| 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/m² 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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# Resynchronization Device Cuts Mortality

BY BRUCE JANCIN
*Denver Bureau*

STOCKHOLM — Results of an extension of the landmark Cardiac Resynchronization in Heart Failure trial show an impressive further widening of the device therapy's mortality advantage over optimal medical management with longer follow-up, John G.F. Cleland, M.D., reported at the annual congress of the European Society of Cardiology.

"CARE-HF provides overwhelming evidence that cardiac resynchronization therapy reduces all-cause mortality, sudden death, and death due to worsening heart failure," said Dr. Cleland, chairman of the study's steering committee and head of cardiology at Castle Hill Hospital, Kingston-upon-Hull, England.

Other new CARE-HF findings presented at the conference included an echocardiographic study providing important new insights into the device therapy's mechanism of action, as well as a favorable cost-effectiveness analysis that concluded cardiac resynchronization therapy (CRT) costs slightly over $24,000 per quality-adjusted life year (QALY) gained.

**'CARE-HF provides overwhelming evidence that [CRT] reduces all-cause mortality, sudden death, and death due to worsening heart failure.'**

CARE-HF was a prospective randomized trial involving 813 patients at 82 medical centers in 12 European countries. Participants had left ventricular (LV) systolic heart failure with an ejection fraction of 35% or less and New York Heart Association class III or IV disease despite optimal pharmacotherapy. They also had to have cardiac dyssynchrony as reflected by a QRS interval of at least 120 msec. They were randomized to optimal medical management alone or with CRT and followed for a mean of 29.4 months.

The main results were presented earlier this year at the annual meeting of the American College of Cardiology and have been published (N. Engl. J. Med. 2005;352:1539-49). At the time, many observers were surprised by the significant 36% reduction in all-cause mortality with CRT and were uncertain how the therapy resulted in an apparent reduction in arrhythmic death. After all, prior CRT trials had shown only a trend toward reduced mortality that did not achieve significance.

The CARE-HF steering committee authorized a 7-month extension of follow-up during which an additional 34 deaths occurred in the control arm and 19 in the CRT arm. The incidence of all-cause mortality after 36.4 months of follow-up was 24.7% with CRT and 38.1% in controls, for a 40% relative risk reduction favoring device therapy. The absolute mortality difference between the two study arms had grown from 9.7% to 13.4%.

Device therapy also conferred a 45% reduction in deaths due to worsening heart failure and a 46% decrease in sudden deaths—even though no study participant had an implantable cardioverter defibrillator (ICD).

Luigi Tavazzi, M.D., presented an analysis of serial echocardiographic studies in 735 CARE-HF participants over 29 months. The results show CRT improved cardiac function in a number of ways.

After 3 months, intraventricular mechanical delay was reduced by half in the CRT group compared with control patients and remained stable thereafter. Mitral regurgitation markedly decreased. LV ejection fraction rose by an absolute 11.2% by study's end with CRT in patients with nonischemic heart failure and by 6.0% in those with an ischemic etiology. LV end diastolic and systolic volumes each showed a net decrease of about 30 mL at 3 months, 45 mL at 18 months, and 60 mL at 29 months with CRT.

"I think that one of the main unresolved issues regarding CRT now seems to be resolved: CRT results in reverse remodeling that is sustained long term both in patients with ischemic and nonischemic heart failure," observed Dr. Tavazzi, professor of cardiology at the University of Pavia (Italy).

Nick Freemantle, Ph.D., professor of clinical epidemiology and biostatistics at the University of Birmingham (England), said his analysis showing CRT cost less than 20,000 Euros per QALY compares favorably with the recent U.K. National Institute for Clinical Effectiveness analysis of bare metal stents for revascularization, which came in at about 24,000 Euros per QALY. A recent Canadian study estimated that carvedilol for heart failure costs 13,000 Euros per QALY.

Discussant Karl Swedberg, M.D., was particularly impressed by the new echocardiographic insights into CRT's effects on cardiac function. Especially noteworthy was the reduction in LV end systolic volume, as this is a key measure of optimal myocardial contractility.

"The change was not small. It suggests the clinical benefits that we see are due to improved myocardial contractility and remodeling," said Dr. Swedberg, professor of medicine at the University of Goteborg (Sweden).

CRT is recommended for many heart failure patients in the 2005 European Society of Cardiology guidelines. The remaining question, given CRT's demonstrated ability to prevent sudden death, is: Which patients need a far more costly ICD or combined CRT/ICD device?

"That discussion will now continue," he predicted.

CARE-HF was sponsored by Medtronic Inc., for which Dr. Cleland has been a consultant and speaker. Dr. Tavazzi and Dr. Freemantle are also consultants to Medtronic. ■