were found for elevated n-dimers4,17,22 and prior use of platelets,10,14,24 The latter was described as a risk factor for growth in 188 patients with SICH treated with tranexamic acid and antihypertensives within 24 hours, but exact timing of CT scans is not mentioned in that study.23 Contrast extravasation on admission CT angiography (“spot sign”) as a predictor of hematoma expansion was also found in an additional retrospective study,24 recently extended to a proposed “spot sign score,”25 and is currently further evaluated by ourselves and others.26 In summary, it is important to realize that many predictor studies differ in such important aspects as time to first CT, observation period, and definitions of HE. Therefore, further systematic and comparable validation of predictors of HE is warranted because this might prevent delay of appropriate therapy, but also influence estimates on prognosis or decisions to withdraw therapy.

Therapeutic Options to Restrict HE

Therapeutic options to restrict HE can be divided into surgical and nonsurgical approaches, whereas the 2 might complement each other.
## Table 2. Predictors of Hematoma Expansion After SICH: Verified or Not

<table>
<thead>
<tr>
<th>Author</th>
<th>Silva¹¹</th>
<th>Leira³</th>
<th>Delgado²²</th>
<th>Broderick²¹</th>
<th>Wada⁶¹</th>
<th>Sorimachi²³</th>
<th>Anderson⁶</th>
<th>Sansing⁷</th>
<th>Barras²²</th>
<th>Naidech¹⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial acronym or abbreviation</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>ICH-FVII Phase 2B (post hoc)</td>
<td>–</td>
<td>–</td>
<td>INTERACT CHANT (post hoc)</td>
<td>ICH-FVII-2B (post hoc)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>183</td>
<td>266</td>
<td>24‡</td>
<td>399</td>
<td>39</td>
<td>188</td>
<td>405</td>
<td>268</td>
<td>90</td>
<td>25†</td>
</tr>
<tr>
<td>Definition of HE in relation to baseline volume</td>
<td>&gt;33%</td>
<td>&gt;33%</td>
<td>&gt;33%</td>
<td>&gt;33% or &gt;12.5 mL*</td>
<td>&gt;33% or &gt;20%</td>
<td>&gt;33% or &gt;12.5 mL</td>
<td>&gt;33%</td>
<td>&gt;33%</td>
<td>Continuous</td>
<td></td>
</tr>
<tr>
<td>First CT until hour</td>
<td>12</td>
<td>12</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Second CT at hours</td>
<td>48+/-6</td>
<td>48+/-6</td>
<td>72</td>
<td>24</td>
<td>24 to 48</td>
<td>48</td>
<td>24</td>
<td>72</td>
<td>24</td>
<td>40.9 [28.2–60]</td>
</tr>
</tbody>
</table>

### Demographic data

| Age | No | – | – | No | – | – | – | – | – |
| Gender | No | – | – | No | – | – | – | – | – |
| Race | – | – | – | No | – | – | – | – | – |
| Body weight | – | – | – | No | – | – | – | – | – |
| Medical history | – | – | – | – | – | – | – | – | – |
| History of hypertension | – | – | – | No | – | – | – | – | – |

### Concomitant medication

| Antplatelet therapy | No | – | – | No | – | – | – | No | – |

### Neuroradiological criteria

| Volume of admission intracerebral hemorrhage | – | – | – | Yes | – | – | – | – | – |
| Volume of peripheral hypodensity | No | – | – | No | – | – | – | – | – |
| Intraventricular hemorrhage volume on first CT | – | – | – | Yes | – | – | – | – | – |
| Intraventricular hemorrhage present at any time | No | – | – | – | – | – | – | – | – |
| Spot sign | – | – | – | – | Yes | – | – | – | – |
| Shape | – | – | – | – | – | – | – | No | – |
| Density heterogeneity | – | – | – | – | – | – | – | Yes | – |

### Clinical, Criteria

| Early neurological deterioration | – | Yes | – | – | – | – | – | – | – |
| Clinical status on admission | No | – | – | – | – | – | – | – | – |

### Laboratory parameters

| Blood glucose | – | – | – | No | – | – | – | – | – |
| Serum cholesterol | – | – | – | No | – | – | – | – | – |
| Serum creatinine | – | – | – | No | – | – | – | – | – |
| D-dimer | No | – | Yes‡ | – | – | – | – | – | – |
| Reduced platelet activity (<550 ARU) | – | – | – | – | – | – | – | – | Yes‡ |

### Markers of inflammation

| Leukocytes | No | – | – | – | – | – | – | – | – |
| Leukocytes >11×10⁰⁰³/mm³ | No | – | – | – | – | – | – | – | – |

(Continued)
Surgical Approach
With respect to the restriction of HE, neurosurgical intervention can have the following aims: removal of the source of hemorrhage, staunching of the bleeding, and elimination of the effects of blood degradation products. The mere removal of blood by open craniotomy or stereotactic aspiration, that is, reduction of mass, cannot be regarded as a measure to restrict HE. Although it could be argued that the removal of blood leads to elimination of deleterious promoters of further bleeding or allows access to a bleeding source, these aspects were not looked at or reported specifically in most of the relevant surgical trials performed so far. Another problem is that most surgical trials did not identify early HE or enroll enough patients early enough to allow conclusions on restriction in the sense of our definitions. Morgenstern and coworkers performed 2 small trials to answer the question of surgical HE restriction either because of a similar time window.30 More interesting with regard to HE might be endoscopic surgery, because iatrogenic bleeding risk might be reduced in an early, less stable phase of SICH and the coagulation of oozing vessels can be combined with hematoma evacuation. Evidence, however, is very limited; 20 years ago, a small prospective randomized trial of endoscopic versus medical treatment of 100 patients with SICH resulted in better outcome and reduced mortality for endoscopic treatment within 48 hour of onset.31 More recently, Cho and colleagues introduced a score for basal ganglia hemorrhage and evaluated its prediction power in endoscopic versus conservative treatment of 226 patients.32 The authors concluded that a midlevel modified intracerebral hemorrhage score of 2 to 4 (based on the determinants Glasgow Coma Score, intracerebral hemorrhage volume, and intraventricular hemorrhage or hydrocephalus) favors endoscopic surgery to improve function or reduce mortality. Unfortunately, due to differences in surgical technique, radiological documentation, and timing of treatment in the aforementioned surgical trials, it is difficult, if not impossible, to draw any conclusions on HE restriction. In fact, evidence that surgery alone can restrict expansion of SICH is presently not existent. Clearly, trials that are tailored more individually with regard to patient characteristics and SICH features are still necessary to elucidate the role of surgery. To date, surgery might add to medical treatment with regard to survival or independence, but this is not very robust, and thus, no general recommendation can be given with regard to surgical prevention of HE.30,33

Nonsurgical Approach
Two major pathophysiological considerations with regard to HE have directed investigators to potential treatment targets:
(1) the driving force, that is, high blood pressure; and (2) the persistence of leakage, that is, compromised coagulation. Thus, the following conservative principles have been tested in clinical trials of reasonable quality: lowering blood pressure, antagonizing anticoagulant therapy, and applying hemostatics.

Effects of Blood Pressure Modulation

The long-standing idea that hypertension, that is, highly increased systolic blood pressure (SBP), is an important cause of HE has led to several investigations. As mentioned, however, findings on hypertension as a risk factor for rebleeding were contradictory. A retrospective analysis by Ohwaki et al showed maximum systolic blood pressure to be independently associated with HE in 76 subjects with SICH receiving CT scans one and 16 hours (average) after onset and a significant cutoff at 150 mm Hg could be found. Although the authors defined HE as an increase in volume of $\geq 140\%$ or $\geq 12.5\ cm^3$ between baseline and second CT, the study is otherwise close to our definitions of restriction of early HE and the population comparable to the trials mentioned subsequently. Another retrospective study reported diastolic blood pressure in the first 24 hours to be decisive and a 15% SBP reduction (ie, SBP $<140\ mm\ Hg$, diastolic blood pressure $<80\ mm\ Hg$) relevant to restrict HE, which, however, the authors defined as “acute” if occurring within 2 weeks (!) after onset. The largest randomized trial addressing the effect of lowering blood pressure in SICH has recently been published, INTERACT (INTEnsive blood pressure Reduction in Acute Cerebral hemorrhage Trial), compared intensive (target SBP $\leq 140\ mm\ Hg$) with guideline-based (target SBP $\leq 180\ mm\ Hg$) blood pressure reduction within the first 6 hours in 404 patients with acute SICH. It yielded safety, feasibility, and a trend toward reduction of hematoma expansion, but no significant arterial thromboembolic events occurred in the group with the highest dose of 160 $\mu g/kg$. The Phase III trial FAST (Factor seven for Acute hemorrhagic Stroke Trial) included 816 patients who did either receive 20 or 80 $\mu g/kg$ of rFVIIa or placebo. This trial confirmed the HE-restrictive properties of rFVIIa. However, this had no clinical effect on functional outcome or on mortality. In a post hoc analysis, we found that limiting the trial population to patients

Appreciating a slight effect of antihypertensives on HE reduction in an overall weak or equivocal context of evidence and considering that (1) autoregulation is often preserved in the acute phase (as opposed to the postacute phase$^{19}$) of SICH; and (2) aggressive lowering of blood pressure theoretically carries the risk of cerebral ischemia in hypertensive patients, it seems reasonable to presently follow current guidelines and lower blood pressure cautiously.40,41

Effects of Antagonization of Anticoagulants

The use of oral anticoagulants such as warfarin, although probably rather a contributing than a causative factor,6 does not only lead to a higher incidence of intracerebral hemorrhage, but also to HE in 27% to 54% of the cases$^{43}$ and well beyond the 24-hour time window that we define as early expansion. This might at least partially explain a substantial increase in mortality of up to 70%. Experts agree that anticoagulation has to be reversed rapidly, but the chosen ways to achieve this differ greatly. It is customary to discontinue oral vitamin K antagonists and substitute vitamin K, but this alone is insufficient for rapid normalization of coagulation. Current questions arise on feasibility, safety, and efficacy of prothrombin-dependent coagulation factors in a concentrated form (prothrombin complex concentrate) versus unconcentrated “fresh-frozen plasma” versus single factors like recombinant coagulation factor VIIa (rFVIIa). The current data situation on these questions is inconsistent and any conclusions drawn toward preference of one of these coagulants are premature. The INCH (International normalized ratio Normalization in Coumadin associated intracerebral Hemorrhage) trial, a multi center randomized controlled trial to compare fresh-frozen plasma with prothrombin complex concentrate, has recently been initiated to answer the question of international normalized ratio early reversal (http://clinicaltrials.gov). At present, it can only be recommended to discontinue warfarin, give vitamin K, and rapidly reverse anticoagulation by whatever protocol is institutionally established.

In the case of heparin-associated intracerebral hemorrhage, only epidemiological data exist, insufficient to support a general recommendation concerning HE restriction. Clinicians are thus left to the reasonable approach to normalize coagulation with protamine sulfate as customary. Low-dose heparin for prophylaxis of deep vein thrombosis does not seem to carry a relevant risk of HE.47

Various hemostatic therapies have been considered for use in spontaneous intracranial hemorrhage. However, most of these have not been tested in larger clinical trials so far. In particular, rFVIIa seemed to be a promising candidate. In the Phase 2b trial that included 399 patients, we demonstrated treatment to significantly restrict HE, improve functional outcome, and reduce mortality despite the fact that significantly more arterial thromboembolic events occurred in the group with the highest dose of 160 $\mu g/kg$. The Phase III trial FAST (Factor seven for Acute hemorrhagic Stroke Trial) included 816 patients who did either receive 20 or 80 $\mu g/kg$ of rFVIIa or placebo. This trial confirmed the HE-restrictive properties of rFVIIa. However, this had no clinical effect either on functional outcome or on mortality. In a post hoc analysis, we found that limiting the trial population to patients
with intracerebral hemorrhage volume <60 mL, with <5 mL of intraventricular hemorrhage, of an age <70 years and treatment within 2.5 hours to reveal positive clinical outcome not only in the FAST, but also in the Phase 2b data set. Another explanation for failure to prove clinical efficacy may be the fact that the pure difference in HE restriction between treatment groups was simply too small to translate into a relevant clinical effect. These differences in hematoma volume range between 2 and 5 mL in rFVIIa-ICH-2b and FAST, comparable to trials on different treatments such as INTERACT and CHANT (Cerebral Hematoma And NXY Treatment trial; see subsequently) that equally failed to show an outcome benefit. Furthermore, there may be an upper threshold of absolute hematoma volume beyond which clinical improvement is not very likely, suggested to be above 60 to 80 mL. These results call for another trial on rFVIIa with stricter selection criteria of inclusion time window, intracerebral hemorrhage (and intraventricular hemorrhage) volume, and age of patients.

**Future Strategies**

Unfortunately, almost all “classical” approaches have failed in controlled trials with regard to outcome, probably for disease-imminent but also for trial-imminent reasons. It is also possible that the critical amount of HE restriction for relevance in outcome was not achieved so far or that long-term complications of SICH have masked the initial effect. Current treatment strategies might also be double-edged swords; surgical intervention can reduce bleeding size but also lead to decompression of tissue and thereby enhance bleeding. Nonsurgical intervention such as hemostasis might stop bleeding, but also compromise normal circulation. Therefore, the right balance and possibly the combination of current treatment regimes as well as the evaluation of alternative future strategies seems urgent. The following sums up several emerging treatment targets:

Surgically, the combination of stereotactic minimal invasive aspiration and clot lysis with recombinant tissue plasminogen activator has been proposed, especially with regard to deep hematomas. A study in 15 (highly selected) patients demonstrated intracerebral hemorrhage volume reduction without the enlargement of perihematoma edema as often feared. Whether this approach can indeed lead to a better outcome is currently being investigated in the MISTIE (Minimally Invasive Stereotactic Surgery rt-PA for ICH Evacuation) trial combining stereotactic clot aspiration (starting 6 hours after clot stabilization) with different doses of recombinant tissue plasminogen activator within the first 72 hours from onset. Although the early administration of recombinant tissue plasminogen activator in the setting of SICH will be interesting with regard to HE as an unwanted effect, this approach can hardly be seen as a measure to restrict HE, because it is only aimed at hematoma evacuation, not at bleeding source elimination. More promising in that respect might be the combination of surgery with hemostatic drugs such as rFVIIa, especially in light of frequent rebleeding in ultraearly operations.

On the nonsurgical side, further elucidation of the way to control blood pressure is encouraged by INTERACT and possibly ATACH. Whether the rapid- and short-acting intravenous antihypertensive clevidipine is beneficial in the acute phase of SICH is currently investigated in the ACCELERATE (The evaluation of patients with acute hypertension and intracerebral hemorrhage with intravenous clevidipine treatment) trial. As to neuroprotectants, although so many have failed in ischemic stroke, the situation might be different in hemorrhage, and lessons from trial-imminent reasons for failure might help to more successfully apply neuroprotectants in SICH. The free radical scavenger NXY-509, having failed in ischemic stroke trials, proved safe and tolerable applied within 6 hours of SICH, but showed no improvement in outcome, however, in a safety trial design. Of other candidates, matrix metalloproteinases might play a relevant role in SICH development and expansion. Data from a mouse model recently showed that inhibition of the gelatinase matrix metalloproteinase-9 by the broad-spectrum inhibitor GM6001 had several beneficial effects, including decreased injury volume and improved functional outcome. Thus, matrix metalloproteinase inhibitors might be promising if safe and feasible in humans. This being completely unclear and most probably a question of the distant future, other ways to achieve endogenous inhibition of matrix metalloproteinases should be pursued. Substances that are already in clinical use for other indications and therefore potentially available for use in patients with SICH have been demonstrated as neuroprotectants restricting HE in experimental animal models of intracerebral hemorrhage by an active South Korean group. These agents comprise the cytokine erythropoietin, the antiinflammatory valproic acid, and the moderate NMDA receptor antagonist memantine. A rather nonselective way of neuroprotection, hypothermia, might have beneficial effects on blood–brain barrier damage, mitochondria dysfunction, cerebral O2 consumption, penumbral depolarizations, excitotoxicity, and development of peri-hematoma edema. Several of these factors are probably involved in the pathophysiology of HE. Hypothermia in SICH, on its own or in combination with decompressive hemicraniectomy, is currently investigated by Kollmar and colleagues (Kollmar R, German Neuro Critical Care Society Annual Meeting 2008, Leipzig, personal communication).

**Conclusion**

Secondary hematoma expansion of spontaneous intracerebral hemorrhage is a frequent, early, and very relevant complication of this devastating disease and demands rapid restricting efforts. Some predictors of HE have been identified, but these are not always accessible treatment targets. Unfortunately, all measures to restrict HE have so far failed to improve outcome in controlled trials. It is still reasonable, however, considering data from available studies and pathophysiological concepts, to follow current guidelines and to reverse the action of prior anticoagulants quickly, to lower extreme SBP cautiously, to aim for homeostasis in vital functions and metabolism, and to find an interdisciplinary treatment strategy with the neurosurgeon. Above all, it is paramount to create, to conduct, or to randomize patients into controlled trials on this subject.

**Disclosures**

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References


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