Author’s response to reviews

Title: Hospitalized cardiovascular events in patients with diabetic macular edema

Authors:

Bao-Anh Nguyen-Khoa (bnguyen@deggegroup.com)
Earl L Goehring Jr. (egoehring@deggegroup.com)
Winifred Werther (wwerther@jhsph.edu)
Anne E Fung (anenefungmd@yahoo.com)
Diana V Do (ddo@jhmi.edu)
Rajendra S Apte (apte@vision.wustl.edu)
Judith K Jones (jkjones@deggegroup.com)

Version: 2 Date: 3 April 2012

Author’s response to reviews: see over
April 3, 2012

Ms April Gerobin
The BioMed Central Editorial Team

Dear Ms. Gerobin,

Enclosed for your consideration is the revised research manuscript entitled "Hospitalized Cardiovascular Events in Patients with Diabetic Macular Edema". Attached is a point-by-point response to the concerns raised by the editors and reviewers.

1. All authors of this research paper directly participated in the planning, execution, analysis or interpretation of this study.
2. All authors of this paper have read and approved the final version submitted.
3. The contents of this manuscript have not been copyrighted or published previously.
4. The contents of this manuscript are not now under consideration for publication elsewhere.
5. The contents of this manuscript will not be copyrighted, submitted, or published elsewhere while acceptance by the Journal is under consideration.
6. There are no directly related manuscripts or abstracts, published or unpublished, by any authors of this paper.

Funding for this study was received from Genentech Inc. (S. San Francisco, Calif). The sponsor had no role in the study's conduct, data collection, data analysis, or data interpretation. Study data were shared with the study sponsor.

Declarations. Dr. Winifred Werther is a senior epidemiologist at Genentech Inc., the study sponsor. Dr. Jones is President of The Degge Group, the research firm. Dr. Nguyen-Khoa and Mr. Goehring are employees of The Degge Group. Drs. Apte and Fung have served as consultants and speakers for Genentech. Drs. Do and Fung have received clinical research funding from Genentech. Dr. Apte has consulted for Eyetech and Allergan, and has equity ownership in Ophthalmic.

We thank you for your reconsideration of this manuscript.

Sincerely,

Bao-Anh Nguyen-Khoa PharmD MPH

Judith K. Jones MD, PhD

President, CEO
Editorial comments:

- Please move the details of commercial funding and employment of the authors from your Acknowledgements section to a Competing Interests section included between the Conclusions and Authors’ contributions.

As instructed.

The questions that are asked of authors are:

Financial competing interests:
* In the past five years have you received reimbursements, fees, funding, or salary from an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? Is such an organization financing this manuscript (including the article-processing charge)? If so, please specify.

As noted in the Competing Interests section, Genentech Inc. sponsored this study (including the article-processing charge). The sponsor manufactures at least 1 ophthalmic medication.

We are not aware of any other organization has given us financial support of any type in the past 5 years that may gain or lose financially from the publication of this manuscript.

* Do you hold any stocks or shares in an organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future? If so, please specify.

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* Do you have any other financial competing interests? If so, please specify. Non-financial competing interests: are there any non-financial competing interests (political, personal, religious, academic, ideological, intellectual, commercial or any other) to declare in relation to this manuscript? If so, please specify.

We do not have any other financial competing interests.

- Please include some context information for the study in the Background section of your abstract.

Context information has been added to the Background of the abstract, as instructed.
Reviewer's report

Title: Hospitalized cardiovascular events in patients with diabetic macular edema

Version: 1 Date: 7 February 2012

Reviewer: Amirul Amirul Islam

Reviewer's report:

Minor Essential Revisions:

The study period is from 1 January 2002 to 31 December 2005, i.e., seven years ago. Will it be really tough to collect data from the recent years which will improve the findings significantly.

This study was conducted during a period in which little or not medications used to treat DME could have affected rate of cardiovascular outcomes. Thus the historical perspective provides a background rate of events for this population.

Study Design: Is it 3 or 4 year period? Should it not be 4 year?

The study period was 4 years, the text has been revised. Thank you.

Statistical analysis: ...............events per 1000 person -years were computed by which software?

We used SAS version 9.1. The text has been revised for clarity.

Results: (first paragraph)->=3 (46.6% vs 11.8%) in Table 1 though Table 1 shows >=2 (56.5% vs 23%). Please add >=3 cut-off to the table or make the correction in the text.

Thank you, the text has been revised.

Incidence of MI: I am wondering how rate of 19.7 or 6.9 MI events/1000 persons were calculated. If you consider 3 years, then rate =( 94/3519)*(1000/3)= 8.9 MI events/1000 person-years. Please check the calculations.

Thank you. We have added the person-year columns to the table, so that the events/person-years calculation is evident to the reader. Please note that the normalized denominator is person-years. This is not the same as "per person per year".

For the incidence of MI the calculation is ( 94 events / 4778.5 person-years)*1000 = 19.7 events per person-year (rounded).

Was Table 4 adjusted for the same varaibles mentioned in Table 5? This was not clearly mentioned.

Table 4 presents the unadjusted event rate for DME and diabetes controls from which the adjusted hazard ratios for Table 5 was derived. The rate 14.7 events per person-year was not calculated from the N denominator 3519, which would be a "per person" proportion. We used the person-year denominator where each subject "contribute" different follow-up times based on the pre-defined censoring rules. This makes use of all the available longitudinal health data for each subject. This is unlike most controlled clinical studies in which a
precisely fixed follow-up period is defined for all subjects, in which case a normalized “per person per time” unit is typically used.

Table 1: (age group 70-79) 516/3519 = 14.7% instead of 4.7%. Thank you, the text has been revised.

Write down the covariates in the footnotes (Tables 3 and 5) those were adjusted for. Otherwise, apparently it seems the models are not adjusted.

All the covariates listed in Tables 3 and 5 were used in the regression model as statistical adjustments. Their hazard ratios represent their adjusted influence on either cohort when present.

We have added a footnote to each table for clarity.

MI events are much higher in Male whereas CVA events are higher in Female. Is there any biological reasons, would be good to add a few sentence in the discussion.

Thank you, we have added a brief remark and citation about the apparently higher rate of CVA in women than men. However, the rates are unadjusted and their confidence intervals overlap, indicating preliminary nonsignificance. Please note that these particular gender results were for supplemental purposes and not the primary objective of the study. Thus we hesitate to overstate any interpretation from these findings.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.
Reviewer's report

Title: Hospitalized cardiovascular events in patients with diabetic macular edema

Version: 1 Date: 17 January 2012

Reviewer: Margaret DeAngelis

Reviewer's report:

This is well presented study however, some items should be addressed to ensure that readers will glean the most from the manuscript:

Minor essential revisions:

1. Use of the term "study arms" on page 5 is misleading, as that is what is commonly used to describe treatment groups in an intervention study/clinical trial. Suggest removing or revising

   Thank you, we have modified the phrase.

2. When using Cox Proportional Hazards models, the Proportional Hazards Assumption must be checked and satisfied. Was this done? If so, please state that it was.

   The proportional hazards assumption was satisfied, and a statement has been added to the text. Thank you.

3. Although the controls were matched to cases on age and sex, what about other possible confounders, i.e. geographic region?

   We kept the matching to age and gender to maintain a robust sample size. Geographic region was not matched, however as presented in Table 1, the differences were not large and we are not aware of any evidence that the marginal difference could influence the outcome.

   Other biological confounders known to influence the outcome were statistically adjusted in the regression model rather than matched.

4. When reporting the results of the Cox models, it is not correct to state "adjusted rates" as this is not what appears to be calculated. It is correct to report the rates and show the significance of the variables within the Cox models but these rates are not adjusted -what is adjusted is the hazard ratio. Please clarify

   We have corrected the text to state that the hazard ratios were adjusted, not the rates. Thank you.

5. Although it is stated that this is a "large insured population with sufficient size to quantify and compare the incidence rates of MI or CVA in patients with DME against matched diabetes controls" -Is there evidence to prove that this study has greater power than previous studies? Please address in discussion

   With a sample of 3,000 subjects DME, we had over 80% power to detect a hazard ratio of 1.25 with 95% confidence (i.e., 25% increased risk of a CV event) within either group. A ratio we felt met a substantial level of clinical significance to readers if identified. Our adjusted HR results were 1.9 and 2.5, which were well above the 1.25 estimate.

   We have added a statement to the Study Sample section support the statistical power.
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests