DOSING REGIMEN AND THE FREQUENCY OF MACULAR HEMORRHAGES IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION TREATED WITH RANIBIZUMAB

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Purpose: The purpose of this study was to investigate if monthly intravitreal ranibizumab decreases risk of macular hemorrhages in patients with choroidal neovascularization secondary to age-related macular degeneration.

Methods: Incidences of macular hemorrhages in the control and ranibizumab groups from three, multicenter, randomized, clinical trials (MARINA, ANCHOR, and PIER) were compared. Two time intervals (Months 0–3 and 5–17) were evaluated to account for transition from monthly to quarterly injections in PIER. Time interval after Month 17 was excluded because of crossover from control to active treatment in all trials.

Results: Months 0–3: All trials showed higher incidence rates of hemorrhages in control compared with ranibizumab groups (ANCHOR: photodynamic therapy [27.3%], 0.3 mg [8.0%], 0.5 mg [8.6%]; MARINA: sham [18.6%], 0.3 mg [8.8%], 0.5 mg [8.8%]; and PIER: sham [16.1%], 0.3 mg [3.4%], 0.5 mg [3.3%]). In ANCHOR and MARINA, data of Months 5–17 showed higher incidence rates in control compared with monthly ranibizumab groups (ANCHOR: photodynamic therapy [47.8%], 0.3 mg [12.5%], 0.5 mg [12.3%]; and MARINA: sham [38.0%], 0.3 mg [13.2%], 0.5 mg [13.0%]), but this was not seen for quarterly ranibizumab groups in PIER (sham [22.4%], 0.3 mg [23.7%], 0.5 mg [28.3%]).

Conclusion: Treatment with monthly intravitreal ranibizumab was associated with reduced risk of new macular hemorrhages when compared with photodynamic therapy (ANCHOR) or sham (MARINA and PIER). There was no difference between PIER quarterly ranibizumab-treated and sham patients.

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Macular hemorrhages are considered to be a hallmark of neovascular age-related macular degeneration (AMD). Reading centers use the presence of subretinal hemorrhages or hemorrhagic pigment epithelial detachments as a criteria for the presence of choroidal neovascularization[1] when grading fundus photographs of patients with AMD in the absence of other imaging modalities such as fluorescein angiography or optical coherence tomography. Even intraretinal hemorrhages can be a sign of serious progression because they have been associated with the early stages of retinal angiomatous proliferation/type 3 neovascularization.[2] Overall, macular hemorrhages are considered to be a sign of disease activity and, when occupying larger areas or located in the subfoveal region, they are usually associated with a poor visual prognosis in a majority of cases.[3–5] Therefore, prevention or suppression of hemorrhagic incidences should help arrest vision loss.

Intravitreal antivascular endothelial growth factor therapy has become the new standard of care for treating neovascular AMD. This therapy has not only changed the management of neovascular AMD but also, for the first time, improved visual function and limited disease activity in the majority of patients for at least two years.[6,7] Thus, it seems reasonable to believe that

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frequent treatment could also potentially limit the occurrence of macular hemorrhages in these patients.

The aim of this exploratory analysis of the data from three Phase 3 clinical trials was to investigate if monthly treatment with intravitreal ranibizumab (Lucentis; Genentech Inc., South San Francisco, CA) decreases the risk of new macular hemorrhages in patients with choroidal neovascularization secondary to AMD.

Material and Methods

An exploratory analysis was conducted using the 2-year safety data from patients enrolled in three, Phase 3, randomized, controlled, multicenter, clinical trials: MARINA,[6] ANCHOR,[7,8] and PIER.[9] Safety-evaluable population included all patients who received at least one study treatment.

Treatment and Follow-up

In MARINA, patients were randomized to sham control or monthly intravitreal ranibizumab injections of 0.3 mg or 0.5 mg. Patients in the ANCHOR study were assigned to verteporfin photodynamic therapy (PDT) (plus monthly sham injections) control or monthly intravitreal ranibizumab injections of 0.3 mg or 0.5 mg (plus sham PDT with saline infusion). In PIER, patients were randomized to sham control or intravitreal ranibizumab injections of 0.3 mg or 0.5 mg. Patients received 3 initial monthly treatments of their assigned dose followed by treatment every 3 months.

In all 3 studies, patients were examined at screening and Day 0. In MARINA and ANCHOR, patients were seen at Day 7 and then monthly from Month 1 through Month 24. In PIER, patients were examined monthly through Month 3 and quarterly starting at Month 5 through Month 23 with additional visits at Months 12 and 24. There was no Month 4 visit in the PIER study. At all study visits, patients were evaluated using Early Treatment Diabetic Retinopathy Study protocol–based best-corrected visual acuity, slit-lamp examination, intraocular pressure measurement, and dilated binocular indirect and high-magnification ophthalmoscopy. Adverse events were collected at every visit except at screening. Fluoroscein angiography and fundus photography were performed at screening and at Months 3, 6, 12, and 24 in MARINA, every 3 months starting at screening up to 24 months in ANCHOR, and at screening and at Months 3, 5, 8, 12, and 24 in PIER. In MARINA and ANCHOR, optical coherence tomography was done at select sites at Days 0 and 7 as well as at Months 1 and 12. In PIER, optical coherence tomography was done at select sites at Day 0 and at Months 1, 2, 3, 5, 8, and 12.

Data Collection

The incidences of new macular hemorrhages detected during these studies were identified based on verbatim reports by the study investigators. All verbatim adverse event descriptions coded to the MEDDRA (Medical Dictionary of Regulatory Activities) preferred term: ''RETINAL HEMORRHAGE'' in the databases were reviewed by the authors (I.B., K.B.F., and N.S.) and reclassified to three categories (''Yes,'' ''Maybe,'' and ''No'') on whether they were macular hemorrhages. Only events coded with ''Yes'' or ''Maybe'' were included in the final analysis (Table 1).

To account for the transition from monthly injections to quarterly injections in the PIER trial after 3 months, the number of events in all studies was evaluated for 2 time intervals: 0 to 3 months (during monthly injections in MARINA, ANCHOR, and PIER) and 5 to 17 months (during monthly injections in MARINA and ANCHOR and quarterly injections in PIER). The 5- to 17-month time interval was further broken down into quarterly intervals: 5 to <8 months, 8 to <11 months, 11 to <14 months, and 14 to 17 months. The time interval between 3 and 5 months

Table 1. Included cases for ''macular hemorrhage'' based on investigator verbatim report coded to the MedDRA (Medical Dictionary for Regulatory Activities) preferred term: ''RETINAL HEMORRHAGE''

New subretinal hemorrhage
Punctate hemorrhage – subretinal
Hemorrhagic pigment epithelial detachment
Peripapillary subretinal hemorrhage
Recurrent subretinal hemorrhage
Worsening of subretinal macular hemorrhage
Macular dot-blot hemorrhage

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The study protocols of the ANCHOR, MARINA, and PIER trials (primary reports of safety and efficacy published previously[6 9]) were approved by the Institutional Review Board, National Competent Authority, or Ethics Committee at each participating clinical center before the start of the study. All US sites were compliant with the Health Insurance Portability and Accountability Act of 1996. The three studies are registered at ClinicalTrials.gov (ANCHOR ID No. = NCT0061594; MARINA ID No. = NCT00056836; PIER ID No. = NCT00090623). Before determination of their full eligibility for enrollment, all patients provided written informed consent for their study participation.

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was excluded because there was no Month 4 study visit in the PIER trial. The time interval after Month 17 was excluded because control patients remaining in the studies were allowed to "crossover" to receive ranibizumab in all 3 studies, and many patients switched to monthly 0.5 mg during this period in PIER. However, all adverse events occurring after the crossover were excluded from the analysis.

Statistical Analysis

Incidences of macular hemorrhages were compared using Pearson chi-square or Fisher exact test (when expected cell counts <5) for treatment comparisons within each study as well as cross-study comparisons within each treatment group. These cross-study comparison tests were performed not for formal comparison but for hypothesis generation only. Statistical significance was defined as $P < 0.05$; although in an exploratory analysis, it is particularly important to consider the risks of false conclusions due to multiple comparisons. All statistical analyses were carried out using SAS software v9.1 (SAS Inc, Cary, NC).

Subgroup Analyses

The influence of selected variables was explored in three separate subgroup analyses comparing the incidences of macular hemorrhages: 1) by baseline angiographic lesion composition, presence of classic (either predominantly classic or minimally classic) versus occult lesions in MARINA and PIER; 2) by baseline presence or absence of anticoagulation/platelet inhibitors; and 3) by baseline presence or absence of blood on fluorescein angiography.

Results

A total of 1,315 patients receiving at least 1 study treatment were analyzed from the 3, randomized, controlled, clinical trials: ANCHOR (n = 420), MARINA (n = 713), and PIER (n = 182). The sample size of each study for the evaluated treatment intervals and study arms is shown in Figure 1.

Incidences of Macular Hemorrhages

Months 0–3: monthly ranibizumab or sham injection. In all 3 trials, a higher percentage of patients developed macular hemorrhages in the control group compared with both the ranibizumab-treated groups during Months 0 to 3. In the ANCHOR trial (Figure 1A), new macular hemorrhages were seen in 27.3% of PDT-treated eyes compared with 8.0% in the 0.3-mg ranibizumab-treated group ($P < 0.0001$) and 8.6% in the 0.5-mg ranibizumab-treated group ($P < 0.0001$).

The MARINA trial (Figure 1B) showed 18.6% in the sham group developing macular hemorrhages compared with 8.8% in the 0.3-mg ranibizumab-treated group ($P = 0.0019$) and 8.8% in the 0.5-mg ranibizumab-treated group ($P = 0.0018$).

In the PIER trial (Figure 1C), 16.1% in the sham group and 3.4% in the 0.3-mg ranibizumab-treated group ($P = 0.019$) and 3.3% in the 0.5-mg ranibizumab-treated group ($P = 0.016$) developed macular hemorrhages.

Months 5–17: monthly ranibizumab or sham injection (MARINA/ANCHOR); quarterly ranibizumab or sham injection (PIER). During Months 5 to 17, the incidence of macular hemorrhages was still higher in the control groups for ANCHOR and MARINA when compared with the ranibizumab-treated groups. The ANCHOR trial (Figure 1, Panel D) had 47.8% of PDT treated patients compared to 12.5% in the 0.3 mg ranibizumab-treated group ($P < 0.0001$) and 12.3% in the 0.5 mg ranibizumab-treated group ($P < 0.0001$) develop a macular hemorrhage. The MARINA trial (Figure 1E) also showed a higher rate of new macular hemorrhages in the sham group with 38.0% compared with lower rates of 13.2% in the 0.3-mg ranibizumab-treated group ($P < 0.0001$) and 13.0% in the 0.5-mg ranibizumab-treated group ($P < 0.0001$).

However, in the PIER trial (Figure 1F), the incidence rates were not lower in the ranibizumab-treated groups compared with the control group (in fact, they were slightly higher although the differences were not statistically significant). 22.4% of patients in the sham group developed new macular hemorrhages when compared with 23.7% in the 0.3-mg ranibizumab-treated group ($P = 0.87$) and 28.3% in the 0.5-mg ranibizumab-treated group ($P = 0.46$).

For quarterly incidences of new macular hemorrhages in the ANCHOR (Figure 2A) and MARINA (Figure 2B) studies after Month 5, the rate in the ranibizumab-treated groups appears stable between 1% and 7%, whereas the control groups (sham/PDT) range from 10% to 22%. In the PIER study (Figure 2C), the overall incidence of new macular hemorrhages ranged from 3% to 17% for the ranibizumab-treated eyes and from 4% to 10% for the control (sham) eyes.

Cross-Study Comparison Between Studies

Given the different patient populations; different control groups; and differences in sample size, follow-up, and crossover regimens, cross-study comparisons (Figure 1) are intended for hypothesis generation only and the data should be reviewed with caution. As a reference (not for formal comparisons), Pearson chi-square or Fisher exact test (when expected cell counts <5) yields the following P values for cross-study

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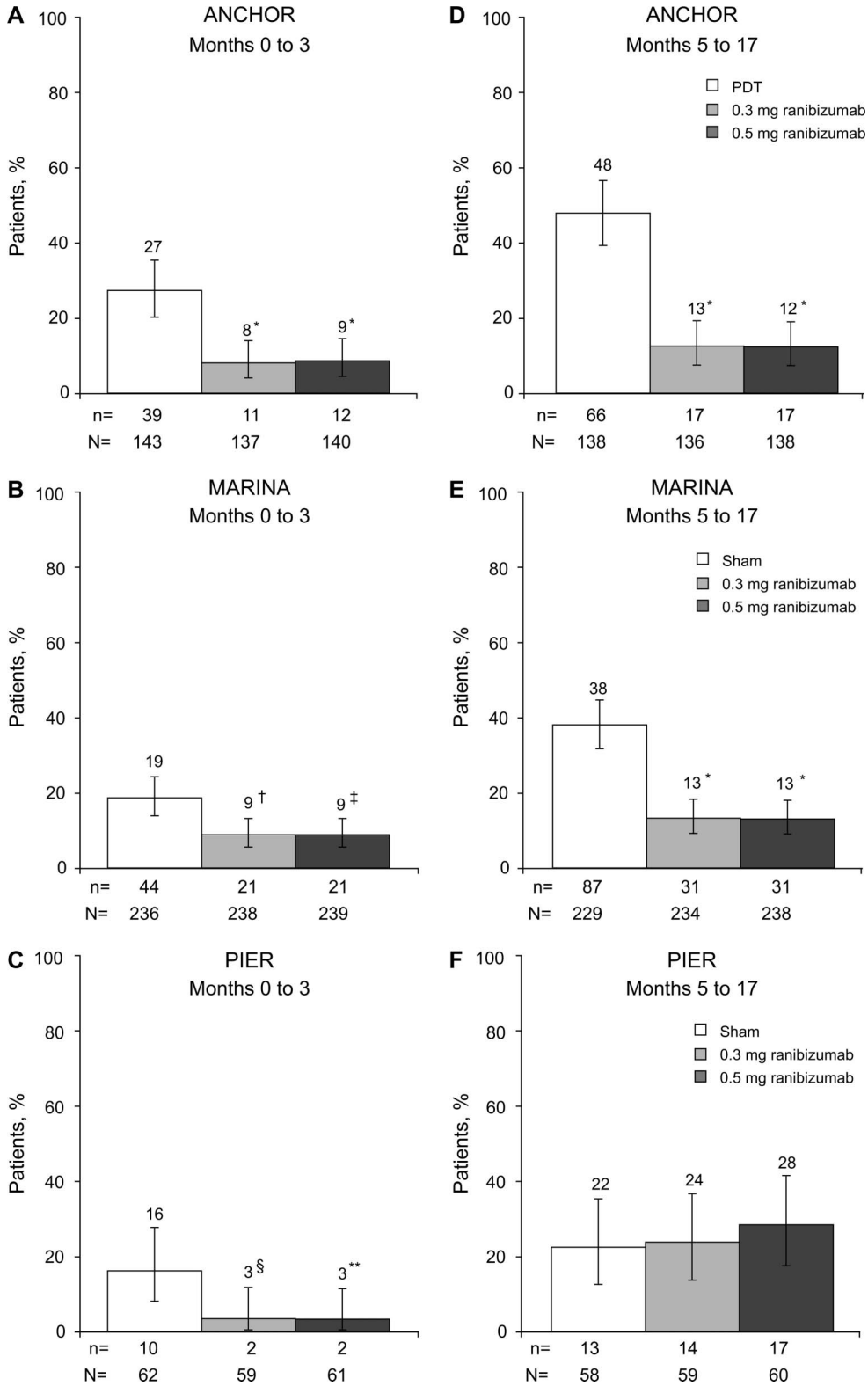

Fig. 1. Summary of the incidences of new macular hemorrhages in the study eye in the ANCHOR (**A** & **D**), MARINA (**B** & **E**) and PIER (**C** & **F**) studies subdivided for the 2 study periods (months 0 3 and months 5 17). *$P < 0.0001$, †P 0.0019, ‡P 0.018 §P 0.019, **P 0.016 vs. control (sham or PDT). Error bars are 95% exact confidence intervals.

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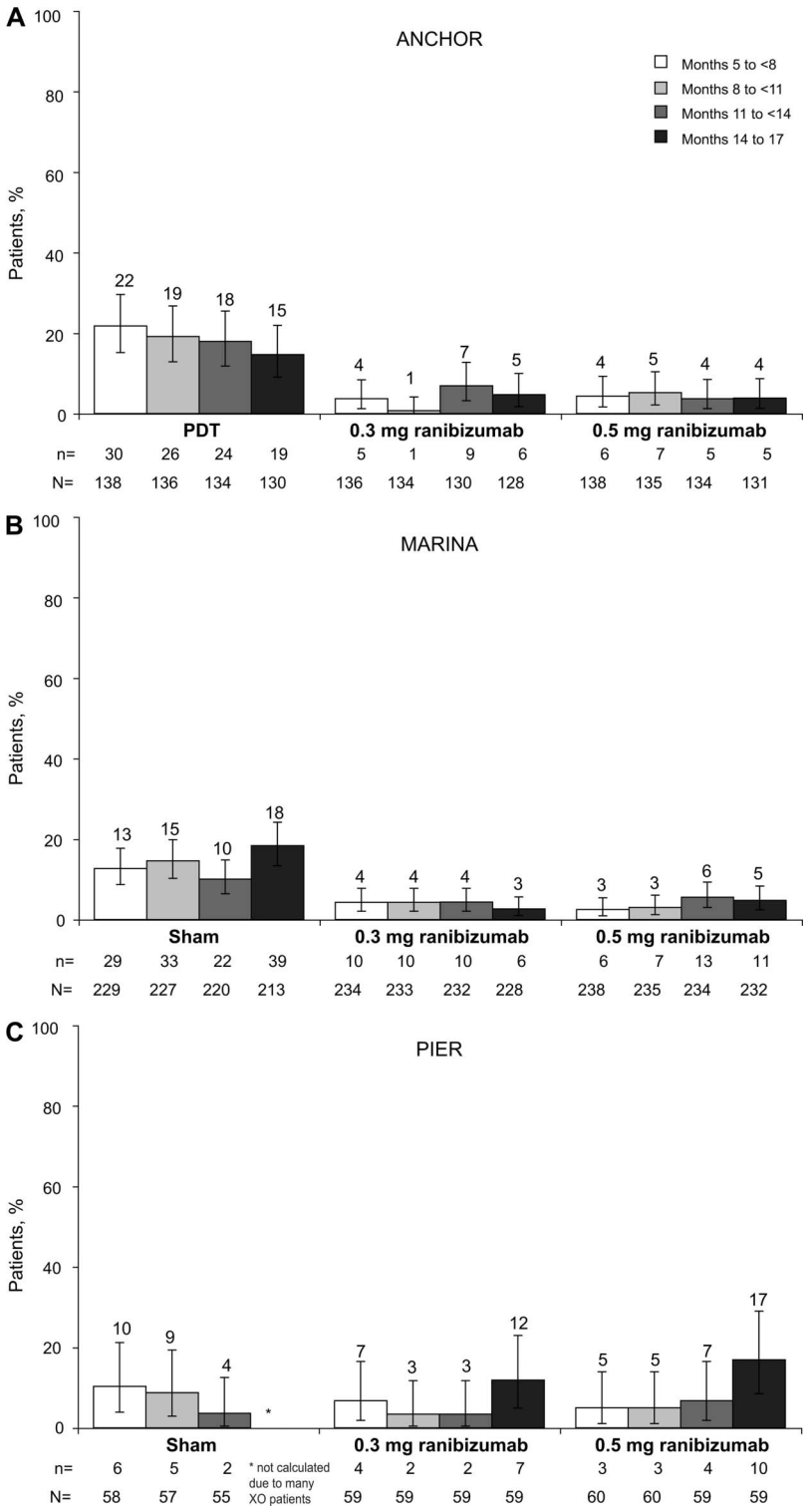

Fig. 2. Quarterly reported incidences of new macular hemorrhages in the ANCHOR (**A**), MARINA (**B**), and PIER (**C**) studies, Months 5 to 17. *Months 14 to 17 for the PIER sham group were excluded from the summary because most patients in sham crossed over to receive 0.5 mg ranibizumab at Month 14. Error bars are 95% exact confidence intervals.

comparison for the incidence of macular hemorrhages within each treatment group.

For the Months 0 to 3 interval, little difference was found between the incidence rates in the PIER and MARINA trials (control [$P = 0.65$], 0.3 mg [$P = 0.27$], and 0.5 mg [$P = 0.18$]). Similarly, little difference was found between the incidence rates in PIER and ANCHOR trials (control [$P = 0.09$], 0.3 mg [$P =$

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0.35], and 0.5 mg [P = 0.24]). For the Months 0 to 3 interval, the incidence of macular hemorrhages was 27% in the ANCHOR PDT arm and 19% in the MARINA sham arm (P = 0.049) although there was little difference between ANCHOR and MARINA in the ranibizumab arms (0.3 mg [P = 0.79] and 0.5 mg [P = 0.94]).

However, at months 5 to 17 differences were observed between the rates in the PIER and MARINA trials for all the study arms including the control group (PIER vs MARINA: control [P = 0.026, rate in PIER less than MARINA], 0.3 mg [P = 0.046, rate in PIER greater than MARINA], and 0.5 mg [P = 0.0039, rate in PIER greater than MARINA]). The comparison of the PIER and the ANCHOR studies also showed similar results with differences between all groups (PIER versus ANCHOR: control [P = 0.0009, rate in PIER less than ANCHOR]), 0.3 mg (P = 0.049, rate in PIER greater than ANCHOR), and 0.5 mg (P = 0.0060, rate in PIER greater than ANCHOR). For the Months 5 to 17 interval, the incidence of macular hemorrhages differed little between ANCHOR and MARINA among the treatment groups (control [P = 0.06], 0.3 mg [P = 0.84], and 0.5 mg [P = 0.84]).

Lesion Composition at Baseline: Presence of Classic (Predominantly Classic or Minimally Classic) or Occult Without Classic

Baseline angiographic lesion composition, as determined by the reading center (Figure 3), did not reveal any significant influence on the subsequent incidences of macular hemorrhages in the MARINA

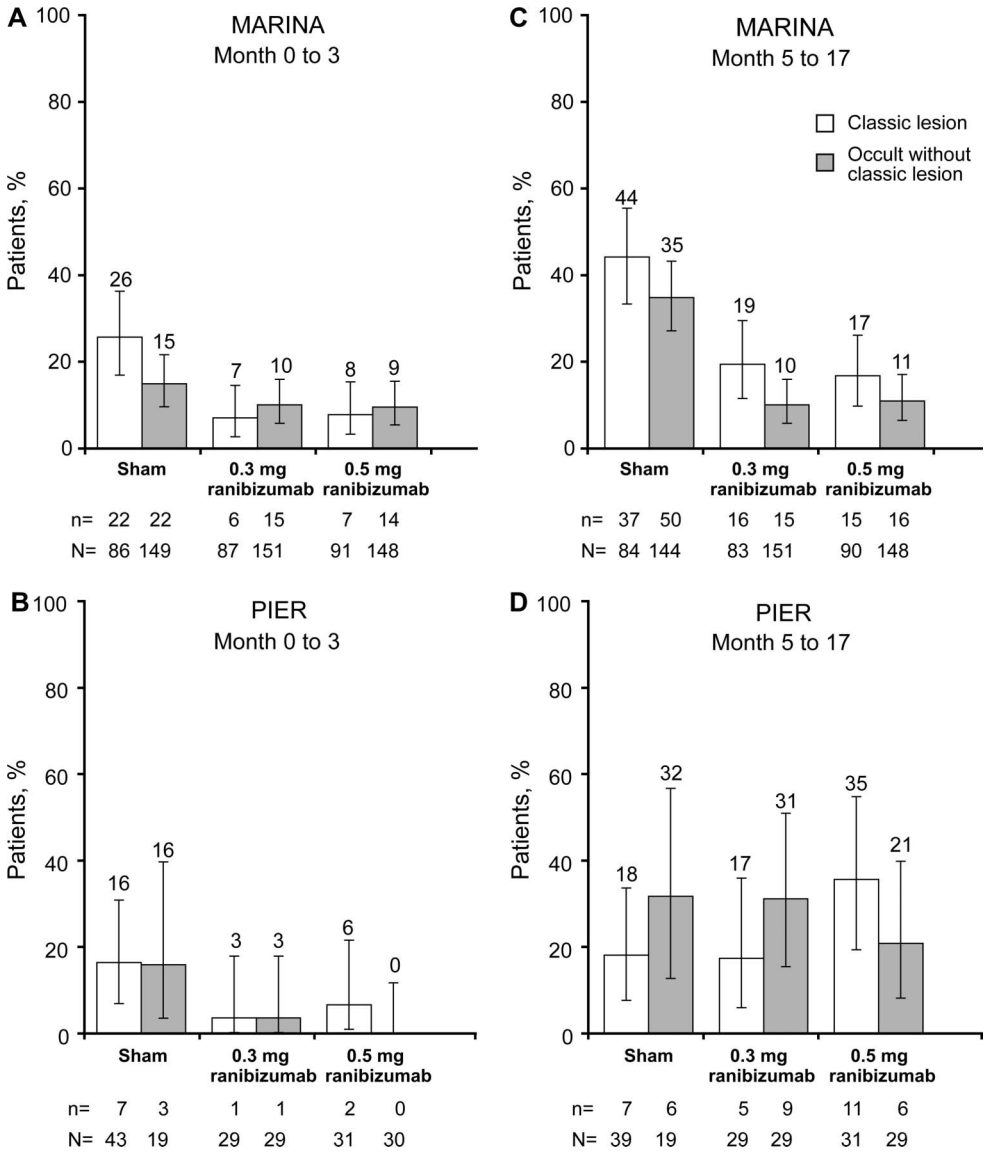

Fig. 3. Macular hemorrhages by baseline lesion type (clas sic vs occult lesions) in the MARINA (**A** & **C**) and PIER (**B** & **D**) studies subdivided for the 2 study periods (months 0 3 and months 5 17). There was only one safety evaluable patient in ANCHOR with occult with out classic lesion at baseline. Therefore, the subgroup analysis by lesion type was not done for ANCHOR. One PIER patient had a baseline lesion type that could not be classified and was excluded from the analysis. Error bars are 95% exact confidence intervals.

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and PIER studies during the first 3 months, except for MARINA sham ($P = 0.041$, 26% classic versus 15% occult without classic). In the Months 5 to 17 interval, the MARINA study showed a trend toward lesions with a classic component to be more likely to develop hemorrhages than occult without classic lesions; the difference was statistically significant for the 0.3-mg group ($P = 0.044$, 19% classic versus 10% occult without classic). However, the PIER study showed a reversed indication during Months 5 to 17 (not statistically significant) where occult lesions were more likely to develop hemorrhages than classic lesions for the sham and the 0.3-mg ranibizumab–treated groups.

The subgroup analysis stratified by lesion type was not done for ANCHOR because of the inclusion criterion that allowed only patients with at least 50% classic lesions in the trial. However, there was one safety-evaluable patient in ANCHOR with occult without classic lesion at baseline.

Role of Anticoagulation/Platelet Inhibitors at Baseline

The incidence of macular hemorrhages was analyzed for patients taking anticoagulants (i.e., warfarin) or platelet aggregation inhibitors (i.e., acetylsalicylic acid [Aspirin], clopidogrel bisulfate [Plavix], etc.) versus patients taking none of these medications at baseline (Figure 4). No statistical differences between the groups were found in ANCHOR, MARINA, or PIER for each time interval.

Presence or Absence of Blood at Baseline

Blood at baseline was categorized as present, absent, questionable, or cannot be graded. For these analyses, present and questionable were combined as present at baseline and compared with absent at baseline (Figure 5).

In ANCHOR, the incidence of macular hemorrhage was higher with blood present at baseline compared with blood absent at baseline except for the control group at Months 0 to 3 and the 0.5-mg group at Months 5 to 17. However, none of the comparisons were statistically significant.

In MARINA, the incidence of macular hemorrhage was higher with blood present at baseline compared with blood absent at baseline in all instances although none were statistically significant.

In PIER, the incidence of macular hemorrhage was higher with blood present at baseline compared with blood absent at baseline except for the control group at Months 5 to 17 and 0.3 mg at Months 0 to 3 where the reverse was found but was not statistically significant. One statistically significant comparison was found, for the sham group at Months 0 to 3 ($P = 0.050$, 22.2% for present versus 0% for absent).

Discussion

Macular hemorrhages of varying degrees and extensions are known to occur as part of the natural course of AMD[3,4] and as complications after interventions for neovascular disease.[10] The outcome can be devastating for the patient and not only lead to visual impairment but also place a significant psychological burden on patients and families.[5]

Controlling the neovascular process with reduction of exudative activity is a logical approach to reduce the risk of developing new hemorrhages secondary to AMD. Sustained inhibition of vascular endothelial growth factor with intravitreal ranibizumab is a promising strategy for such a therapeutic/preventive concept.[6,11]

The analysis of the safety data of the three major controlled clinical trials (ANCHOR, MARINA, and PIER) presents the unique opportunity to evaluate large treated patient cohorts and controls for the incidence of macular hemorrhages in randomized double-blind studies with standardized treatment protocols. Patients on monthly ranibizumab in MARINA, ANCHOR, and PIER were significantly less likely to develop macular hemorrhages when compared with the control groups. In PIER, no benefit of ranibizumab over sham was observed after the patients were switched to the quarterly protocol. It should be noted that the evaluation of the PIER study data is complicated as a result of the study arms being significantly smaller and some patients of the sham group having crossed over (15 at Month 14 and another 17 at Month 17) to receive 0.5-mg ranibizumab. Baseline angiographic lesion composition as well as medications for anticoagulation and platelet aggregation inhibition did not influence the risk of developing macular hemorrhages in any of the study treatment groups. Baseline presence of blood was mostly consistent as to incidence of macular hemorrhages being higher in the group with blood present at baseline versus blood absent at baseline, but only 1 of the 18 comparisons among study treatment groups was statistically significant.

This study is also limited by several factors, which include but are not limited to the retrospective nature of the data review as well as the differences in follow-up, treatment protocols, and control group composition of the individual studies. In the PIER study, the number of patients is significantly smaller when compared with the MARINA and ANCHOR studies. In addition, the follow-up intervals after the initial 3 months were only quarterly in PIER, which may result in missed events and lead to an underestimation of the number of events. Finally, because none of the studies required monthly fundus photographic documentation, identification of macular hemorrhages is dependent on verbatim reports

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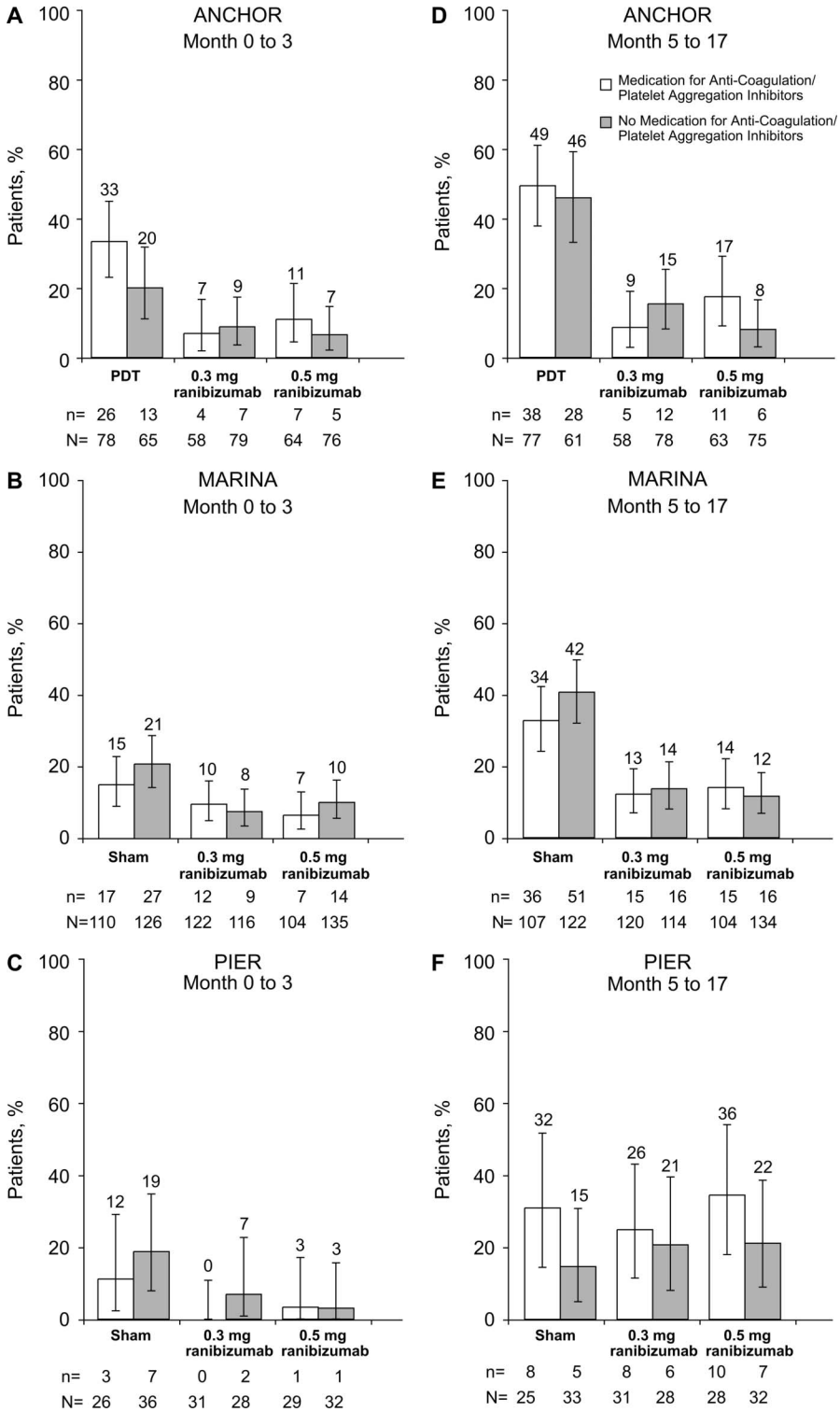

Fig. 4. Macular hemorrhages by base line medication for anticoagulation/ platelet inhibitors in the ANCHOR (**A** & **D**), MARINA (**B** & **E**) and PIER (**C** & **F**) studies subdivided for the 2 study periods (months 0 3 and months 5 17). Error bars are 95% exact confidence intervals.

of adverse events by the individual investigators who may have varying definitions/methods of identification. However, in spite of its limitations, the results of this analysis may give the treating ophthalmologists additional information on how to manage their patients with AMD and to achieve best functional results and visual preservation.

In conclusion, although none of the treatment arms in MARINA, ANCHOR, and PIER showed a complete absence of new macular hemorrhages during the study

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period, monthly application of 0.3-mg or 0.5-mg ranibizumab significantly decreased the risk of developing new macular hemorrhages when compared with the control groups (sham or PDT). As seen in PIER, switching from monthly to quarterly injection intervals may not have the same beneficial effect and could put the patient at an increased risk for vision-threatening complications.

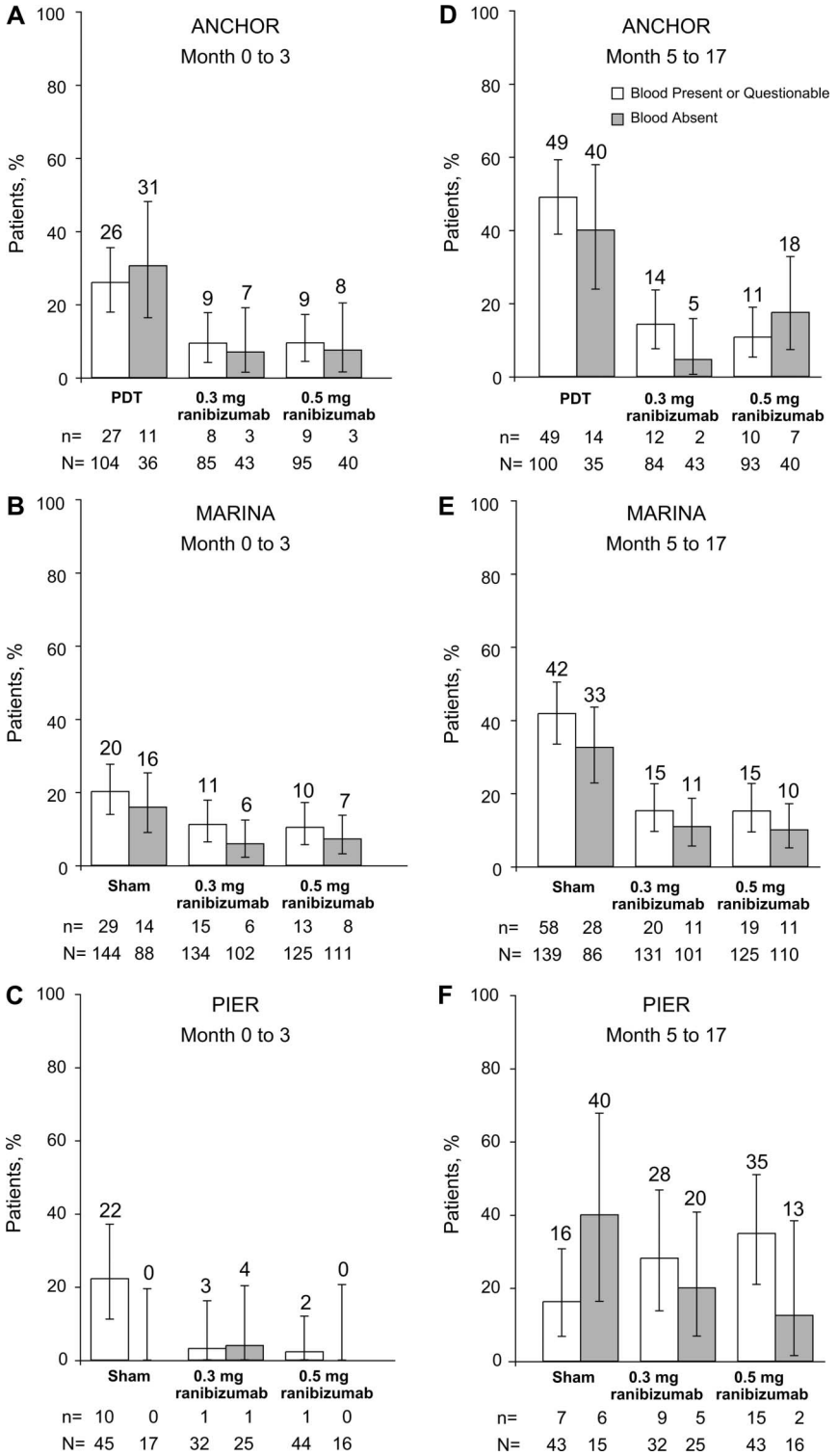

Fig. 5. Macular hemorrhages by baseline presence or absence of blood in the ANCHOR (**A** & **D**), MARINA (**B** & **E**) and PIER (**C** & **F**) studies subdivided for the 2 study periods (months 0 3 and months 5 17). Error bars are 95% exact confidence intervals.

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Key words: age-related macular degeneration, choroidal neovascularization, ranibizumab, macular hemorrhage.

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