Retraction notice to “Plasma PCSK9 levels and clinical outcomes in the TNT (Treating to New Targets) Trial” [J Am Coll Cardiol 2012;59:1778–1784]

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The main findings of the TNT Trial were published in 2005 (1). Since that time, members of the Steering Committee and other investigators have published 32 papers based upon additional analyses of TNT. The data for these papers were derived from analyses of the TNT clinical database, managed by Pfizer. The clinical database has been crosschecked many times and the data in it is valid. During the trial, blood samples were drawn from the patients at regular intervals for subsequent analysis. We performed a nested case-control study that included 507 patients who experienced a CV event and 1,020 control patients in the main biomarker analysis, and 496 patients who experienced a CV event and 1,117 control patients in the PCSK9 analysis. The biomarker database was separate from the clinical database. An anonymization code was run in 2007 to link patients from one database to the other.

In late 2012, the TNT frozen blood samples were integrated into a large automated biobank that includes samples from other Pfizer trials. At that time discrepancies were noted among the samples, indicating that an error had occurred when the samples were anonymized in 2007. Further investigation revealed that the code created to manually anonymize the data was accidentally run twice. During the first run, anonymized subject identifiers were successfully assigned to both biosamples and clinical data. However, after this first run had passed quality control checks, the anonymization code was re-run inadvertently, replacing the first correct set of identifiers with a random and incorrect set. We do not understand how or why the code was re-run. The study team, who were blinded as to patient identity, thus reported on mismatched clinical and biomarker data. The investigators of the biomarkers study were puzzled that none of the 18 biomarkers were predictive of cardiovascular events. However we were reassured because on-treatment LDL-cholesterol, HDL-cholesterol and triglyceride levels were all strongly predictive of events, and we reported this in the paper. These lipid levels were part of the clinical database, and thus were not subject to the error that occurred with the biomarkers. In the PCSK9 analysis, PCSK9 levels were predictive of events in the atorvastatin 10-mg group (p 0.039) but not in the 80-mg group. This finding, which we now realize is totally spurious, was not unexpected and raised no red flags. Similarly, the failure of vitamin D levels to predict events, as reported in the AHJ paper, was not surprising.

Since the error was discovered, we have created a new anonymized clinical and biomarker database by restoring the original set of anonymized identifiers. We are currently reanalyzing the data according to our original study plans. However, the nested case-control feature of the original study design has been lost because the patient selection for biomarker sampling was random. Only approximately one tenth of patients now had an event, compared to one third in the original study design. Thus, the power to detect a difference in the level of a biomarker between patients with and without events has been attenuated.

All authors of these manuscripts are anguished to have made this mistake and publishing incorrect information.

REFERENCES

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