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Safety Profile of Extended-Release Niacin in the AIM-HIGH Trial

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TO THE EDITOR: The results of the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial were published in the *Journal* in 2011.¹ This study showed no incremental clinical benefit from the addition of high-dose extended-release niacin (Niaspan, AbbVie) to statin therapy during a 36-month mean follow-up period in 3414 patients who had stable atherosclerotic disease, low baseline levels of high-density lipoprotein (HDL) cholesterol, and elevated triglyceride levels. In that article, we provided data on adverse events resulting in a reduction in the dose or discontinuation of the study drug. These results were largely consistent with the previously established side-effect profile of niacin (e.g., itching, flushing, gastrointestinal symptoms, and increased blood glucose levels). Less common adverse events, including abnormal liver-function tests and myopathy, were also reported.

Because of an excess in certain serious adverse events observed in the Heart Protection Study 2: Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE),^{2,3} including unanticipated increases in infections and bleeding, there has been

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interest in whether similar patterns of serious adverse events were observed in the AIM-HIGH trial.⁴ It is important to note that in HPS2-THRIVE, a different study drug (Tredaptive, Merck), a proprietary extended-release niacin preparation combined with laropiprant, a prostaglandin D₂ receptor-1 antagonist, was used to retard cutaneous flushing. Here we describe the rates of serious adverse events in the AIM-HIGH trial. Additional information regarding all adverse events (including both serious and nonserious adverse events) is provided in the Supplementary Appendix (available with the full text of this letter at NEJM.org).

All serious adverse events were recorded on standard case-report forms. Terms were coded with the use of the *Medical Dictionary for Regulatory Activities* (MedDRA), version 15.0, and classified according to the System Organ Class categorization and MedDRA preferred term. A standardized MedDRA query⁵ was used to identify serious hemorrhagic adverse events.

Overall, 34.2% of patients who received extended-release niacin and 32.5% of patients who received placebo had serious adverse events during follow-up ($P = 0.30$). There were significant between-group differences in the numbers of serious adverse events in the System Organ Class categories of gastrointestinal disorders (7.4% vs. 5.5%, $P = 0.02$) and infections and infestations (8.1% vs. 5.8%, $P = 0.008$). The overall observed rate of serious hemorrhagic adverse events was low, with no significant difference between the two groups in the trial (3.4% vs. 2.9%, $P = 0.36$) (Table 1).

Although the full list of serious adverse events suggests certain similarities with the data from HPS2-THRIVE, particularly regarding serious adverse infectious events, the nonsignificant numerical excess in adverse bleeding events with niacin cannot be considered definitive. Accordingly, there are compelling reasons to interpret these data with caution. The data, and the relevant considerations, are discussed in the Supplementary Appendix.

In summary, in the AIM-HIGH trial, treatment with extended-release niacin was associated with significantly increased rates of certain serious adverse events, as well as increased rates of dose reductions or drug discontinuation related in most cases to known side effects of niacin. Examination of the entire record of all adverse events suggests other possible side effects of this proprietary extended-release formulation. The findings concerning certain serious adverse infectious events associated with niacin have not been previously reported. However, lacking additional clinical and scientific confirmation, we believe that they should be considered to be provisional and exploratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. The AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*. 2011; 365:2255–2267. [Erratum, *N Engl J Med* 2012;367:189.]. [PubMed: 22085343]
2. HPS-2 THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 25,673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. *Eur Heart J*. 2013; 34:1279–1291. [PubMed: 23444397]
3. Armitage J. HPS2-THRIVE Collaborative Group. HPS2-THRIVE: randomized placebo-controlled trial of ER niacin and laropiprant in 25,673 patients with pre-existing cardiovascular disease. (http://www.hps2-thrive.org/hps2-thrive_ACC_slides.ppt).
4. The HPS2-THRIVE Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med*. 2014; 371:203–212. [PubMed: 25014686]
5. Standardised MedDRA queries. (<http://www.meddra.org/standardised-meddra-queries>).

Table 1

Serious Adverse Events.*

MedDRA System Organ Class	Extended-Release Niacin plus Statin (N = 1718)	Placebo plus Statin (N = 1696)	P Value
<i>no. (%)</i>			
Any adverse event	587 (34.2)	551 (32.5)	0.30
Blood and lymphatic system disorders	24 (1.4)	18 (1.1)	0.37
Cardiac disorders [†]	175 (10.2)	190 (11.2)	0.34
Gastrointestinal disorders	127 (7.4)	93 (5.5)	0.02
Abdominal pain	22 (1.3)	10 (0.6)	0.04
Gastroesophageal reflux disease	0	5 (0.3)	0.03
Rectal hemorrhage	11 (0.6)	3 (0.2)	0.06
Vomiting	20 (1.2)	9 (0.5)	0.04
General disorders and administration-site conditions	58 (3.4)	56 (3.3)	0.90
Hemorrhagic events [‡]	59 (3.4)	49 (2.9)	0.36
Hepatobiliary disorders	24 (1.4)	17 (1.0)	0.29
Infections and infestations	139 (8.1)	98 (5.8)	0.008
Appendicitis	8 (0.5)	1 (0.1)	0.04
Bronchitis	7 (0.4)	1 (0.1)	0.07
Cellulitis	26 (1.5)	13 (0.8)	0.04
Injury, poisoning, and procedural complications	55 (3.2)	50 (2.9)	0.67
Clinical investigations	23 (1.3)	16 (0.9)	0.28
Metabolic and nutrition disorders	39 (2.3)	28 (1.7)	0.19
Musculoskeletal and connective-tissue disorders	78 (4.5)	91 (5.4)	0.27
Neoplasms benign, malignant, and unspecified, including cysts and polyps	72 (4.2)	73 (4.3)	0.87
Non-small-cell lung cancer	0	4 (0.2)	0.06
Nervous system disorders	63 (3.7)	70 (4.1)	0.49
Paresthesia	0	5 (0.3)	0.03
Psychiatric disorders	26 (1.5)	21 (1.2)	0.49
Renal and urinary disorders	44 (2.6)	46 (2.7)	0.78
Reproductive system and breast disorders	9 (0.5)	5 (0.3)	0.42
Respiratory, thoracic, and mediastinal disorders	51 (3.0)	49 (2.9)	0.89
Skin and subcutaneous-tissue disorders	10 (0.6)	16 (0.9)	0.23
Surgical and medical procedures	6 (0.3)	5 (0.3)	0.78
Vascular disorders	59 (3.4)	62 (3.7)	0.73

* Adverse events are listed according to the system organ classes and the preferred terms in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 15.0. All system organ class categories are listed for which at least five events were recorded in either trial group. For any system organ class category in which a significant between-group difference was detected, individual preferred terms are listed; these terms are restricted to those with a P value of less than 0.10 for the between-group difference.

[†] This category does not include efficacy end points as defined in the protocol.

[‡]This category was identified by means of the standardized MedDRA query for hemorrhagic adverse events.