Adverse Event	amlodipine M=% (N=1218)	amlodipine F=% (N=512)	Placebo M=% (N=914)	Placebo F=% (N=336)
Edema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitations	1.4	3.3	0.9	0.9
Somnolence	1.3	1.6	0.8	0.3

The following events occurred in ≤1% but >0.1% of patients treated with amlodipine in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship: **Cardiovascular:** arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis. **Central and Peripheral Nervous System:** hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo. **Gastrointestinal:** anorexia, constipation, dyspepsia,** dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia. **General:** allergic reaction, asthenia,** back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease. **Musculoskeletal System:** arthralgia, arthrosis, muscle cramps,** myalgia. **Psychiatric:** sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization. **Respiratory System:** dyspnea,** epistaxis. **Skin and Appendages:** angioedema, erythema multiforme, pruritus,** rash,** rash erythematous, rash maculopapular. **Special Senses:** abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus. **Urinary System:** micturition frequency, micturition disorder, nocturia. **Autonomic Nervous System:** dry mouth, sweating increased. **Metabolic and Nutritional:** hyperglycemia, thirst. **Hemopoietic:** leukopenia, purpura, thrombocytopenia. The following events occurred in ≤0.1% of patients treated with amlodipine in controlled clinical trials or under conditions of open trials or marketing experience: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia. Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina. Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine. The following postmarketing event has been reported infrequently with amlodipine treatment where a causal relationship is uncertain: gynecomastia. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine. Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles. **The Atorvastatin Component of CADUET:** Atorvastatin is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin calcium. The most frequent adverse events thought to be related to atorvastatin calcium were constipation, flatulence, dyspepsia, and abdominal pain. Clinical Adverse Experiences: Adverse experiences reported in ≥2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment, are shown in Table 3.

Table 3. Adverse Events in Placebo-Controlled Studies (% of Patients)

Body System/ Adverse Event	Placebo N=270	atorvastatin 10 mg N=863	atorvastatin 20 mg N=36	atorvastatin 40 mg N=79	atorvastatin 80 mg N=94
BODY AS A WHOLE					
Infection	10.0	10.3	2.8	10.1	7.4
Headache	7.0	5.4	16.7	2.5	6.4
Accidental Injury	3.7	4.2	0.0	1.3	3.2
Flu Syndrome	1.9	2.2	0.0	2.5	3.2
Abdominal Pain	0.7	2.8	0.0	3.8	2.1
Back Pain	3.0	2.8	0.0	3.8	1.1
Allergic Reaction	2.6	0.9	2.8	1.3	0.0
Asthenia	1.9	2.2	0.0	3.8	0.0
DIGESTIVE SYSTEM					
Constipation	1.8	2.1	0.0	2.5	1.1
Diarrhea	1.5	2.7	0.0	3.8	5.3
Dyspepsia	4.1	2.3	2.8	1.3	2.1
Flatulence	3.3	2.1	2.8	1.3	1.1
RESPIRATORY SYSTEM					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
SKIN AND APPENDAGES					
Rash	0.7	3.9	2.8	3.8	1.1
MUSCULOSKELETAL SYSTEM					
Arthralgia	1.5	2.0	0.0	5.1	0.0
Myalgia	1.1	3.2	5.6	1.3	0.0

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT): In ASCOT involving 10,305 participants treated with atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with atorvastatin was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up. The following adverse events were reported, regardless of causality assessment, in patients treated with atorvastatin in clinical trials. The events in italics occurred in ≥2% of patients and the events in plain type occurred in <2% of patients. **Body as a Whole:** *Chest pain*, face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema. **Digestive System:** *Nausea*, gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice. **Respiratory System:** *Bronchitis, rhinitis,* pneumonia, dyspnea, asthma, epistaxis. **Nervous System:** *Insomnia, dizziness*, paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypesthesia, hypertonia. **Musculoskeletal System:** *Arthritis,* leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis. **Skin and Appendages:** Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer. **Urogenital System:** *Urinary tract infection*, urinary frequency, cystitis, hematuria, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, albuminuria, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage. **Special Senses:** Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion. **Cardiovascular System:** Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension. **Metabolic and Nutritional Disorders:** *Peripheral edema*, hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia. **Hemic and Lymphatic System:** Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia. ***Postintroduction Reports with Atorvastatin:*** Adverse events associated with atorvastatin therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), and rhabdomyolysis. ***Pediatric Patients (ages 10-17 years):*** In a 26-week controlled study in boys and postmenarchal girls (n=140), the safety and tolerability profile of atorvastatin 10 to 20 mg daily was generally similar to that of placebo (see **PRECAUTIONS, Pediatric Use**).

OVERDOSAGE: There is no information on overdosage with CADUET in humans. **Information on Amlodipine:** Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg in dogs (11 or more times the maximum recommended clinical dose on a mg/m^2 basis) caused a marked peripheral vasodilation and hypotension. Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg amlodipine and an unknown quantity of benzodiazepine in a suicide attempt developed shock which was refractory to treatment and died the following day with abnormally high benzodiazepine plasma concentration. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted. If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit. **Information on Atorvastatin:** There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

*Based on patient weight of 50 kg.

**These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

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Use of Proteomics for Ovarian Ca Spurs Debate

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

Systematic bias in the design of several underlying studies raises doubt over whether a serum proteomics test based on those studies can accurately identify ovarian cancer, two independent biostatisticians have argued.

The researchers, both of the University of Texas M.D. Anderson Cancer Research Center, Houston, have been unable to reproduce the high sensitivity and specificity rates reported in a 2003 study of the technique (J. Natl. Cancer Inst. 2005;97:307-9).

The problem, said Keith A. Baggerly, Ph.D., and Kevin R. Coombes, Ph.D., lies not in the fundamental concept—that cancer-shed proteins in serum may be able to identify patients who have even very early-stage cancer—but in the way the data sets were processed in both the 2003 study and the original 2002 National Cancer Institute (NCI) study upon which it was based.

'We're not saying proteomics doesn't work. It may very well work. But these data sets can't be used to say this approach works.'

"We're not saying proteomics doesn't work," Dr. Baggerly said in an interview. "It may very well work. But these data sets can't be used to say this approach works."

The method involves using mass spectroscopy to display proteins in serum as a series of peaks and valleys of varying strength. A computer-driven mathematical algorithm finds unique patterns expressed in the serum of patients with the disease. Several researchers are investigating proteomics' application in ovarian cancer, using different algorithms and spectrometers. All of the decoding work is being performed on three publicly available sets of spectral data, which were processed as part of the original proof-of-concept study by NCI researchers led by Emmanuel F. Petricoin III, M.D. (Lancet 2002;359:572-7).

Dr. Baggerly and Dr. Coombes reanalyzed the data used in a 2003 paper by Wei Zhu, Ph.D., and associates, of the State University of New York at Stony Brook. By using the same NCI data sets—samples from women with ovarian cancer, women with benign ovarian cysts, and healthy controls—but a new protein-recognition pattern, Dr. Zhu achieved perfect discrimination (100% sensitivity, 100% specificity) of patients with ovarian cancer, including early-stage disease, from normal controls (PNAS 2003;100:14666-71). Dr. Zhu's results were even better than those originally reported by Dr. Petricoin and colleagues in their 2002 study.

When Dr. Baggerly reanalyzed the Zhu data, he was unable to arrive at the same results. The Zhu study identified a pattern involving 18 protein peaks that separated controls from cancers. For Dr. Baggerly, the pattern resulted in significant accuracy in the first data set, which contained serum from all three groups, but not in the second data set, which contained only serum from cancer patients and healthy controls.

In the second data set, 13 of the 18 peak differences changed signs—that is, peaks associated with cancer in the first group were associated with controls in the second group, and peaks first associated with controls switched to cancers. "This reversal isn't consistent with a persistent difference between cancer samples and control samples," Dr. Baggerly said.

The researchers then chose 18 random protein peaks from the same regions of spectral data as Dr. Zhu's peaks. The random peaks separated cancer samples from controls up to 56% of the time, depending on the strength of the signals used. Because the pattern of protein expression was inconsistent between the data sets, they concluded, the values did not represent biologically important changes in the serum of cancer patients.

The problem, Dr. Baggerly asserts, is that Dr. Zhu processed the serum samples in a nonrandomized way that the spectra were acquired in the initial study by Dr. Petricoin and his collegues.

"They ran all the controls on one day and all the cancers on the next day," Dr. Baggerly said. "This is the worst kind of design when you are using a machine that can be subject to external factors," such as changes in calibration or mechanical breakdown.

In fact, he said, a June 2004 study in which Dr. Petricoin participated also suffered from just such a problem (Endoc. Relat. Cancer 2004;11:163-78). This study used a different mass spectrometer, which began to break down on day 3 of running the samples. In a letter to the editor, Dr. Petricoin admitted the problem, but said, "We cannot detect whether the cancer data acquired on the previous day were convincingly negatively affected by the spectrometer failure."

Dr. Baggerly contends that a better design involving randomizing sample processing would allow separation of differences due to biology from those due to external factors.

His failure to find reproducibility does not surprise Dr. Petricoin and his colleague, Lance A. Liotta, M.D., who participated in the 2002 and 2004 studies. Their commentary appears in the same journal. Each of the data sets, all of which are available without restriction online, was generated with different machines and methods to test those machines and methods.

"We would be surprised if the experimentally designed process changes between these two studies did not result in altered spectra. In fact, a goal of these experiments was to study the spectral alterations produced by changing the process," they said. ■