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Randomized Trial of Clazosentan in Patients With Aneurysmal Subarachnoid Hemorrhage Undergoing Endovascular Coiling

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Background and Purpose—Clazosentan, an endothelin receptor antagonist, has been shown to reduce vasospasm after aneurysmal subarachnoid hemorrhage (aSAH). CONSCIOUS-3 assessed whether clazosentan reduced vasospasm-related morbidity and all-cause mortality postaSAH secured by endovascular coiling.

Methods—This double-blind, placebo-controlled, phase III trial randomized patients with aSAH secured by endovascular coiling to ≤14 days intravenous clazosentan (5 or 15 mg/h) or placebo. The primary composite end point (all-cause mortality; vasospasm-related new cerebral infarcts or delayed ischemic neurological deficits; rescue therapy for vasospasm) was evaluated 6 weeks postaSAH. The main secondary end point was dichotomized extended Glasgow Outcome Scale (week 12).

Results—CONSCIOUS-3 was halted prematurely following completion of CONSCIOUS-2; 577/1500 of planned patients (38%) were enrolled and 571 were treated (placebo, n=189; clazosentan 5 mg/h, n=194; clazosentan 15 mg/h, n=188). The primary end point occurred in 50/189 of placebo-treated patients (27%), compared with 47/194 patients (24%) treated with clazosentan 5 mg/h (odds ratio [OR], 0.786; 95% CI, 0.479–1.289; *P*=0.340), and 28/188 patients (15%) treated with clazosentan 15 mg/h (OR, 0.474; 95% CI, 0.275–0.818; *P*=0.007). Poor outcome (extended Glasgow Outcome Scale score ≤4) occurred in 24% of patients with placebo, 25% of patients with clazosentan 5 mg/h (OR, 0.918; 95% CI, 0.546–1.544; *P*=0.748), and 28% of patients with clazosentan 15 mg/h (OR, 1.337; 95% CI, 0.802–2.227; *P*=0.266). Pulmonary complications, anemia, and hypotension were more common in patients who received clazosentan than in those who received placebo. At week 12, mortality was 6%, 4%, and 6% with placebo, clazosentan 5 mg/h, and clazosentan 15 mg/h, respectively.

Conclusions—Clazosentan 15 mg/h significantly reduced postaSAH vasospasm-related morbidity/all-cause mortality; however, neither dose improved outcome (extended Glasgow Outcome Scale).

Clinical Trial Registration—URL: http://clinicaltrials.gov. Unique identifier: NCT00940095.

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Key Words: aneurysmal subarachnoid hemorrhage ■ clazosentan ■ CONSCIOUS-3 ■ phase III ■ placebo-controlled ■ randomized ■ endovascular coiling

Angiographic vasospasm is an important cause of mortality and disability following aneurysmal subarachnoid hemorrhage (aSAH).[1] Vasospasm contributes to delayed ischemic neurological deficits (DIND) that occur in up to 40% of aSAH cases, and half of patients with DIND develop ischemic infarctions.[2] As vasospasm after aSAH is unpredictable, common, difficult to manage, and associated with poor outcome, prevention is a highly desired management strategy;

prophylactic nimodipine is widely used, although its efficacy is limited.[3]

Clazosentan is a selective endothelin receptor antagonist, which was investigated for prevention of angiographic vasospasm in patients with aSAH in the phase IIb CONSCIOUS-1 (Clazosentan to Overcome Neurological Ischemia and Infarct Occurring After Subarachnoid Hemorrhage) study.[4] In CONSCIOUS-1, clazosentan (1, 5, and 15 mg/h doses)
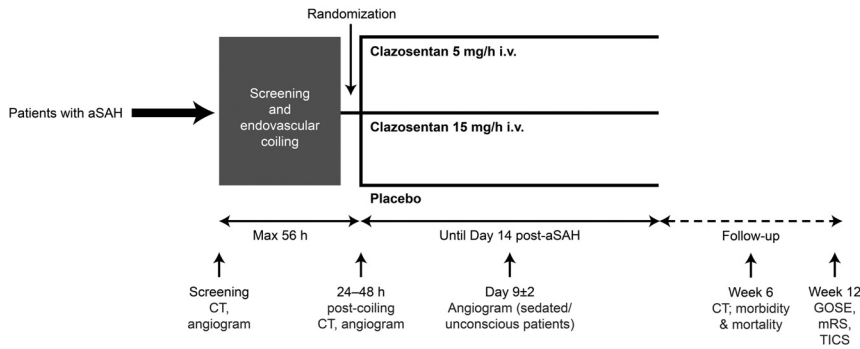
Figure 1. Study design. aSAH indicates aneurysmal subarachnoid hemorrhage; mRS, modified Rankin Scale; GOSE, Assessment of Glasgow Outcome Scale, extended version.

produced a dose-dependent reduction in moderate or severe angiographic vasospasm, with a 65% relative risk reduction with the highest dose ($P<0.0001$); this suggests that endothelin-1 plays an important role in the pathogenesis of angiographic vasospasm.[5,6]

On the basis of CONSCIOUS-1, 2 phase III studies (CONSCIOUS-2 and CONSCIOUS-3) were designed to assess the effect of clazosentan on the incidence of cerebral vasospasm-related morbidity and all-cause mortality, and clinical outcome, in patients with aSAH. In CONSCIOUS-2, patients who had their aneurysm secured by clipping received placebo or clazosentan 5 mg/h; however, no significant effect was seen with clazosentan.[7,8] Use of 15 mg/h clazosentan in CONSCIOUS-3 was based on CONSCIOUS-1, where the effect of clazosentan was less with 5 mg/h in patients with aneurysms secured by coiling than by clipping, as explained in detail previously.[4,8]

CONSCIOUS-3 was initiated on July 10, 2009. Recruitment was halted prematurely (October 2010) after completion of CONSCIOUS-2, in part because the 5 mg/h dose did not achieve its primary end point in clipped patients; also, this dose had a similar relative risk reduction in angiographic vasospasm in CONSCIOUS-1 as did the highest dose (15 mg/h) being tested in CONSCIOUS-3 in coiled patients.[7] In addition, stopping the study was recommended by the Data and Safety Monitoring Board.

Methods

This was a phase III, prospective, multicenter, international, randomized, double-blind, placebo-controlled trial (NCT00940095; Figure 1). Eligible patients were age 18 to 75 years with aSAH caused by ruptured saccular aneurysm, which was secured by endovascular coiling; they had any thick clot (short axis ≥4 mm) on baseline computed tomographic (CT) scan, World Federation of Neurological Surgeons (WFNS) grades I–IV before coiling procedure, and were able to start study drug within 56 hours of aneurysm rupture. Women of childbearing potential were included only following a negative pregnancy test. Written informed consent was obtained.

Exclusion criteria included: giant aneurysms (largest diameter ≥25 mm); intraventricular or intracerebral blood in the absence of subarachnoid blood; vasospasm on precoiling angiogram; a major complication during coiling procedure; current ruptured aneurysm previously secured (successfully or not) by clipping; missing digital subtraction angiography at the end of the coiling procedure; or several aneurysms, among which the ruptured one was not identifiable with certainty and that were not all secured during the coiling procedure. Intravenous nimodipine or intravenous nicardipine within 4 hours, or intravenous fasudil within 24 hours, before study drug initiation, was not permitted.

After coiling, patients were randomized (1:1:1) to receive intravenous clazosentan (5 or 15 mg/h) or placebo for up to 14 days postaSAH; the investigator completed a randomization form on an interactive, independent, Web-response system, which assigned a randomization number for each patient according to a predefined scheme. Randomization was stratified by site. The randomization code was only available to authorized individuals with no involvement in study conduct or analysis until the time of unblinding.

Sites managed patients according to guidelines developed for the study and were consistent with published recommendations.[3,8] Early detection and management of lung complications were addressed. Drugs or procedures not considered standard care were prohibited. Oral, but not intravenous, nimodipine was permitted.

The study protocol was approved by local Institutional Review Boards and was completed in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki, and with the laws and regulations of the country in which the clinical research was conducted.

Assessments

Before the coiling procedure, all patients underwent CT scan and digital subtraction angiography or CT angiography. Additional CT scans were performed 12 to 48 hours after the coiling procedure (a 12-hour postprocedure CT scan was mandatory for sedated patients; up to 48 hours for neurologically assessable patients), at discharge (unless this occurred after the 6-week visit; a scan at 14 days postaSAH was also acceptable), 6 weeks after aSAH, and in cases of worsening neurological condition or DIND. Angiograms were performed after coiling to document the completeness of occlusion, or with symptoms suggestive of DIND and/or cerebral infarct. In patients who were sedated or in whom neurological scales were not assessable, an angiogram was performed at 9 ± 2 days postaSAH. When neurological worsening occurred, investigators performed investigations to determine whether medical complications (including, but not limited to: hydrocephalus, neurological or systemic infection, hypotension, adult respiratory distress syndrome, pulmonary edema, renal failure, multiorgan failure, metabolic disorders, myocardial infarction, diffuse brain swelling, intracerebral hemorrhage, seizures, and/or rebleeding) were the primary or contributing cause.

After treatment, neurological assessments were performed every 6 hours until day 14 (irrespective of study drug duration) using the modified Glasgow Coma Scale and the abbreviated National Institutes of Health Stroke Scale.[9,10] Assessment of Glasgow Outcome Scale, extended version (GOSE),[11] and modified Rankin Scale[12] were carried out at week 12 by trained centralized interviewers via a structured telephone interview.

Clinical and imaging data were reviewed by a centralized Critical Events Committee.[8] The Critical Events Committee included an image review committee of neuroradiologists, who provided independent evaluation of CT scans and angiograms (each brain image was reviewed by 2 neuroradiologists, with a third adjudicating if discrepancies occurred), and a Clinical Review Committee (CRC; cases were reviewed by 2 neurosurgeons and 1 neurointensivist from a pool of 9 CRC members; unanimity or consensus agreement was required). Consensus meetings were held to discuss cases where
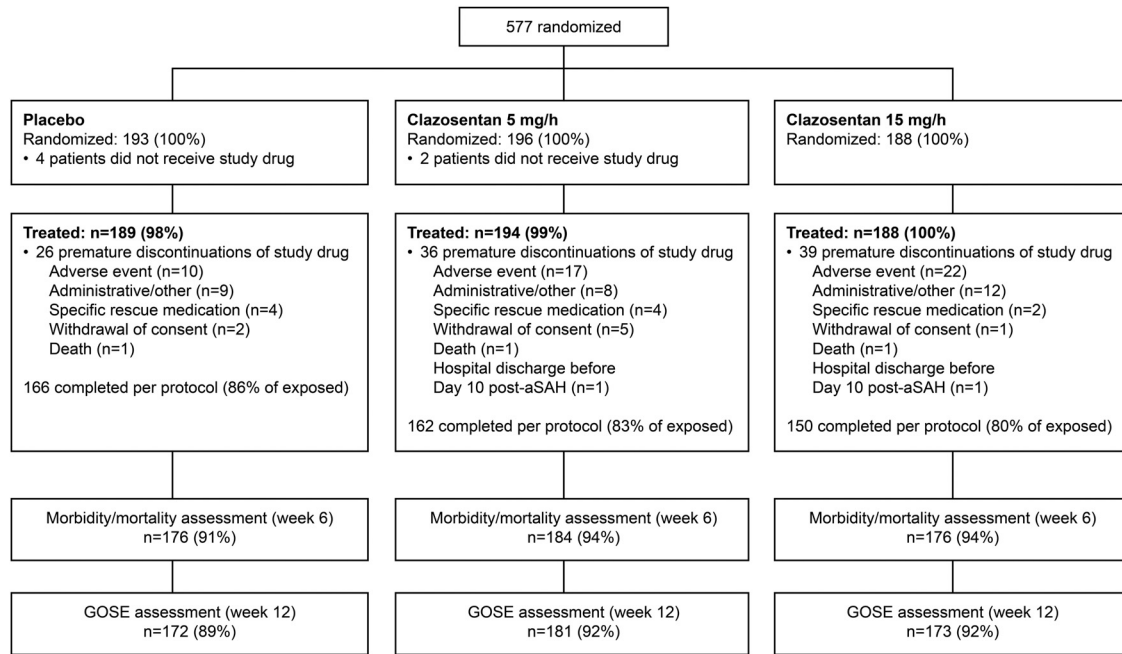
Figure 2. Participant flow. aSAH indicates aneurysmal subarachnoid hemorrhage; GOSE, Assessment of Glasgow Outcome Scale, extended version.

there was disagreement; if unanimity was not achieved after the consensus meeting, the CRC chairman (or should the chairman already be involved in the primary review, the deputized neurointensivist) adjudicated the case, made the final assessment, and documented the assessment in a CRC adjudication form. The CRC made the final assessment via a Web-based system, which provided electronic access to the brain images, whereas the image review committee reported on the clinical data for each patient under review. Operating through a charter, the CRC considered whether events for each component of the primary efficacy end point were met, and also gauged the contribution of vasospasm to poor clinical outcome (GOSE≤4) at week 12.

The primary efficacy end point assessed vasospasm-related morbidity and all-cause mortality within 6 weeks postaSAH, as defined by at least 1 of: death; vasospasm-related cerebral infarction (where vasospasm was the primary cause or a relevant contributing factor); DIND caused by vasospasm (where vasospasm was the primary cause or a relevant contributing factor); or neurological signs or symptoms, in the presence of a positive angiogram, leading to rescue therapy. DIND was defined as a decrease of ≥2 modified Glasgow Coma Scale points or an increase of ≥2 points on the abbreviated National Institutes of Health Stroke Scale lasting for ≥2 hours. For patients in whom neurological scales were not assessable, DIND was defined as administration of valid rescue therapy, which included initiation or increase in dose of an intravenous vasopressor with or without fluid therapy, intra-arterial vasodilator, or balloon angioplasty.

The main secondary end point was the GOSE, dichotomized as good (>4) or poor (≤4), at week 12. Additional secondary end points included occurrence of the individual components of the composite primary end point and total volume of all new or worsened cerebral infarcts at week-6 postaSAH. Planned supplementary analyses assessed the impact of subgroups (WFNS grade, clot size, age, and sex) on the primary and main secondary end point. Safety end points included death up to week 12 and treatment-emergent adverse events (AE).

Statistical Analyses

Assuming a relative risk reduction of 30% (odds ratio [OR], 0.603) with at least 1 dose of clazosentan (5 or 15 mg/h) and a placebo event rate of 35%, sample size of 1470 was calculated. A 2-group, continuity-corrected Chi-square test had approximately 90% power

to reject the null hypothesis (comparison-wise, 2-sided, error rate of 2.5%). Assuming that 2% of enrolled patients would not receive treatment, the planned sample size was 1500 patients.

This trial was halted prematurely after nonsignificant results from CONSCIOUS-2 became apparent,[7] and after recommendations from the Data and Safety Monitoring Board; as such, planned confirmatory analyses were not performed, and formal testing of the global null hypothesis was not carried out. Treatment effect of the 2 clazosentan doses was tested in an exploratory manner using logistic regression adjusting for WFNS grade (≤II, >II) assessed at admission, and was described using OR with corresponding 95% CIs. The incidence rates of the individual components of the composite primary end point are displayed together with the exact 95% CIs, and the relative risk reduction in each dose group with the corresponding 95% CIs (normal approximation). Dichotomized GOSE was analyzed using the same statistical methods as for the primary end point.

In the case of a missing assessment for the morbidity component of the primary end point, or missing information on the vital status, the worst case (ie, presence of vasospasm-related morbidity and mortality) was assumed. For GOSE, if no score was available, a score of 5 was assigned when there was no clinical evidence of previous neurological impairment, and a score of 3 was given in any other situation when a patient was alive at week 12. Baseline demographics were analyzed using descriptive statistics; all values are mean and SD, or percent.

Efficacy analyses were based on the full analysis set, defined as all treated patients (ie, all those randomized and who started infusion). Patients exposed to treatment, with at least 1 postbaseline safety measurement, were included in the safety data set.

Additional information on the rationale, study design, and methodology has been published.[8]

Results

Baseline Characteristics

CONSCIOUS-3 was conducted between July 10, 2009 and January 26, 2011 (last patient, last visit) at 106 centers in 27 countries; 577 of 1500 patients (38% of the planned sample size) had been randomized at the time of study termination, and 571 patients (placebo, n=189; clazosentan 5 mg/h,

Table 1.   Baseline Demographic and Disease Characteristics (All-Treated)

Characteristic	Placebo n=189	Clazosentan 5 mg/h n=194	Clazosentan 15 mg/h n=188	Total n=571
Men	55 (29)	59 (30)	58 (31)	172 (30)
Mean (SD) age, y	54 (11)	52 (11)	53.6 (11)	53.1 (11)
Age range, y	23 to 75	23 to 75	19 to 76	19 to 76
WFNS admission grade				
Grade I	96 (51)	99 (51)	103 (55)	298 (53)
Grade II	56 (30)	48 (25)	53 (28)	157 (28)
Grade III	6 (3)	5 (3)	3 (2)	14 (3)
Grade IV	24 (13)	37 (19)	26 (14)	87 (15)
Grade V	5 (3)	4 (2)	2 (1)	11 (2)
Motor deficit present at admission	19 (10)	21 (11)	18 (10)	58 (10)
No. of aneurysms secured (ruptured and unruptured)				
1	183 (97)	183 (94)	177 (94)	543 (95)
2	6 (3)	10 (5)	10 (5)	26 (5)
>2	0	1 (<1)	1 (<1)	2 (<1)
Size of coiled ruptured aneurysm				
≤15 mm	183 (98)	193 (100)	181 (97)	557 (98)
>15 mm	5 (3)	1 (<1)	6 (3)	12 (2)
Key locations of ruptured aneurysms				
Supraclinoid ICA	19 (10)	22 (11)	31 (17)	72 (13)
MCA	16 (9)	19 (10)	23 (12)	58 (10)
ACA	10 (5)	21 (11)	13 (7)	44 (8)
ACoA	74 (39)	62 (32)	62 (33)	198 (35)
PCoA	31 (16)	39 (20)	35 (19)	105 (18)
Distal VA	11 (6)	5 (3)	8 (4)	24 (4)
Basilar artery	22 (12)	22 (11)	15 (8)	59 (10)
Clot size at baseline				
Diffuse thick	116 (61)	118 (61)	111 (59)	345 (61)
Local thick	58 (31)	54 (28)	56 (30)	168 (30)
Diffuse thin	12 (6)	17 (9)	17 (9)	46 (8)
Local thin	3 (2)	2 (1)	4 (2)	9 (2)
Unable to assess	0	2 (1)	0	2 (<1)
Common CT findings at baseline				
Intraventricular hemorrhage	162 (85.7)	161 (83.4)	156 (83.0)	479 (84.0)
Hydrocephalus	122 (64.6)	117 (60.6)	115 (61.2)	354 (62.1)
Intraparenchymal hemorrhage	35 (18.5)	36 (18.7)	32 (17.0)	103 (18.1)

Values are n (%) unless otherwise stated.

WFNS indicates World Federation of Neurological Surgeons; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; ACoA, anterior communicating artery; PCoA, posterior communicating artery; CT, computed tomography; VA, vertebral artery.

n=194; clazosentan 15 mg/h, n=188) had received treatment. Participant flow is shown in Figure 2. AEs were the most common reason for discontinuation of study drug in all arms; administrative/other reasons included: stopping drug by mistake, early hospital discharge, and other technical/logistical reasons. Demographic and clinical characteristics were similar across all groups at baseline (Table 1).

Patients received study treatment for a mean±SD of 12±2 days, 12±3 days, and 12±3 days in the placebo, clazosentan 5 mg/h, and 15 mg/h groups, respectively; treatment commenced 18±12 hours, 20±12 hours, and 18±12 hours, respectively, after aneurysm coiling. Oral nimodipine was administered to 94% (placebo), 95% (clazosentan 5 mg/h), and 95% (clazosentan 15 mg/h) of patients.

Data for the primary end point were substituted for 1 patient with missing data in the clazosentan 5 mg/h group. For the GOSE secondary end point, 4 patients had data substituted in the placebo group (2 patients, GOSE score 3; 2 patients, GOSE score 5), 6 in the clazosentan 5 mg/h group (6 patients, GOSE score 3; 0 patients, GOSE score 5), and 3
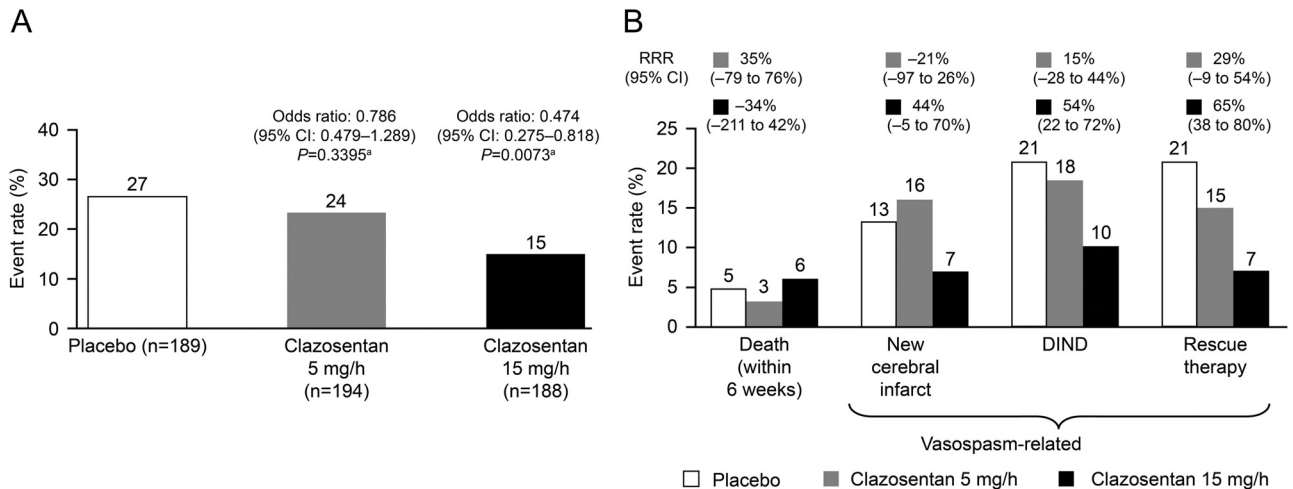
Figure 3. Event rate (%) for: **A**, all-cause mortality and vasospasm-related morbidity at 6 weeks (all-treated, end point substituted); and **B**, each of the individual components of the primary composite end point (all-treated, end point substituted; planned analysis, secondary end point). DIND indicates delayed ischemic neurological deficits.

patients in the clazosentan 15 mg/h group (2 patients, GOSE score 3; 1 patient, GOSE score 5).

Efficacy

Vasospasm-related morbidity and all-cause mortality occurred in the all-treated population in 50/189 of patients (27%) in the placebo group compared with 47/194 patients (24%) and 28/188 patients (15%) in the 5 and 15 mg/h clazosentan groups, respectively; a significant improvement was seen with 15 mg/h clazosentan (OR, 0.474; 95% CI, 0.275–0.818; $P=0.007$), but not with 5 mg/h (OR, 0.786; 95% CI, 0.479–1.289; $P=0.340$; Figure 3A).

Event rates in the all-treated population for each individual component of the composite end point are shown in Figure 3B; a higher proportion of patients required rescue therapy in the placebo group (21%) compared with clazosentan 5 mg/h (15%) and 15 mg/h (7%). DIND was significantly reduced with clazosentan 15 mg/h (10%) as compared with placebo (21%). Rates of vasospasm-related new cerebral infarcts were 13%, 16%, and 7% with placebo, clazosentan 5 mg/h, and clazosentan 15 mg/h, respectively. There was no effect of treatment on mortality within 6 weeks (Figure 3B).

Poor functional outcome (GOSE score ≤4; end point substituted) occurred in 24% of patients in the all-treated placebo group compared with 25% (OR, 0.918; 95% CI, 0.546–1.544; $P=0.748$) and 28% (OR, 1.337; 95% CI, 0.802–2.227; $P=0.266$) in the clazosentan 5 mg/h and clazosentan 15 mg/h groups, respectively.

In the placebo group, the Critical Events Committee-confirmed new cerebral infarct median total volume at week 6 was 14.44 cm^3 (range, 0.44–376.68 cm^3) compared with 8.26 cm^3 (range, 0.12–553.59 cm^3) and 8.26 cm^3 (range, 0.05–794.47 cm^3) in the clazosentan 5 mg/h and clazosentan 15 mg/h groups, respectively.

Results from planned subgroup analyses of vasospasm-related morbidity and all-cause mortality according to sex, age, baseline clot size, and WFNS grade at baseline are shown in Figure 4.

Safety and Tolerability

During the study, 91%, 86%, and 92% of patients receiving placebo, clazosentan 5 mg/h, and clazosentan 15 mg/h, respectively, experienced ≥1 AE. Severe AE incidence was 25% (placebo) 28% (clazosentan 5 mg/h), and 29% (clazosentan 15 mg/h); the rate of AEs considered by the investigator to be related to treatment was 24%, 34%, and 37%, respectively. A higher proportion of patients receiving clazosentan (5 mg/h and 15 mg/h) prematurely discontinued treatment compared with the placebo group; the main reason for discontinuation from study drug was AEs (Figure 2). Incidence of AEs of specific interest is shown in Table 2. Compared with placebo, pulmonary complications, hypotension, and anemia were more common with clazosentan; hypotension was more frequent in the 15 mg/h dose group than in the 5 mg/h dose group.

Of treated patients, 6% (placebo), 4% (clazosentan 5 mg/h), and 6% (clazosentan 15 mg/h) died within 12 weeks of aSAH; causes of death reported for >1% of patients in any group were cerebral infarction (2%, <1%, and 3%), cerebrovascular spasm (2%, <1%, and <1%), and brain edema (2%, <1%, and <1%), respectively.

Discussion

This randomized, double-blind, placebo-controlled, phase III trial investigated vasospasm-related morbidity and all-cause mortality with clazosentan 5 or 15 mg/h administered for up to 14 days in patients with aSAH secured by endovascular coiling. The trial was halted early because of nonsignificant findings with clazosentan 5 mg/h in the parallel CONSCIOUS-2 clipping study.[7] For the lower dose, data from the present study support findings from CONSCIOUS-2, ie, clazosentan 5 mg/h had no significant effect on vasospasm-related morbidity or all-cause mortality 6 weeks postaSAH (composite primary end point) or functional outcome, but the 15 mg/h of clazosentan did significantly reduce vasospasm-related morbidity or all-cause mortality within 6 weeks postaSAH. There was a marked reduction in rescue therapy with clazosentan 15 mg/h, likely because of the corresponding reduction of DIND. However, the
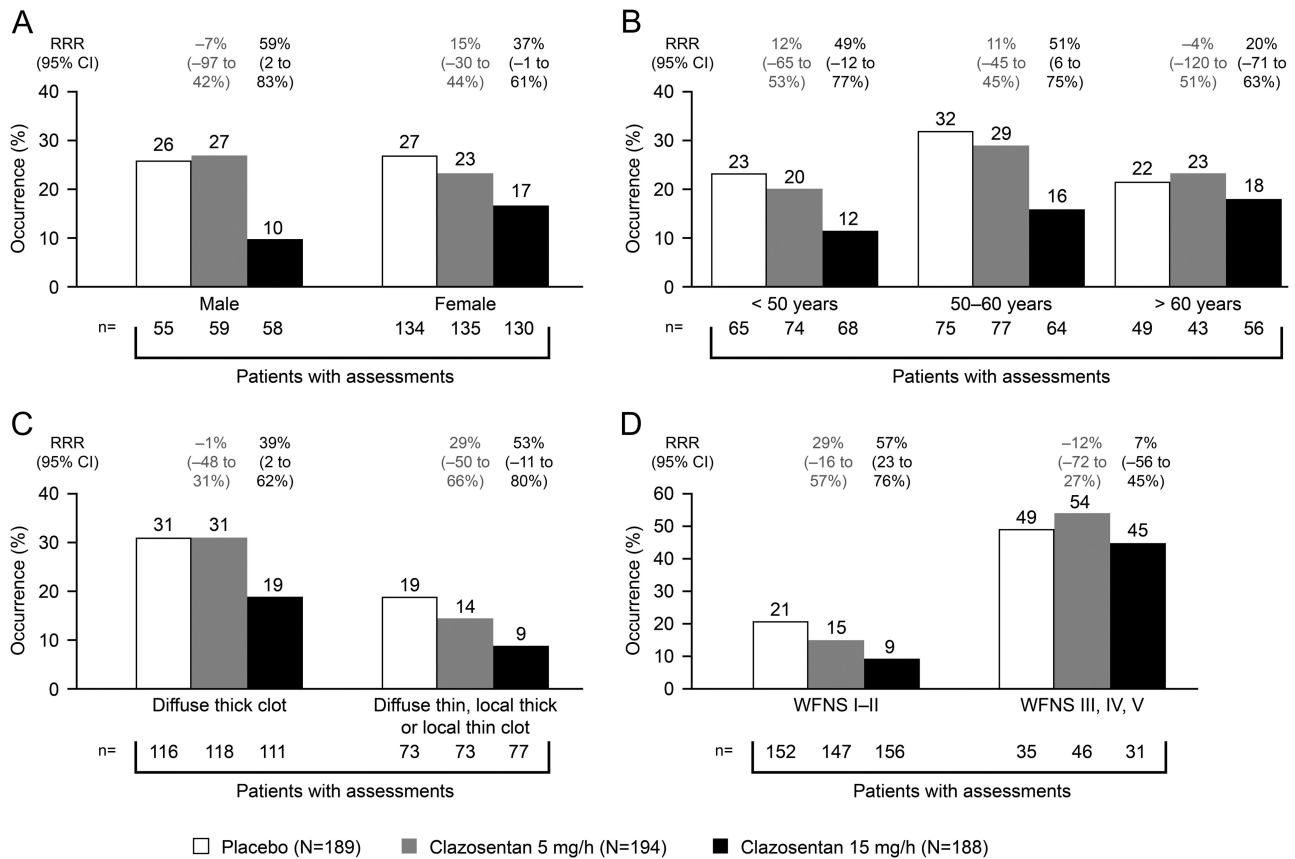
Figure 4. Effect of **A**, sex, **B**, age, **C**, baseline clot size, and **D**, WFNS grade at baseline on occurrence (%) of vasospasm-related morbidity and all-cause mortality (all-treated; end point substituted).

reduction in the primary end point did not lead to improved outcome at week 12, as measured by GOSE.

Despite an impressive and significant effect on vasospasm-related ischemic events, some explanations for the lack of effect of 15 mg/h clazosentan dose on GOSE can be hypothesized. The most important is that because of early stopping of this trial, the planned number of patients was not enrolled;

Table 2. Adverse Events of Specific Interest Occurring Up to 1 Day After Study Drug Discontinuation and Up to Week 6 Post aSAH (Safety Population)

Grouping of MedDRA Terms; Patients With ≥1 AE n (%)	Placebo n=189	Clazosentan 5 mg/h n=194	Clazosentan 15 mg/h n=188
Lung complications	40 (21)	70 (36)	70 (37)
Lung complications related to pulmonary edema	16 (9)	37 (19)	32 (17)
Hypotension	13 (7)	21 (11)	30 (16)
Hepatobiliary events	35 (19)	39 (20)	28 (15)
Anemia	18 (10)	25 (13)	24 (13)
Rhythm/conduction disorders	23 (12)	16 (8)	20 (11)
Cerebral hemorrhage	5 (3)	7 (4)	7 (4)
Cardiac ischemic events	3 (2)	8 (4)	6 (3)
Eye disorders	0	0	6 (3)

aSAH indicates aneurysmal subarachnoid hemorrhage; MedDRA, medical dictionary for regulatory activities; AE, adverse events.

therefore, its low statistical power may explain the lack of effect observed with 15 mg/h of clazosentan. The possibility exists that the tolerability profile of the drug negated any therapeutic benefit, or that interaction with oral nimodipine contributed to AEs. For example, intravenous nimodipine is associated with low blood pressure,[13] and it is possible that oral administration of nimodipine with clazosentan may have contributed to the higher rate of hypotension in the active treatment groups compared with placebo. Microthromboembolism, microcirculatory dysfunction, cortical spreading ischemia, and delayed neuronal injury have been postulated to contribute to DIND and outcome, and might not be prevented by clazosentan.[1,14–16] Indeed, although clazosentan has been shown to be effective on large-artery vasospasm,[4] little is known about its effect on microcirculation. Rescue therapy may provide a positive effect on outcome that obscures the benefit of clazosentan. Assuming rescue therapy prevents ischemia from vasospasm and improves clinical outcome, the 3-fold-more frequent use of rescue therapy (composite end point component) in the 15 mg/h group compared with the placebo arm could account for the lack of treatment effect observed on GOSE.[17–19]

The results from CONSCIOUS-2 and CONSCIOUS-3 raised questions regarding the efficacy of endothelin-1 antagonists in preventing vasospasm; however, the possibility remains that these agents may have clinical utility as part of a complex treatment regimen for aSAH. For future trials, investigating different (eg, shorter) durations of clazosentan

administration could be considered to attempt to separate the positive effects from any deleterious consequences of treatment.[20,21] In addition, restricting the use of nimodipine concomitantly with clazosentan may help to determine the relevant contributions of each agent to changes in cerebral vasospasm-related morbidity and all-cause mortality, and in functional outcome. Initiating surgical procedures as early as possible, and ensuring that this is coupled with the appropriate pharmacological interventions, remains the current focal points for treatment of patients with aSAH.

Adverse events (lung complications, hypotension, and anemia) were consistent with those observed in CONSCIOUS-1 and CONSCIOUS-2; it is likely that these side effects could be managed using appropriate adjunct therapy. There were no new safety concerns in this study compared with in the previous 2 trials. An equal proportion of patients in the clazosentan 15 mg/h and placebo groups died during the study, with cerebral infarction being the most frequently reported primary cause of death in these groups.

Conclusions

Clazosentan 15 mg/h reduced cerebral vasospasm-related morbidity and all-cause mortality. However, clazosentan did not improve outcome, possibly because of increased rescue therapy in the placebo group. Compared with placebo, pulmonary complications, anemia, and hypotension were more common in patients receiving clazosentan. Although clazosentan does not appear to provide benefit in clinical outcome, it prevented DIND and rescue therapy, which could be further investigated based on analysis of the patients treated in the clazosentan studies.

Disclosures

Dr Macdonald receives grant support from Actelion Pharmaceuticals Ltd, and is a stockholder of Edge Therapeutics. Drs Macdonald, Higashida, Keller, Mayer, Molyneux, Raabe, Vajkoczy, Wanke, and Kassell are consultants for Actelion Pharmaceuticals Ltd. Dr Keller has been on speakers' bureaus for Zoll Medical, received research grants from Swiss National Science Foundation, and is a stockholder in NeMoDevices. Dr Molyneux has been a consultant for Micrus Endovascular, and receives grant support from the Medical Research Council UK and Cerecyte Coil Trial Micrus Inc. Ms Bach and Drs Frey, Nowbakht, and Roux are employees and stockholders of Actelion Pharmaceuticals Ltd.

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