Importance  Myelofibrosis (MF) is a BCR-ABL–negative myeloproliferative neoplasm characterized by anemia, splenomegaly, debilitating constitutional symptoms, and shortened survival. Fedratinib, a JAK2-selective inhibitor, previously demonstrated clinically beneficial activity in patients with MF in early-phase trials.

Objective  To evaluate the efficacy and safety of fedratinib therapy in patients with primary or secondary (post–polycythemia vera or post–essential thrombocythemia) MF.

Design, Setting, and Participants  Double-blind, randomized, placebo-controlled phase 3 study in 94 sites in 24 countries in which 289 adult patients (≥18 years of age) with intermediate-2 or high-risk primary MF, post–polycythemia vera MF, or post–essential thrombocythemia MF were randomly assigned between December 2011 and September 2012 to once-daily oral fedratinib, at a dose of 400 mg or 500 mg, or placebo, for at least 6 consecutive 4-week cycles.

Main Outcomes and Measures  The primary endpoint was spleen response (≥35% reduction in spleen volume from baseline as determined by magnetic resonance imaging or computed tomography) at week 24 and confirmed 4 weeks later. The main secondary endpoint was symptom response (≥50% reduction in total symptom score, assessed using the modified Myelofibrosis Symptom Assessment Form).

Results  The primary endpoint was achieved by 35 of 96 (36% [95% CI, 27%-46%]) and 39 of 97 (40% [95% CI, 30%-50%]) patients in the fedratinib 400-mg and 500-mg groups, vs 1 of 96 (1% [95% CI, 0%-3%]) in the placebo group (P < .001). Symptom response rates at week 24 were 33 of 91 (36% [95% CI, 26%-46%]), 31 of 91 (34% [95% CI, 24%-44%]), and 6 of 85 (7% [95% CI, 2%-13%]) in the fedratinib 400-mg, 500-mg, and placebo groups, respectively (P < .001). Common adverse events with fedratinib treatment were anemia, gastrointestinal symptoms, and increased levels of liver transaminases, serum creatinine, and pancreatic enzymes. Encephalopathy was reported in 4 women who received fedratinib 500 mg/d. A diagnosis of Wernicke encephalopathy was supported by magnetic resonance imaging in 3 cases and suspected clinically in 1 case.

Conclusions and Relevance  Fedratinib therapy significantly reduced splenomegaly and symptom burden in patients with MF. These benefits were accompanied by toxic effects in some patients, the most important being encephalopathy of unknown mechanism. Clinical development of fedratinib was subsequently discontinued.

Trial Registration  clinicaltrials.gov identifier: NCT01437787
M
eyelofibrosis (MF) is a BCR-ABL–negative myeloproliferative neoplasm that can present de novo (primary MF) or after transformation of polycythemia vera (PV) or essential thrombocythemia (ET). Myelofibrosis is characterized by anemia, splenomegaly, debilitating constitutional symptoms, and shortened survival. Gain-of-function mutations resulting in constitutive activation of the Janus kinase (JAK) signal transducer and activator of transcription signaling pathway are common in patients with MF, with mutations in JAK2 (eg, JAK2 V617F) and myeloproliferative leukemia (MPL) occurring most frequently. Recently, calreticulin mutations have been found in a high proportion of JAK2-negative, MPL-negative patients. Currently, the only potentially curative treatment for patients with MF is allogeneic stem cell transplantation. However, most patients are not candidates for such treatment and alternative conventional drug treatments are palliative and often of limited benefit. Ruxolitinib phosphate, a JAK1/2 inhibitor, was recently approved for the treatment of intermediate- or high-risk MF. However, not all patients respond to ruxolitinib, and others may lose response over time. Alternative treatments are therefore needed.

Fedratinib (SAR302503/TG101348) is a JAK2-selective inhibitor that demonstrated clinical benefit in patients with MF in early-phase clinical trials. Compared with ruxolitinib, fedratinib is a more specific inhibitor of JAK2 (vs other JAK family kinases) and appears to have activity against a broader family of kinases and kinase mutants. To further evaluate the efficacy and safety of fedratinib, we conducted a randomized, double-blind, placebo-controlled phase 3 trial (JAKARTA) in patients with intermediate-2 or high-risk MF.

Methods

Eligibility Criteria

Eligible patients were at least 18 years old with a diagnosis of primary MF, post-PV MF, or post-ET MF with high-risk or intermediate-2 risk disease according to 2008 World Health Organization and modified International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria, life expectancy at least 6 months, and Eastern Cooperative Oncology Group performance status of 0 to 2. Patients had palpable splenomegaly (>5 cm below the left costal margin) and platelet count at least 50 × 10^3/μL (to convert to billions per liter, multiply by 1.0).

Study Design

The trial was conducted at 94 sites in 24 countries. Patients were randomized (1:1:1) to receive oral fedratinib 400 mg, 500 mg, or matched placebo once daily for at least 6 consecutive 4-week cycles. Randomization and treatment allocation was performed centrally via an interactive voice response system, which assigned each patient a unique 9-digit patient identification number. The interactive voice response system generated separate patient randomization lists, allocated the treatment arm, and instructed the study personnel as to which kit and treatment number to dispense to the patient. Patients continued to receive their assigned treatment until they experienced disease progression or relapse (modified IWG-MRT criteria), excess toxic effect, or other criteria outlined in the protocol. Dosing was interrupted following the occurrence of certain adverse events (AEs), as defined in the study protocol, with the recommendation that dosing be restarted at a level 100 mg/d below that at which the event was observed (see Trial Protocol in Supplement 1). Crossover from placebo to fedratinib was permitted after 24 weeks, or before if the patient experienced progressive disease as predefined in the study protocol. Crossover patients were randomized (1:1) to 1 of the 2 fedratinib doses.

The protocol was approved by institutional review boards at each study site. The study was conducted according to the principles of the Declaration of Helsinki. All patients provided written informed consent. Data were collected by the investigators and analyzed by the study sponsor with oversight, feedback, and approval from the investigators and a data-monitoring committee.

Study End Points

The primary end point was the proportion of patients with at least a 35% reduction in spleen volume (measured by magnetic resonance imaging [MRI] or computed tomography) from baseline to week 24 (end of cycle 6) and confirmed 4 weeks later. The proportion of patients with at least a 35% reduction in spleen volume from baseline to 24 weeks regardless of confirmation was a secondary end point. The main secondary end point was the proportion of patients with at least a 50% reduction in total symptom score (TSS) (calculated as the weekly mean value of the daily total score for 6 key symptoms [night sweats, pruritus, abdominal discomfort, early satiety, pain under ribs on left side, and bone or muscle pain]) from baseline at 24 weeks, assessed using the modified Myelofibrosis Symptom Assessment Form e-diary. Change in JAK2 V617F allele burden was an exploratory end point. Adverse events were coded using National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Statistical Analysis

Assuming a 15% drop-out rate, 75 patients per arm provided 90% power to detect a treatment difference in spleen re-
sponse at a 2-sided α level of .05, assuming response rates of 30% in either fedratinib arm and 5% in the placebo arm. Unless stated, analyses were performed using the intention-to-treat population. For analysis of spleen and symptom response, patients with missing valid assessments at week 24 or who experienced disease progression before 24 weeks were considered nonresponders. Safety was assessed throughout the study period in all patients who received at least 1 dose of study medication. Comparison of the primary endpoint and key secondary endpoint of symptom response between placebo and each drug arm was performed using the χ² test at a 2-sided α level of .025. Summary and descriptive statistics were generated for all other endpoints.

**Results**

**Characteristics of the Patients**

A total of 289 patients were enrolled from December 2011 to September 2012, with 96, 97, and 96 patients randomly assigned to fedratinib 400 mg, 500 mg, and placebo, respectively. Baseline patient characteristics are shown in eTable 1 in Supplement 2. At the analysis cutoff date (March 21, 2013), 64 (67%), 59 (61%), and 1 (1%) patients in the fedratinib 400-mg, 500-mg, and placebo groups were still receiving their originally assigned treatment. In the placebo group, 24 patients discontinued treatment and 10 patients crossed over to fedratinib before the end of week 24. After this point, 60 additional patients crossed over to fedratinib; an additional patient was randomized but died before receiving study treatment. Detailed patient disposition is shown in Figure 1.

**Spleen Volume Reduction**

The proportion of patients with at least a 35% reduction in spleen volume (spleen response) at 24 weeks, and confirmed 4 weeks later, was significantly higher (P < .001 for the comparison of each dose with placebo) in the fedratinib 400-mg (35 [36%]) and 500-mg (39 [40%]) groups compared with placebo (11%) (Table 1). Response rates at week 24 (without confirmation) were 47% (45 patients at 400 mg), 49% (48 patients at 500 mg), and 1% (1 patient with placebo; P < .001) (Table 1). Information regarding spleen volume reduction for patients without confirmation of spleen response at 24 weeks is shown in eTable 2 in Supplement 2. Among patients with available data, all except 3 patients in the fedratinib 400-mg group and 2 patients in the fedratinib 500-mg group experienced some degree of spleen volume reduction at 24 weeks of up to 70%, whereas a majority of patients (44 of 59 [75%]) in the placebo group had an increase in spleen volume at this

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*One patient in the placebo group was randomized but died before taking the first dose of medication.*
Spleen response rates were higher in the fedratinib groups compared with placebo regardless of baseline platelet count, disease subtype, risk status, or JAK2 mutational status (Table 1).

**Symptom Response**

In patients with available baseline TSS, the proportions of patients with a reduction of at least 50% in the TSS from baseline to week 24 were 33 of 91 (36% [95% CI, 26%-46%]), 31 of 91 (34% [95% CI, 24%-44%]), and 6 of 85 (7% [95% CI, 2%-12%]) in the 400-mg, 500-mg, and placebo groups, respectively. Both active treatment groups showed clinically and statistically significant differences vs placebo on the basis of a step-down procedure for controlling multiplicity of statistical comparison ($P \leq .001$ at a significance level of .025 for each comparison).

In fedratinib-treated patients with baseline TSS greater than 0, median TSS decreased from baseline at 4 weeks, with the benefit continuing to 24 weeks (Figure 3A). The changes in TSS for individual patients at week 24 (baseline TSS > 0) are shown in Figure 3B. Twenty-six patients in the placebo group, vs 14 and 9 in the fedratinib 400-mg and 500-mg groups, showed no improvement in TSS.

**JAK2 Allele Burden**

At baseline, 62 of 96 (65%), 72 of 97 (74%), and 59 of 96 (61%) of patients in the 400-mg, 500-mg, and placebo groups were JAK2 V617F positive. No meaningful changes were observed in allele burden during treatment (median [range] changes at 24 weeks: +0.4% [−99% to 196%], +0.8% [−77% to 115%], and +2% [−74% to 96%] in the 400-mg, 500-mg, and placebo groups, respectively).

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**Table 1. Spleen Responses**

<table>
<thead>
<tr>
<th>Splenic Responsea</th>
<th>Fedratinib 400 mg (n = 96)</th>
<th>Fedratinib 500 mg (n = 97)</th>
<th>Placebo (n = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 24</td>
<td>Confirmed Week 24</td>
<td>Week 24</td>
</tr>
<tr>
<td>All patients, No. (%) [95% CI]</td>
<td>45 (47) [37-57]a</td>
<td>35 (36) [27-46]a</td>
<td>48 (49) [40-59]a</td>
</tr>
<tr>
<td>Baseline platelet count, ×10^3/μL, proportion (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥100</td>
<td>40/82 (49)</td>
<td>32/82 (39)</td>
<td>42/82 (51)</td>
</tr>
<tr>
<td>&lt;100</td>
<td>5/14 (36)</td>
<td>3/14 (21)</td>
<td>6/15 (40)</td>
</tr>
<tr>
<td>Disease subtype, proportion (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary MF</td>
<td>29/62 (47)</td>
<td>21/62 (34)</td>
<td>32/63 (51)</td>
</tr>
<tr>
<td>Post-ET MF</td>
<td>6/10 (60)</td>
<td>5/10 (50)</td>
<td>4/9 (44)</td>
</tr>
<tr>
<td>Post-PV MF</td>
<td>10/24 (42)</td>
<td>9/24 (38)</td>
<td>12/25 (48)</td>
</tr>
<tr>
<td>Risk status, proportion (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>30/57 (53)</td>
<td>23/57 (40)</td>
<td>26/47 (55)</td>
</tr>
<tr>
<td>High risk</td>
<td>15/39 (38)</td>
<td>12/39 (31)</td>
<td>22/50 (44)</td>
</tr>
<tr>
<td>JAK2 mutational status, proportion (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wild type</td>
<td>10/30 (33)</td>
<td>9/30 (30)</td>
<td>8/20 (40)</td>
</tr>
<tr>
<td>Mutant</td>
<td>34/62 (55)</td>
<td>25/62 (40)</td>
<td>37/72 (51)</td>
</tr>
</tbody>
</table>

Abbreviations: ET, essential thrombocythemia; MF, myelofibrosis; PV, polycythemia vera.

*Conversion factor: To convert platelet count to billions per liter, multiply by 1.0.

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a Defined as at least a 35% reduction in spleen volume.

b $P < .001$ vs placebo ($\chi^2$ test).
Safety
Among fedratinib-treated patients, 148 of 193 (77%) completed 24 weeks of treatment (400 mg, 79 of 96 [82%]; 500 mg, 69 of 97 [71%]), compared with 62 of 95 (65%) of placebo-treated patients. Details regarding drug exposure are provided in Table 3 in Supplement 2. A total of 24 (25%) (400 mg), 32 (33%) (500 mg), and 38 (40%) (placebo) patients had discontinued treatment at the analysis cutoff date. The percentages of patients discontinuing because of AEs at any time during the first 24 weeks were 14% (13 of 96), 25% (24 of 97), and 8% (8 of 95) in the 400-mg, 500-mg, and placebo groups, respectively. Thrombocytopenia (7 patients), cardiac failure, vomiting, and diarrhea (4 patients each) were the most common AEs leading to fedratinib discontinuation (eTable 4 in Supplement 2).

The most common hematologic AE was anemia (Table 2). Fedratinib treatment was associated with a decrease in hemoglobin levels, with nadir reached after 12 to 16 weeks (eFigure 1 in Supplement 2). Thereafter, mean hemoglobin levels showed partial recovery in the 400-mg group but not in the 500-mg group. Among 19 patients who were red blood cell transfusion dependent at baseline, 15 became transfusion independent during fedratinib treatment (7 of 8 [400 mg], 5 of 5 [500 mg], and 3 of 6 [placebo]).

Figure 3. Symptom Responses

A. Median percentage change in total symptom score (TSS) to week 24 in the dose groups. Ranges around median values are wide, so error bars are omitted for clarity. B. Percentage change in total symptom score from baseline at week 24 in individual patients, according to dose group. Data are shown for patients with TSS greater than 0 at baseline and TSS data at week 24. MF-SAF indicates Myelofibrosis Symptom Assessment Form.
Thirty of 178 (17%) fedratinib patients and 21 of 92 (23%) placebo patients who were transfusion independent at baseline became transfusion dependent during treatment. Rates of thrombocytopenia, leukopenia, and neutropenia were higher in both fedratinib groups vs placebo (Table 2). Fedratinib discontinuation due to thrombocytopenia was more frequent among patients with baseline platelet levels less than 100 × 10³/μL (31% [400 mg, 5 of 14; 500 mg, 4 of 15] vs <1% [1 of 164] for those with baseline platelet levels ≥100 × 10³/μL).

The most common nonhematologic AEs with fedratinib treatment were diarrhea, vomiting, and nausea (Table 2). Gastrointestinal toxic effects led to fedratinib dose reductions or interruptions in 38 patients (20%) (14 of 96 [15%] 400 mg and 24 of 97 [25%] 500 mg), and permanent discontinuation of fedratinib therapy in 16 patients (8%) (7 [7%] and 9 [9%]). The incidence of gastrointestinal toxic effects was highest during the first cycle of treatment and decreased thereafter (eFigure 2 in Supplement 2).

Infections occurred in 40 patients (42%) (grade 3 or 4, 2 patients [2%]) and 38 patients (39%) (12 patients [12%]) in the 400-mg and 500-mg groups, respectively, compared with 26 patients [27%] (4 patients [4%]) in the placebo group. Urinary tract infections were the most commonly reported (8 patients in each fedratinib group), although no specific class of infection was observed in 10% or more of patients.

The incidence of alanine aminotransferase and aspartate aminotransferase elevations was more frequent with fedratinib treatment than with placebo (Table 2). These elevations were generally mild to moderate, asymptomatic, and reversible with fedratinib dose reduction or interruption. Similarly, increased levels of serum creatinine, amylase, and lipase were also more commonly noted in fedratinib-treated patients (Table 2).

Transformation to acute myeloid leukemia was reported in 1 patient in each of the fedratinib groups and in 2 patients in the placebo group. A total of 24 patients died during the first...
Given the key role played by JAK2-dependent signaling in normal hematopoiesis, it is not surprising that cytopenias are a common adverse effect of JAK inhibitor therapy.9,10,13,14 Accordingly, hemoglobin levels decreased following initiation of fedratinib therapy, and anemia was the most common hematologic toxic effect observed in this study. However, similar to the experience with ruxolitinib wherein the incidence of treatment-emergent anemia is also relatively high,20 hemoglobin levels in the present study showed partial recovery after 16 weeks of fedratinib treatment, albeit in the 400-mg group only, and only 1 patient from each active treatment group discontinued therapy because of anemia. Gastrointestinal toxic effects were frequent, although only 8% of patients discontinued treatment on this basis. Lack of protocol-mandated guidelines for prophylaxis, early recognition, and treatment of gastrointestinal toxic effects at the time of study initiation may have contributed to the high incidence of such events.

During the analysis period of the present study, 1 case of WE and 1 case of encephalopathy of unknown origin were reported. Following database lock, the study sponsor received 2 additional reports of WE, 1 in the present study and 1 in another fedratinib trial. These reports prompted a full clinical hold of the fedratinib program. Subsequently, reports were received of a fourth suspected case in the present study (later confirmed) and 3 additional cases (2 confirmed) in other fedratinib trials. Wernicke encephalopathy is underrecognized in the general population,20 as well as in patients with myeloproliferative neoplasms,21 given that only a minority of patients present with the classic triad of encephalopathy, oculomotor dysfunction, and gait ataxia. Predisposing factors for WE resulting from thiamine deficiency in nonalcoholic patients include malnutrition, recurrent vomiting and/or diarrhea, chemotherapy, renal disease, and magnesium depletion.22 Vomiting (with or without nausea and/or diarrhea) was common among patients who developed encephalopathy while receiving fedratinib in the present study, although similar gastrointestinal events were frequent in patients who received fedratinib across all studies and cannot be considered the dominant contributing factor. Relevant comorbidities observed in some affected patients included weight loss and/or cachexia, hyponatremia, and malnutrition. All 7 confirmed cases of WE noted in the fedratinib program occurred in women, and in every case the event occurred at the 500-mg dose level. Furthermore, in several patients with WE, plasma fedratinib levels when measured early in the study were higher than the mean for the overall study population. Despite this, it was difficult to establish a conclusive link between fedratinib dose level and WE, given that the overall demographic and clinical risk characteristics were not unique to the patients who developed WE and given the variability in drug exposure at a given dose level due to pharmacokinetic differences. Because the primary mechanism for development of WE was not identified, there were insufficient data to conclude that patients receiving fedratinib at doses of 400 mg or less were not at risk of developing WE, particularly given that this AE may not be fully reversible even with timely thiamine therapy. Fedratinib in Patients With Primary or Secondary Myelofibrosis

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Febrtinib has been shown to cross the blood-brain barrier in animal models, and consequently a direct effect of febrtinib on neurologic function, either through JAK inhibition or off-target effects, cannot be excluded.\textsuperscript{23} To date, WE has not been specifically reported in trials with other JAK inhibitors, although it may be relevant that clinical development of the JAK2-selective inhibitor XL019\textsuperscript{24} and the JAK1/JAK2 inhibitor AZD1480\textsuperscript{25} was discontinued as a result of neurologic toxic effects. Furthermore, treatment-emergent peripheral neuropathy has been reported in up to 44% of patients with MF treated with the JAK1/2 inhibitor momelotinib.\textsuperscript{26} Following a thorough risk-benefit analysis, once the cases of WE were recognized, the sponsor decided to permanently discontinue clinical development of febrtinib.

The main limitation of the study was its early termination before sufficient follow-up to allow analysis of progression-free survival or overall survival and other long-term efficacy and safety outcomes. There were also slight imbalances between the treatment groups with regard to baseline disease risk status and median platelet counts.

Conclusions

Febrtinib treatment demonstrated significant clinical benefit in patients with intermediate-2 or high-risk MF. These benefits were offset by a risk of developing encephalopathy, the mechanism and reversibility of which remain to be confirmed.

Invited Commentary

JAK/STAT Pathway Inhibitors and Neurologic Toxicity

Above All Else Do No Harm?

Bart L. Scott, MD; Pamela S. Becker, MD, PhD

Oncologists long ago recognized the fallacy of primum non nocere. The truth is that some harm may be deemed acceptable as long as the perceived benefits have the potential to outweigh the risks. Janus-associated kinase (JAK)/signal transducers and activators of transcription (STAT) pathway inhibitors have demonstrated efficacy in the treatment of myelofibrosis, resulting in reduction of splenomegaly and constitutional symptoms, and improved survival.\(^1\)\(^2\) The COMFORT-I and COMFORT-II trials led to Food and Drug Administration approval for the JAK1/JAK2 inhibitor ruxolitinib for patients with myelofibrosis, and the RESPONSE trial, to approval for patients with polycythemia vera who are unresponsive or intolerant to hydroxyurea therapy. The principal adverse effects of ruxolitinib in the treatment of myelofibrosis include anemia, thrombocytopenia, ecchymosis, dizziness, and headache. A distinct neurological adverse effect, peripheral neuropathy, was reported in up to 44% of patients treated with the JAK1/JAK2 inhibitor momelotinib. In fact, neurologic toxic effects including dizziness, ataxia, aphasia, dysarthria, and amnesia led to termination of the clinical development of the JAK1/JAK2 inhibitor AZD1480.\(^4\)

In this issue of JAMA Oncology, Pardanani and colleagues\(^3\) describe the results of a double-blind, placebo-controlled, randomized, international multicenter clinical trial with a JAK2-selective inhibitor, fedratinib, in patients with primary or secondary myelofibrosis. Although the drug was shown to be effective in reducing spleen size, it was also noted to occasionally exhibit substantial central nervous system (CNS) toxicity. Four patients (2% of those receiving fedratinib) developed Wernicke encephalopathy (WE) in this trial, and an additional 3 patients developed WE in other fedratinib studies. The clinical trial of WE includes ocular signs, cerebellar dysfunction, and confusion, and it is typically due to thiamine deficiency, with higher prevalence in alcoholics. However, treatment with thiamine did not reverse the symptoms in all the cases reported in the randomized trial, unlike the more classic presentation. Other conditions associated with WE listed in the European Federation of Neurological Societies guidelines include cancer, bariatric surgery, hyperemesis gravidarum, and fasting and/or starvation. Although magnetic resonance imaging findings are highly specific and can confirm the diagnosis of WE, the majority of cases are only recognized post mortem.

In summary, the JAK/STAT pathway inhibitors are associated with a myriad of neurological adverse effects, including dizziness, peripheral neuropathy, ataxia, aphasia, dysarthria, amnesia, and now, with fedratinib, Wernicke encephalopathy. Perhaps the relative differences in CNS adverse effects with these medications have more to do with the ability of the agent to cross the blood-brain barrier than any intrinsic differences in the metabolic pathways or mechanisms of action. However, there is 1 report of a JAK2/STAT3 inhibitor causing cell cycle arrest and apoptosis of neural stem cells derived from glioblastoma,\(^5\) suggesting that an active JAK/STAT pathway does exist in the CNS that might be directly affected by such inhibition.

The investigators attempted to identify factors that placed patients at higher risk for development of WE. They observed