



Recombinant human activated protein C in sepsis: previous concerns and current usage

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Recombinant human activated protein C (rhAPC) was approved by the FDA for clinical use in severely septic patients approximately 2 years ago. This approval, based upon the results of the Phase III clinical trial, Phase III Protein C Worldwide Evaluation in Severe Sepsis (PROWESS), was not without opposition as concerns regarding rhAPC's inconsistent effects during the trial, incomplete understanding of its mechanism of action, and its safety profile within various subgroups were questioned during the FDA's evaluation. In light of these concerns, we have attempted to assess rhAPC's cost effectiveness by first comparing its performance in recent clinical use to that of the Phase III trial and then by examining other potentially less expensive treatments with effects that may overlap with rhAPC. Recent postmarketing analysis suggests a higher mortality rate in patients with similar disease severity (number of injured organs) during the clinical use of rhAPC when compared with the Phase III trial. Furthermore, the clinical use of rhAPC may also be associated with a higher incidence of bleeding risk or other adverse events that necessitate the discontinuation of treatment with rhAPC. A recent meta-analysis and other Phase III trials assessing agents with antithrombotic or anti-inflammatory properties, suggest that both heparin and physiologic-dose steroids may offer less expensive alternatives to rhAPC. The results of recently completed and ongoing Phase IV trials will be helpful in defining rhAPC's role in the treatment of sepsis.

Given the high lethality associated with sepsis and septic shock, many healthcare professionals welcomed the encouraging results from the Phase III Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial showing that drotrecogin (Xigris®, Eli Lilly) α -activated (i.e., recombinant human activated protein C [rhAPC]) significantly reduced the risk of death [1]. Based on these results it was believed by many that rhAPC would be rapidly available for clinical use [2,3]. Generally, when there are no alternative therapies for a lethal disease such as sepsis, a new drug should receive rapid approval and clinical acceptance if the original trial results are consistent, the agent's mechanism of action is well understood and its safety profile is strong. In the case of rhAPC however, further review raised sufficient concerns for half of the 20 members of the US Food and Drug Administration (FDA) Advisory Committee to recommend that the agent undergo additional Phase III testing prior to clinical use [4,5]. In 2002 the FDA did approve rhAPC for the treatment of severely septic patients but because of these concerns, restricted its use to those with a high risk of death [6]. The US FDA also requested that the manufacturer conduct additional Phase IV

studies to assess the effects of rhAPC in several subgroups. rhAPC has now been in clinical use for almost 2 years. It is worthwhile at this time to not only review the questions and concerns raised during the FDA evaluation of rhAPC but also try to assess just how cost-effective its recent clinical use has been.

Questions regarding the effects of rhAPC in the pivotal Phase III trial *Lack of consistency of trial results*

Analysis by the US FDA of the Phase III trial results showed that rhAPC was substantially more beneficial in the second half of the trial. This change appeared to be due in part to an amendment introduced into the trial modifying the trial enrollment criteria [4]. This amendment, which occurred after the trial was nearly half completed, was designed to more effectively exclude patients from the study that were likely to die from conditions not related to sepsis and thus unlikely to benefit from rhAPC. One interpretation of these results was that the study amendment had increased the sensitivity in the second half of the trial to detect a beneficial effect related to rhAPC. However, 2 months after the amendment, but still well

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before the end of the trial, a change was also introduced into the manufacturing process of rhAPC. Although an analysis did not show differences between the products used in the first compared with the second parts of the study, the FDA in its evaluation noted that the complexity of rhAPC might still have permitted undetected differences to exist [4]. Thus, variation in the efficacy of rhAPC between the two parts of the study may have been a function of inconsistent effects related to the change in drug manufacturing process. However, rhAPC available for clinical use at present is from the more recent manufacturing process.

Unclear mechanism of action

A primary mechanism of the effect of rhAPC was originally ascribed to its ability to supplement reductions in endogenous protein C caused by sepsis, thereby inhibiting thrombosis in the microvascular space and limiting inflammation [1]. Despite this proposed mechanism, the Phase III trial revealed that rhAPC was just as effective in patients who were not protein C deficient as in patients who were [4]. Furthermore, in contrast to rhAPC, two other antithrombotic agents tested in large Phase III clinical sepsis trials, antithrombin III (KyberSept trial) and tissue factor pathway inhibitor (Optimized Phase III Tifacogin in Multicenter International Sepsis [OPTIMIST] trial), failed to show significant benefit [7,8]. Since all three agents were associated with increased bleeding in patients with severe sepsis as a result of their antithrombotic effects, whether rhAPCs marked improvement in survival is related to its anticoagulant effects is unclear.

rhAPC has a wide range of other biological effects which not only inhibit coagulation but inflammation as well. Although these anti-inflammatory effects may result from reductions in intravascular thrombin formation, these alone cannot explain why rhAPC appeared so much more efficacious than antithrombin-III and tissue factor pathway inhibitor. Independent of its effects on thrombin however, rhAPC also influences endothelial and leukocyte inflammatory pathways [9]. Following binding to endothelial protein C receptor (EPCR), rhAPC may directly inhibit nuclear factor (NF)- κ B and the subsequent activation of cellular pathways leading to oxidation, adhesion, cytokine release, apoptosis and nitric oxide production [9]. Although suppression of NF- κ B was thought to be a mechanism of action for many

of the mediator-specific anti-inflammatory agents (e.g., antitumor necrosis factor antibodies) which failed in large clinical trials, these agents did not directly inhibit its activation, as rhAPC appears capable of, nor were they anticoagulants. rhAPC did reduce interleukin (IL)-6 levels in the PROWESS trial. However, it is worthwhile to note that in healthy volunteers challenged with lipopolysaccharide, rhAPC did not have evident anti-inflammatory effects [10]. Better understanding of the mechanism of action of rhAPC during sepsis is likely to improve our ability to use it therapeutically.

Safety

Two important safety concerns arose during the FDA's review of the PROWESS trial. The first was related to potential increases in the incidence of serious bleeding that would occur with wide clinical use of rhAPC. Evaluation of the Phase III trial demonstrated that, compared with placebo, bleeding was significantly increased in patients receiving rhAPC during study drug infusion (APC 2.4% vs. placebo 1.0%, $p = 0.02$) [4]. A similar increased risk of bleeding has also been reported in the Phase IV ENHANCE study (a global, single-arm, open-label trial in patients with severe sepsis) [11]. However, compared with the Phase III trial in which four intracranial hemorrhages occurred with rhAPC, two (0.23%) during drug infusion, in a subsequent compassionate-use protocol enrolling 520 patients that was reported during the FDA evaluation, 13 intracranial hemorrhages occurred, eight (1.5%) of which were during rhAPC infusion [4]. This difference represented an almost eightfold increase. Collectively, these findings suggested that the incidence of intracerebral hemorrhage or other serious bleeding events during the clinical use of rhAPC might be substantially greater in the absence of the oversight associated with Phase III trials.

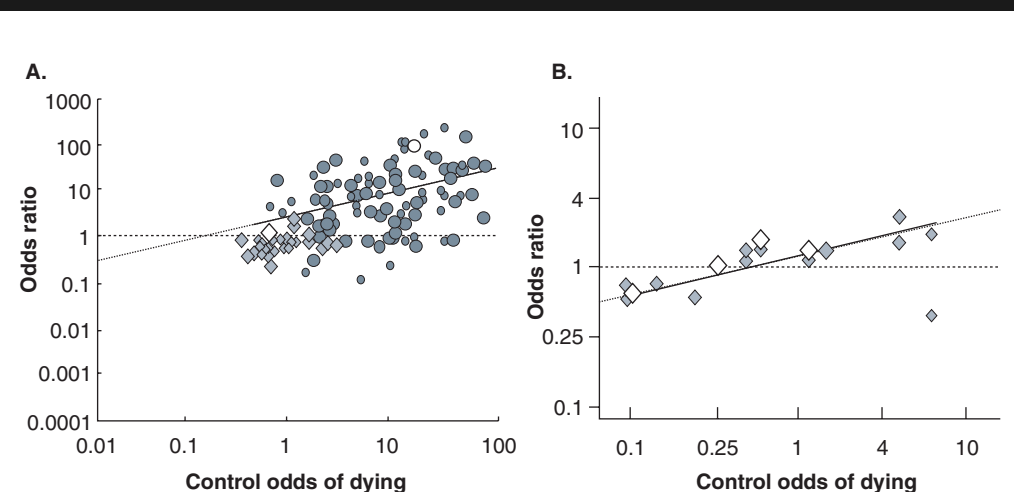
The second safety concern related to a potential interaction between rhAPC's efficacy and a patient's predicted risk of death. In the PROWESS trial, rhAPC became less beneficial as the patient's severity of illness on admission, measured by Acute Physiology and Chronic Health Evaluation (APACHE) II score, decreased [4]. In patients with very low APACHE scores, rhAPC had effects which could be harmful, although these did not reach significance. Of note, while the severity of illness influenced the efficacy of rhAPC, it did

not alter its hemorrhage risk. This relationship between severity of illness and rhAPC was of particular concern in light of other studies showing that the risk of death due to sepsis is likely to influence the efficacy of other agents with anti-inflammatory effects. These studies had analyzed the effects of several mediator-specific anti-inflammatory agents (i.e., antitumor necrosis factor agents, IL-1 receptor antagonist, platelet-activating receptor antagonist and antibradykinin and antiprostaglandin agents) in prior preclinical and clinical trials [12]. A metaregression analysis of the preclinical studies showed that the efficacy (i.e., odds ratio of survival) of these other anti-inflammatory agents was highly dependent on risk of death (i.e., control odds). Analysis of clinical trials testing these same agents showed a similar relationship. Anti-inflammatory agents were significantly more efficacious in septic patients

with higher risk of death and were ineffective or harmful in those with low risk. This relationship was confirmed in prospective animal studies. A comparison of rhAPC to the analysis carried out on these other anti-inflammatory agents showed that the effects of all of these therapies were similarly influenced by risk of death (Figure 1) [12,13].

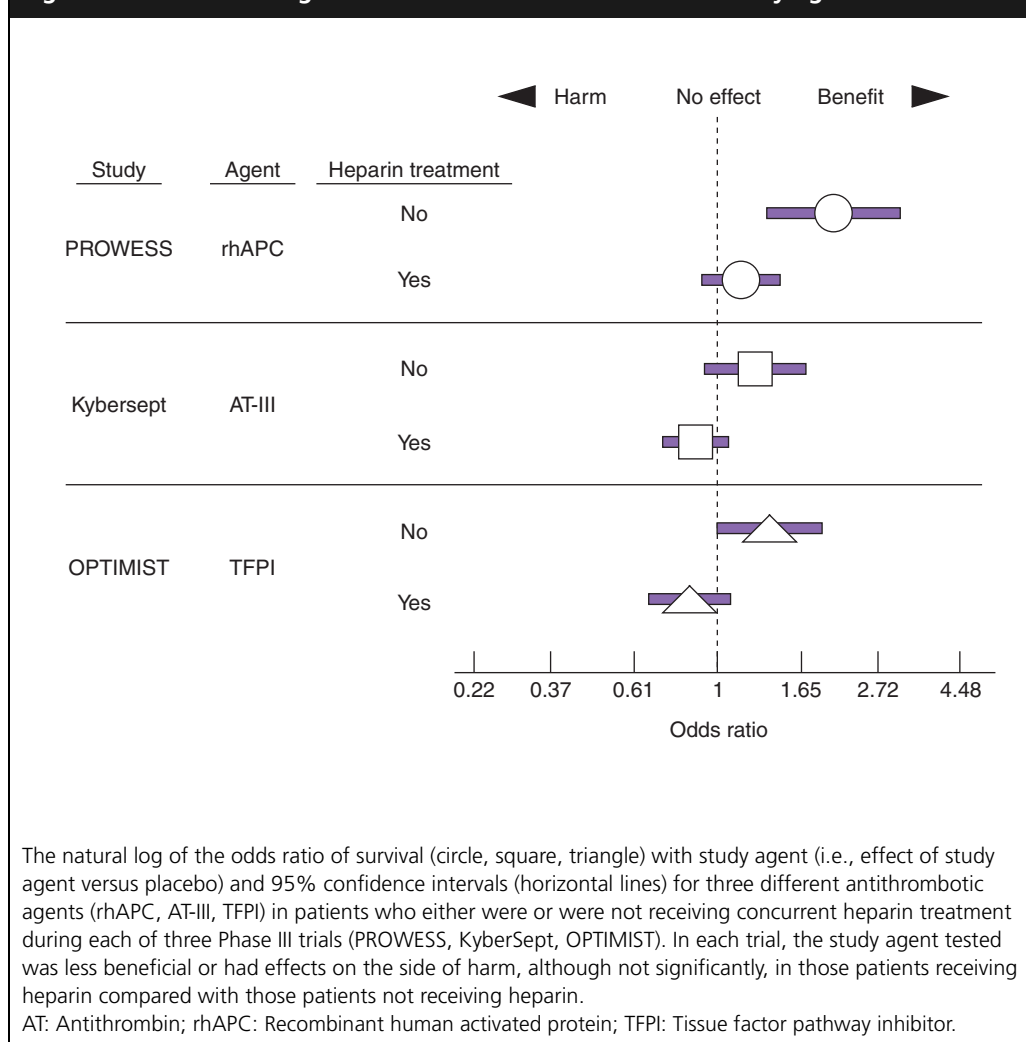
Another analysis has also shown that risk of death as reflected by APACHE score influenced the effects of rhAPC on quality-adjusted life-years (QALYs), another measure of outcome [14,15]. QALY is an estimate of the number of functional years of life that patients will achieve after study. This analysis demonstrated that there was a monotonic relationship between APACHE II quartile and mean QALYs [15]. Overall the influence of APACHE score both on the odds ratio of survival and QALYs was very similar.

Figure 1.



A. The weighted regression line shows the relationship between control odds of dying (x-axis) and the odds ratio of survival (y-axis) with treatment for 95 experiments (gray circles, varying in diameter based on sample size) in 38 published animal studies cited in 22 clinical trials testing five different anti-inflammatory agents (i.e., antitumor necrosis factor agents, IL-1 receptor antagonist, platelet-activating receptor antagonist and antibradykinin and antiprostaglandin agents) [12,13]. As risk of death decreased across these studies, overall, the beneficial effects of these agents were found to decrease in a highly significant pattern ($p = 0.0001$) [5]. The limited efficacy of these same agents in 22 clinical trials (gray diamonds) testing them at lower control odds were very consistent with the 95 preclinical experiments. The effect of rhAPC in a clinical trial (open diamond) and cited preclinical trial (open circle) were very similar to these other five agents. In one Phase III trial of IL-1ra and one of P-55 TNFs, septic patients were categorized at study entry into groups based on their predicted risks of death as determined by a modified APACHE II score, respectively. **B.** The observed control odds and odds ratio of survival with these two anti-inflammatory treatments for these risk categories (gray diamonds) as well as a weighted regression line for the relationship. This relationship was highly significant for these two agents ($p = 0.0002$). The effects of APC in patient subgroups with varying predicted risks of death (open diamonds) were very similar to these other two agents.

APACHE: Acute Physiology and Chronic Health Evaluation; IL: Interleukin; rhAPC: Recombinant human activated protein; TNF: Tumor necrosis factor.

Figure 2. The natural log of the odds ratio of survival with study agent.

Based on this relationship between disease severity and the efficacy of rhAPC, the USA FDA restricted the use of this agent to patients with severe sepsis and a high risk of death, as determined by an APACHE score or other measures. The FDA also required that the manufacturer perform additional testing in patients with a very low risk of death. At this time, the Administration of drotrecogin α -activated in Early Severe Sepsis (ADDRESS) trial, originally designed to test the efficacy of rhAPC in 11,000 low-risk patients, has been stopped for futility after enrollment of only approximately 2000 patients [Pers. Comm.].

Cost effectiveness of rhAPC based on present clinical experience

Since its approval, rhAPC has been in clinical use for almost 2 years. Based on original concerns raised with its evaluation, it is appropriate

to try to assess just how cost-effective its use has been. Several such cost assessments have now been published, one of which compares the costs of rhAPC with other potential therapies [14,16]. However, two questions one might ask are the following:

- Have the original Phase III trial results with rhAPC been reproduced clinically
- Are less expensive alternative treatments to rhAPC available clinically

Reproducibility of trial results

Postmarketing data collection of a recently approved drug, while important for identifying side effects not recognized in prior Phase III trials, also permits an estimate of the effectiveness of the drug during clinical use outside the safeguards of a controlled trial [17–19]. Such an evaluation of rhAPC was carried out by Novation

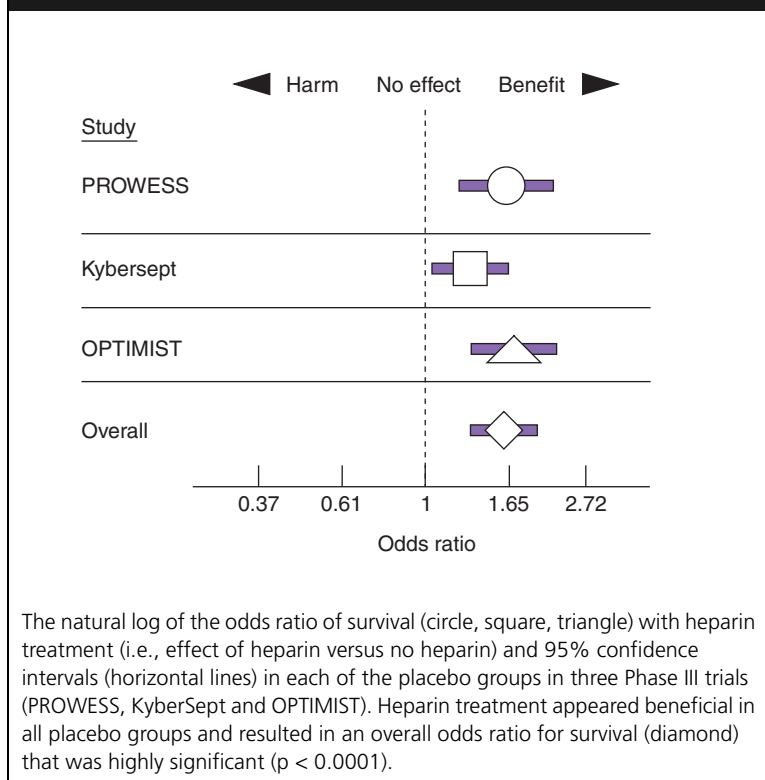
(TX, USA), independent of the manufacturer of rhAPC. It included 368 septic patients at 72 separate institutions, who received rhAPC over a 6 month period from May to November of 2002 [20]. Compared with a mortality rate of 26% with rhAPC in 850 patients treated during the Phase III trial, during clinical use the mortality rate was 44%. Such an increase, while significant ($p = 0.001$), would not be surprising since rhAPC was only approved for patients with severe sepsis and a high risk of death. Indeed, the indications for rhAPC during clinical use were in fact very consistent with FDA recommendations. However, this difference persisted even after stratifying patients based on their number of injured organs, a measure of disease severity. In patients reported to have two, three, four, or five injured organs, mortality rates were consistently greater with rhAPC during clinical use (37.3, 51.3, 56.3 and 52.4%, respectively) than in the Phase III trial (20.7, 26.2, 38.7 and 32.3%, respectively). Although there may be several reasons for this difference, one is that use of rhAPC clinically differed from the PROWESS trial. Consistent with this, 178 patients receiving rhAPC during clinical use had warnings or contraindications

that would have precluded their enrollment in the Phase III trial. The overall mortality rate in these patients was increased compared with patients who did not have warnings or contraindications (50 vs. 39%, $p = 0.03$). Thus, it is possible, that clinical use different from the Phase III trial may have decreased rhAPCs efficacy and increased its risk in some patients. Similar to the compassionate use trial of rhAPC noted above, the evaluation by Novation found that the incidence of serious bleeding events were increased in a trend approaching significance compared with the Phase III trial ($p = 0.08$) [4]. In addition, adverse drug events, most related to bleeding and the need to discontinue the administration of rhAPC because these events, were both significantly greater during clinical use than in the PROWESS trial (adverse drug events in clinical use 19.3% vs. PROWESS 12.5%, $p = 0.002$ and discontinuation rate due to adverse drug event in clinical use 11 vs. PROWESS 6%, $p = 0.004$).

Availability of less expensive alternative treatments

A primary mechanism of action of rhAPC was reported to be its antithrombotic effects [1]. However, data from the PROWESS trial and the two other recent trials testing either antithrombin III (KyberSept trial) or tissue factor pathway inhibitor (OPTIMIST trial) suggest that low-dose heparin, a much less costly antithrombotic agent than rhAPC, may also be beneficial in patients with sepsis [7,8]. In each of these trials the experimental antithrombotic agent tested was less beneficial in patients receiving concurrent heparin therapy (Figure 2). While there are many potential reasons for this, one is that heparin treatment had beneficial antithrombotic effects which negated those of the study drugs [21]. Consistent with this possibility, in patients receiving placebo in each of these trials, those on heparin treatment had better outcomes compared with those not receiving it (Figure 3). Overall, this possible effect of heparin appeared very significant, although this may reflect variable levels of disease severity in patients who did or did not receive heparin. It is noteworthy that a recent large Phase III trial in critically ill patients demonstrated that low-molecular-weight heparin administration significantly improved clinical outcome compared with placebo [22]. However, whether heparin alone is beneficial in patients with sepsis requires further study.

Figure 3. The natural log of the odds ratio of survival with heparin treatment.



rhAPC was also reported to have beneficial anti-inflammatory effects [1]. However, low-dose corticosteroids may offer a less expensive alternative for this indication as well. Although low-dose corticosteroids may correct relative adrenal insufficiency, this treatment also has substantial anti-inflammatory effects [23]. A meta-analysis has recently demonstrated that, in contrast to earlier trials testing very high doses of corticosteroids, in five recent trials lower doses of this agent significantly increased the overall odds ratio of survival and improved hemodynamic function [24]. These beneficial effects with low-dose corticosteroids were independent of whether patients demonstrated evidence of hypoadrenalism.

Thus, both low-dose corticosteroids and heparin may have effects on survival in sepsis similar to those with rhAPC. However, unless these agents are tested directly, it cannot be elucidated how similar these effects are. It is evident though that the costs of these agents are very different. Compared with a 4-day course of rhAPC costing almost US\$6800, a 7-day course of low-dose corticosteroids costs \$50 and a 28-day course of low-dose heparin costs \$68. Since the cost of rhAPC is constant worldwide regardless of each country's gross domestic product (GDP), less costly therapies could have wide applicability.

Expert opinion

At the time of rhAPC's approval, questions remained regarding the consistency of the Phase III trial results, its mechanism of action and its safety profile. The manufacturer of rhAPC is actively conducting trials attempting to address some of these questions. Based on

recommendations by the FDA, rhAPC should be considered for patients with severe sepsis resulting in multiple organ failure who have a low risk of bleeding complications and a high risk of death as reflected by initial APACHE or other score [6]. It should be noted though that APACHE II scores have never been validated for defining the need for therapy. Postmarketing data raises the possibility that administration of rhAPC different from that of the Phase III trial may reduce its efficacy and increase its risks. Furthermore, agents frequently employed in patients with sepsis, such as low-dose corticosteroids or heparin, may duplicate and negate the benefits of rhAPC. Although Phase IV testing may alter patient selection compared with original Phase III trials, Phase IV testing should continue to assess the effects of rhAPC in the presence and absence of these other agents, while controlling for severity of disease. If these trends persist, it will be hard to rationalize the use of rhAPC along with these other far less expensive agents without formal testing in randomized controlled trials. It will also be important to understand how the institution of other potentially life-saving treatments in critically ill patients, such as optimal blood sugar control, will impact the use of rhAPC.

Outlook

The formal results of recently undertaken Phase IV trials testing the use of rhAPC in patients with a low risk of death and its effects in the presence or absence of heparin may help to clarify its role in the treatment of sepsis. Additional studies evaluating rhAPC's effect in conjunction with other commonly employed treatments of sepsis are also needed in the next 5 years. If these studies suggest a reduced efficacy, a reappraisal of rhAPC's cost-effectiveness will be warranted.

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Highlights

- Clinical use different from the Phase III trial may have changed the risk and efficacy of activated protein C (APC) in patients with sepsis.
- Clinical use of APC may be associated with a risk of hemorrhage greater than during the phase III trial.
- The results of Phase IV trials testing the effects of APC in differing subgroups will be valuable for clinicians administering APC.
- Alternate less costly therapies such as physiologic dose steroids and low-dose heparin may have effects that duplicate those of APC.

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