Elite Controller and ART-treated HIV+ Statin versus ASA Treatment Intervention Study (ECSTATIN)

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ART	Antiretroviral Therapy
ASA	Aspirin
ATV	Atorvastatin
AUC	Area under the curve
BRB	Biostatistics Research Branch
CRP	C-Reactive Protein
CMRS	Clinical and Molecular Retrovirology Section
CRIMSON	Clinical Research Information Management System of the NIAID
CV	Cardiovascular
EC	Elite Controller
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAV IgG	Hepatitis A Virus Immunoglobin G
HAV IgM	Hepatitis A Virus Immunoglobin M
HBcAb	Hepatitis B Core Antibody
HBsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B Surface Antigen
HCMC	Hennepin County Medical Center
HCV Ab	Hepatitis C antibody
HLA	Human Leukocyte Antigen
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMOB	Intramural Clinical Management and Operations Branch
IMT	Intima-Media Thickness
IND	Investigational New Drug
IRB	Institutional Review Board
LLD	Lower limit of detection
LIR	Laboratory of Immunoregulation
mL	Milleliter
MR	Magnetic Resonance
N	Number (typically refers to number of subjects/sample size)
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NSAID	nonsteroidal anti-inflammatory drugs
OHRP	Office for Human Research Protections
PBMC	Peripheral Mononuclear Cells
PCR	Polymerase Chain Reaction
PI	Principal Investigator
RCHSPB	Regulatory Compliance and Human Subjects Protection Branch
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
sTF	soluable tissue factor

SVR	Sustained virologic response
ULN	Upper Limit of Normal
UP	Unanticipated Problem
UPnonAE	Unanticipated Problem that is not an Adverse Event

PROTOCOL SUMMARY

Full Title:	Elite Controller and ART-treated HIV+ Statin versus ASA Treatment Intervention Study (ECSTATIN)
Short Title:	Immune Activation in Elite Controllers
Clinical Phase:	Phase 1
Protocol	14-I-0039
Conducted by:	NIAID-DIR
Principal Investigator:	Irini Sereti, M.D.
Sample Size:	N=80 Elite Controller (EC) Group: N=40 Randomization arms: aspirin (ASA): N=20 atorvastatin (ATV): N=20 Treated Progressor Group (ART<50): N=40 Randomization arms: ASA: N=20 ATV: N=20
Accrual Ceiling:	N=120
Study Population:	Subjects (≥18 years) infected with the human immune-deficiency virus type 1 (HIV-1) grouped ECs (no opportunistic infections [OIs], no antiretroviral therapy [ART], stable CD4 T cell counts greater than 3 years, HIV-RNA less than the lower limit of detection (LLD) of commercially available assays) OR on continuous combination ART ≥4 years with HIV-RNA less than the lower limit of detection (LLD) of commercially available assays). Transient measurements of detectable viremia, or "blips," are allowed, if flanked by viral loads less than the lower limit of detection.
Accrual Period:	4 Years
Study Design:	This is an open-label, randomized controlled trial intended to study potential modifiers of immune activation in HIV-1 infected ECs (no OIs, no ART, stable CD4 T cell counts greater than 3 years, viral load less than the LLD of the assay used) (EC group) and treated progressers on continuous combination ART for ≥ 4 years with HIV-RNA below the limit of detection in commercially available assays (<40, <48, or <50 copies/mL, depending on the assay used) for greater than 3 years (ART <50 group). After screening at

	either Hennepin County Medical Center or the NIH Clinical Center, subjects will be enrolled on study at the NIH Clinical Center and will enter a 3 month observation period (to establish baseline values for biomarkers/cellular markers). At Month 3, participants will be randomized within each group to receive once daily oral dose of ASA 81 mg or ATV 40 mg (dose adjusted for subjects on antiretroviral regimens with significant interactions, see Section 5.3.1) and will be treated for 9 months, followed by 3 months of discontinuation of study drug.
Study Duration:	Start Date: November 2013 End Date: November 2019
Study Agent/ Intervention Description:	- ASA, 81 mg, once daily, PO for 9 months - ATV, 40 mg (dose adjusted for subjects on antiretroviral regimens with significant interactions, see Section 5.3.1), once daily, PO for 9 months
Primary Objective:	To evaluate changes from baseline in sCD14 after 9 months of treatment with ASA or ATV, in EC and Treated Progressor (ART <50) groups combined.

Secondary Objectives:

- To evaluate changes in soluble biomarkers including sCD14, IL-6, D-dimer, hsCRP, soluable tissue factor (sTF), sCD163 and other related markers of inflammation and coagulation in EC and ART <50 copies/mL groups treated with ASA or ATV with groups combined as well as independently within each group and arm, at 6, 9, and 12 months.
- To evaluate changes in T cell activation (measured by HLA-DR/CD38 co-expression), monocyte immune activation (measured by activated monocyte subsets expressing either $CD14^{++}CD16^{+}$ and $CD14^{var}CD16^{+}$ and markers of activation, CCR5 and TF, and migration, CCR2 and CX3CR1 and other relevant markers), at 6, 9, and 12 months.
- Assess if a 3-month wash out period (at Month 15) following 9 months of study drug results in biomarker and cellular activation changes.
- To compare changes of biomarkers and cellular markers between EC and ART <50 groups.
- To compare changes of biomarkers and cellular markers between ASA and ATV arms of each group and in both groups combined.

- To evaluate changes in plasma viral load, as measured by single copy assay in EC and ART <50 groups treated with ASA or ATV from baseline, to months 3 and 12.
- Assess tolerance of ASA and ATV treatment for 6 months in HIV+ participants without clinical indication for these drugs.
- Assess prevalent atherosclerotic disease in EC vs ART <50 groups by MR imaging of carotids at baseline.
- Assess changes in MR imaging of carotids after 9 months of ASA or ATV in EC or ART <50 groups, and both groups combined.
- Correlate MR vascular imaging with soluble and cellular biomarkers of inflammation.
- To assess in an exploratory study the microbiome of EC versus ART<50 groups and the possible influence of ASA or statin therapy

1 PRÉCIS

Despite dramatic improvements in mortality with antiretroviral therapy (ART), HIV-infected persons remain at risk of developing non-infectious complications, including cardiovascular, renal, and neurological disease. A small subset of the HIV-infected population achieve durable control of HIV virus in the absence of ART. These individuals, termed elite controllers (ECs), remain ART naïve, have stable CD4 T cell counts for many years and have no history of opportunistic infections. Despite the lack of AIDS complications, recent evidence suggests ECs may exhibit heightened immune activation that may contribute to a potentially increased risk for non-infectious complications, similar to successfully treated progressors.

In the current 2 group, randomized, open label trial, we intend to study the effects of a lipid lowering agent vs aspirin (ASA) on immune activation in HIV-1 infected participants. One group will consist of ECs who are HIV-1 infected, maintain HIV-RNA levels less than the LLD of commercially available assays in the absence of ART, have no history of ART or opportunistic infections (OIs) and have stable CD4 T cell counts for greater than 3 years. The second group will enroll HIV-1 infected Treated Progressors (henceforth referred to as ART <50) who have maintained HIV-RNA below the limit of detection in commercially available assays (<40, <48, or <50 copies/mL) for greater than 3 years on ART (treatment duration greater than 4 years). Up to 2 months after the screening and enrollment visit, each group will enter a 3 month observation period (to establish baseline values for biomarkers/cellular markers). After 3 months, participants from each group will be randomized to either ASA, 81 mg PO daily, or atorvastatin (ATV), 40 mg (dose adjusted for subjects on antiretroviral regimens with significant interactions, see Section 5.3.1), and will be treated for 9 months, followed by 3 months of a wash out period (see Figure 1). The primary end point will be change of sCD14 after 9 months of study intervention from Month 3 to Month 12 in each treatment arm, with groups combined (EC and ART <50). Secondary objectives will be to compare changes in soluble biomarkers (sCD14, IL-6, D-dimer, hsCRP, sTF, sCD163 and other relevant markers of inflammation and coagulation) and cellular activation markers between study groups and treatment arms (ASA vs statin and EC vs ART<50 and with groups combined), to evaluate cardiovascular (CV) disease prevalence in EC vs ART <50 by MR imaging of carotids, to determine MR measurements and correlations with biomarkers and cellular activation markers, and to investigate changes in plasma viremia as measured by single copy assay over time.

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

2.1.1 Immune Activation in HIV-infected Persons

HIV-infected individuals are currently at increased risk for non-infectious complications, including cardiovascular, renal and hepatic disease, bone loss and neurocognitive impairment, despite decreased risk of AIDS due to the development of ART [1, 2]. Biomarkers linked to non-AIDS complications (venous thromboembolism, cardiovascular disease and renal disease) including D-dimer, soluble (s) tissue factor (TF), sCD14, C-reactive protein (CRP), and proinflammatory cytokines have been observed at higher levels in HIV seropositive compared to seronegative persons [3-7]. Furthermore, elevated levels of biomarkers associated with inflammation, coagulation and monocyte activation (D-dimer, CRP, IL-6, and sCD14) have been found to be independent predictors of all-cause mortality and increased risk of AIDS [8-10]. Even in the presence of ART-induced viral suppression, HIV-infected individuals remain at a heightened risk of atherosclerotic disease and increased carotid intima-media thickness (IMT) and show increased inflammation and monocyte activation [11, 12] [13]. In HIV-negative subjects, the $CD14^{++}CD16^{+}$ activated monocyte phenotype independently predicts cardiovascular disease [14]. Monocytes are known to migrate to developing atherosclerotic plaques by chemotaxis and differentiate into macrophages on site. Macrophage activation leads to the production of oxygen radicals, inflammatory cytokines, and chemokines, ultimately causing deleterious tissue damage and increased inflammation [15].

2.1.2 Immune Activation in Elite Controllers

A small subset of the HIV-infected population (<0.5 percent) are able to maintain stable CD4 T cell counts and suppressed HIV RNA below the limit of detection in the absence of ART for decades [16-18]. Now termed elite controllers (ECs), these individuals are thought to control HIV replication through protective class I HLA haplotypes [19-21] and strong HIV-specific CD8 T cell responses [22-24]. However, despite suppression of viral replication below the limits of detection, ECs have higher rates of immune activation as measured by soluble biomarkers of inflammation such as D-dimer, IL-6, CRP, and markers of monocyte activation including soluble (s) CD163 and TF (tissue factor) [25-28] compared to healthy controls. In some cases, ECs have been noted to have higher levels of immune activation than those observed in HIV-infected progressors on effective ART (D-dimer and sTF) [29] and may possibly be at increased risk for cardiovascular complications [27].

2.1.3 Imaging and Cardiovascular Disease

For decades, imaging techniques have been used to quantify the degree of cardiovascular disease and atherosclerosis through evaluation of IMT, lumen diameter, and the presence of plaques in the coronary and carotid arteries [30, 31] [32]. Imaging studies initially utilizing B-mode ultrasonography, established an association between carotid IMT and cardiovascular events, namely increased risk of stroke and myocardial infarction [33-35]. Increasingly, carotid IMT has been used as a surrogate marker of atherosclerosis and has been shown to be a predictor of future cardiac events [32, 36]. Given the rising cost of health care in the United States, carotid ultrasonography is now being ultilized to determine

the degree of atherosclerosis in populations at increased risk for cardiovascular disease (HIV-seropostive, diabetics, autoimmune connective tissue diseases, etc) [13, 37, 38]. Consistent with previous findings that HIV-infected individuals have increased levels of biomarkers and inflammation linked to cardiovascular disease (see Section 2.1.2), HIV-infected subjects also have a greater mean carotid IMT compared to HIV-negative controls [13]. Furthermore, HIV infection has been shown to be an independent risk factor of carotid IMT [13]. These findings have been extended to ECs, who have also been shown to have higher levels of carotid IMT than HIV-seronegative controls [28] and increased coronary atherosclerosis (determined by CT) [27]. Recently, the use of magnetic resonance (MR) imaging to measure atherosclerosis has been explored and compared to carotid ultrasonography [39]. MR imaging offers high spatial resolution and has been established as accurate and sensitive for measuring plaque size and carotid IMT [40-42].

2.1.4 Effects of Statins on Cardiovascular Disease and Immune Activation

HMG-CoA reductase inhibitors, or statins, are the current first-line treatment for reduction of low-denisty lipoprotein (LDL) cholesterol [43] and have been shown to prevent cardiovascular disease, myocardial infarction and stroke in both patients with established cardiovascular disease and subclinical disease [44, 45]. Statins greatly decrease all-cause mortality and act to reduce low-density lipoprotein cholesterol and C reactive protein, known independent predictors of cardiovascular events [46-50]. Studies have also focused on the ability of statins to impede or reverse progression of cardiovascular disease, measured by atheroma volume and carotid IMT. Among the statins currently available on the market, atorvastatin (ATV) has emerged as a statin of choice in studying the effects of statins on cardiovascular disease regression, given it's availability as a generic medication, the widespread familiarity with its use, and well-characterized safety profile [51, 52]. While atorvastatin is a CYP3A substrate, less potent drug interactions have been observed with CYP3A inhibitors than with other statins metabolized through this pathway [53]). ATV has been shown to have a comparable ability to lower LDL cholesterol and raise HDL cholesterol compared with other statins and has been associated with a reduction in cardiovascular events [53-57]. In a study of atorvastatin in patients with stable cardiovascular disease, regression of carotid IMT was noted that correlated with changes in inflammation, thrombosis and endothelial activation profiles [58] and atorvastatin has been associated with reductions in pro-inflammatory cytokines, including CRP [59] and sCD14 [60] in high risk patients.

2.1.5 Platelet Aggregation and HIV

Platelets aggregate and adhere to the site of vascular injury and secrete products such as adenosine diphosphate, thrombin, epinephrine, and thromboxane A2 that mediate clot formation and amplify the platelet response **[61]**. While platelets play a critical role in the maintenance of the endothelium and homeostasis through plug formation, exhuberant platelet activation is associated with increased carotid IMT **[62, 63]** and ultimately increased arterial and venous thromboembolic events **[64, 65]**. Increased thromboxane metabolites, a secretion product of activated platelets, have been linked to accelerated atherogenesis and acute coronary syndromes **[66-68]**. Increased platelet aggregation is also associated independently with mortality and cardiovascular events **[69]**. Given that HIV-infected individuals have increased risk of thrombotic and cardiovascular events, it is not surprising that they exhibit heightened platelet activation. Specifically, HIV-infected

individuals are known to have increased expression of P-selectin, a marker of platelet activation that is critical in the recuirment and adhesion of pro-inflammatory leukocytes to the site of endothelial injury **[70]**. In a case control matched study, we found that soluble vascular cell adhesion molecule-1 (sVCAM-1), a biomarker upregulated by vascular endothelial cells in response to proinflammatory cytokines, was significantly elevated in HIV-infected individuals preceding an incident cardiovascular event compared to HIV-infected controls [7]. Furthermore, HIV-infected individuals have increased circulating platelet-monocyte complexes, an additional marker of platelet activation **[71, 72]**.

2.1.6 Effect of Aspirin on Cardiovascular Disease and Immune Activation

Aspirin (ASA) is a potent COX-1 inhibitor that prevents the formation of prostaglandin H2 and thus thromboxane A2, a vasoconstrictor important in recruitment of circulating platelets and granule secretion [73]. In HIV-uninfected individuals, ASA has been used for decades to prevent cardiovascular disease, including incidence of myocardial infarction and stroke [73-75]. Numerous placebo-controlled trials with doses ranging from 50 mg daily to 1300 mg daily have confirmed the antithrombotic properties of ASA [76], with 81 mg or 325 mg the most commonly prescribed doses in the United States. However, ASA usage (even 100 mg on alternate days) is associated with increased risk of gastrointestinal (GI) bleeding [75, 77]. Despite the adverse GI effects of ASA, it has a favorable safety profile at low doses and remains one of the most commonly used drugs worldwide [74, 78].

2.1.7 Targeting Cardiovascular Disease in HIV-infected Persons

A new study proposed by the AIDS Clinical Trial Group (ACTG) is designed to target immune activation in ECs through treatment with ART (A5308, NCT 01777997), with a primary endpoint looking at co-expression of HLA-DR and CD38 on CD8 T cells at 24 and 48 weeks on ART. ART may pose some risks in terms of side effects and may cause a potential decrease or even loss of HIV-specific responses in this unique population. Recently, studies have shown a trend towards decreased mortality with HMG Co-A reductase inhibitors (or statin) therapy [79] and decreased markers of immune activation, as measured by sCD14, with ASA [80] and with statin therapy in HIV positive individuals [81]. In a substudy of the SATURN-HIV trial (a randomized, double-blind trial of ATV in HIV positive individuals, targeting subclinical cardiovascular disease), significant reductions were observed in soluble and cellular markers of monocyte activation after as little as 6 months (24 weeks) on therapy [81], and in a subanalysis of the SMART study, sCD14 was associated with mortality [10]. Additionally, it has been recently reported in a preliminary study that statin use (predominately rosuvastatin and pravastatin) reduces the risk of cancer in HIV-infected persons [82]. We propose to target immune activation with low-dose ASA or ATV therapy in both ECs and ART-treated HIV+ patients with suppressed viremia (ART <50), with change from month 3 in sCD14 as a primary outcome after 9 months of intervention (ASA vs ATV).

2.1.8 Gut microbiome and inflammation in HIV infected persons

The gut microbiome in HIV infected people may be playing a role in inflammatory responses (STM McCune) and to investigate this we will study stool microbiome at baseline [86].

2.2 Rationale

It is well-established that HIV-seropositive persons are at increased risk of cardiovascular disease. Within the HIV-infected population, there exists a unique subset of HIV-infected individuals, termed ECs, who maintain stable CD4 T cells counts and suppressed plasma HIV-RNA in the absence of antiretroviral therapy (ART). Despite their ability to control HIV viral replication, recent studies have demonstrated heightened immune activation and atherosclerosis in ECs compared to HIV-uninfected individuals [27, 28]. While ART is known to decrease immune activation in HIV-infected persons, it is costly, poses some risk of adverse effects, and may decrease HIV-specific immune responses in this group. In addition, as ART-treated persons still maintain higher levels of biomarkers that are linked to all cause mortality and have excess cardiovascular risk, it is feasible that ART alone in EC will not reverse the small decrease of inflammation and may necessitate treatment with both ART and an additional anti-inflammatory intervention. ATV and ASA are 2 well-studied and well-tolerated drugs known to decrease immune activation and prevent cardiovascular events with minimal side effects.

We propose to study the effects of ATV and ASA on biomarkers and cellular markers of immune activation and carotid-intima thickness. ECs and HIV-infected persons with suppressed HIV-RNA on ART (Treated Progressors) will be randomized to either a ATV or ASA open-labeled study arm. Because ATV bioavailability is increased when co-administered with certain antiretrovirals [53] the study dose would be adjusted in subjects on antiretroviral regimens with significant interactions (see Section 5.3.1). ASA will be dosed at 81 mg daily. At these doses, there is limited risk for adverse effects from either medication despite good anticipated efficacy.

The impact of 9 months of ATV or ASA therapy will be assessed through changes in biomarkers and cellular markers of activation, with the primary endpoint set as a change in sCD14, which has been linked to all-cause mortality in HIV-infected individuals. Additional biomarkers will include high sensitivity C reactive protein (hsCRP), soluble Tissue Factor (sTF), IL-6 and D-dimer. Furthermore, markers of T cell and monocyte activation will also be investigated. Lastly, we will observe the impact of therapy on cardiovascular disease progression through MR imaging of the carotid arteries. This study is utilzing MR imaging over carotid ultrasonography as it offers increased resolution, is free of radiation and provides similar results to ultrasonography. A washout period is included to elucidate if changes in biomarkers and cellular markers can be attributed to either ATV or ASA.

3 STUDY OBJECTIVES

3.1 Primary Objective

- To evaluate changes from baseline in sCD14 after 9 months of treatment with ASA, or ATV, in ECs and in Treated Progressors (ART <50), with the groups combined.

3.2 Secondary Objectives

- Compare changes in soluble biomarkers (sCD14, IL-6, D-dimer, hsCRP, sTF, sCD163 and other relevant markers of inflammation and coagulation) and cellular activation markers between study groups and treatment arms (ASA vs statin and EC vs ART<50 and with groups combined) at 6, 9, 12 months, and after 3 month washout at 15 months. Comparisons between EC and ART<50 will be adjusted for CD4, smoking status and age.
- Evaluate cardiovascular (CV) disease prevalence in EC vs ART <50 by MR imaging of carotids at baseline and follow how it changes over time
- Determine MR measurements and correlations with biomarkers and cellular activation markers
- Investigate changes in plasma viremia as measured by single copy assay
- To assess in an exploratory sudy the microbiome of EC versus ART<50 groups and the possible influence of ASA or statin therapy
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3.3 Description of the Study Design

We propose a study of 40 ECs and 40 Treated Progressors (ART <50) who between screening and 2 months after screening will enter a 3-month observation period to establish baseline values for biomarkers/cellular markers. At Month 3, subjects will be randomized to either ASA, 81 mg daily, or ATV, 40 mg (dose adjusted for subjects on antiretroviral regimens with significant interactions, see Section 5.3.1).

Study treatment will continue for 9 months until month 12 (primary end point), followed by a 3 month washout period (see

Figure 1).

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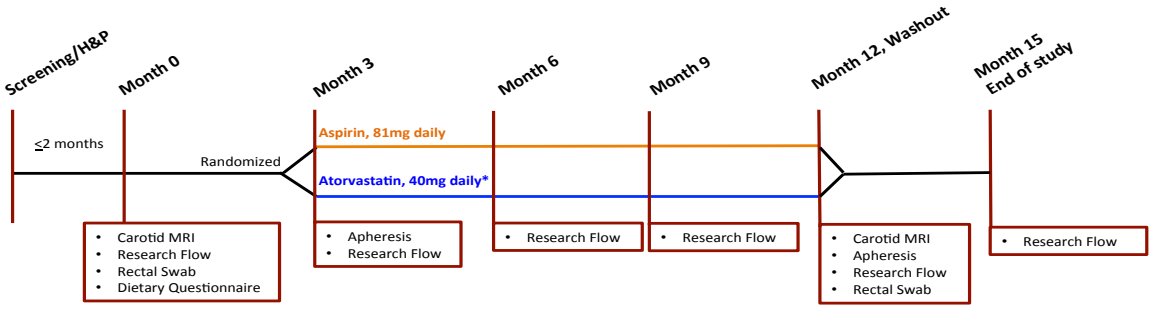
Figure 1

Figure 1. Study Schema



* ATV will be dose adjusted for subjects on ART regimens with significant interactions.
**PBMCs, Serum, Plasma, Safety Labs, and Fasting Lipid Profile will be collected at each study visit.

3.4 Study Endpoints

3.4.1 Primary Endpoint

The primary end point will be change of sCD14 from Month 3 to Month 12 in the 2 groups combined (EC and ART <50).

3.4.2 Secondary Endpoints

- To evaluate changes in soluble biomarkers (sCD14, IL-6, D-dimer, hsCRP, sCD163, sTF as well as other relevant markers of inflammation and coagulation) in EC and ART <50 groups treated with ASA or ATV, independently within each group and arm and with groups combined, at 6, 9, and 12 months.
- To evaluate changes in T cell activation (measured by HLA-DR/CD38 co-expression), monocyte immune activation (measured by activated monocyte subsets expressing either $CD14^{++}CD16^{+}$ and $CD14^{var}CD16^{+}$ and markers of activation, CCR5 and TF, and migration, CCR2 and CX3CR1), at 6, 9, 12 months of study.
- To investigate differences in HLA type, which has been implicated as a mechanism of viremic control in ECs, between groups and treatment arms, as it relates to treatment response.
- Assess if a wash out period following 9 months of therapy results in biomarker and cellular activation changes after 3 months (Month 15).
- To compare changes of biomarkers and cellular markers between EC and ART <50 groups after adjusting for smoking, CD4 counts and age.
- To compare changes of biomarkers and cellular markers between ATV and ASA arms of each group and in both groups combined.
- To evaluate changes in plasma viral load, as measured by single copy assay in EC and ART <50 groups treated with ASA or ATV at baseline, 3 and 12 months.
- Assess toxicity profile of ASA versus ATV in the study population.
- Assess prevalent atherosclerotic disease in EC vs ART<50 by MR imaging of carotids.
- Assess changes in MR imaging of carotids after 9 months of statin or ASA in each group and both groups combined.
- Correlate MR vascular imaging with soluble and cellular biomarkers of inflammation.

3.4.3 Exploratory Endpoints

Change in carotid IMT by MR between Month 0 and Month 9.

4 STUDY POPULATION

4.1 Rationale for Subject Selection

Selection criteria for ECs were created based on the well-established definition that EC/Long-term Non-progressors are HIV-1 infected subjects with a suppressed viral load of <40 (or <48 or <50) copies/mL (depending on the assay used) in the absence of ART. Additionally, they have no history of opportunistic infections and stable CD4 T cells counts [83]. Selection criteria for Treated Progressors (ART <50) are based on the

accepted standard that HIV-1 infected individuals on ART who achieve virological suppression have a HIV-RNA level of <40 (or <48 or <50) copies/mL.

Since this study is seeking to establish the biomarker, cellular and cardiovascular effects of treatment with ATV and ASA, participants must not have received statin or ASA therapy for 6 months prior to the screening visit. In order to eliminate any confounding effects, patients will also be excluded if they have received any immunomodulating therapy, systemic corticosteroids or chronic daily nonsteroidal anti-inflammatory drugs (NSAID) use unless discussed with and approved by the study investigator.

4.2 Recruitment Plan

Subjects will be recruited from the NIH Clinical Center, particularly from the NIH CCMD/NIAID OP8 Clinic, and from University of Minnesota Hennepin County Medical Center. The study may also be advertised through web based campaign as study visits are infrequent and we may need to recruit from outside the local area.

Subjects recruited from University of Minnesota, Hennepin County will sign consents at this site and all screeining procedures including initial history and physical Assesments, lab work to determine eligibility will be done before sending them to NIH clinical Center OP8 clinic. These subjects will continue into month 0 and complete the rest of the study visits at NIH.

Prior to study implementation, sites must obtain Institutional Review Board (IRB) approvals. Health care providers and research personnel at participating institutions will identify potentially eligible subjects. Once a subject for study entry is identified and expresses interest in learning about the study, the subject will be approached by the study team about participation in the protocol. If the subject remains interested, study details and the informed consent form (ICF) will be reviewed with the candidate by the study PI/designee. If the subject is willing to participate in the study, he or she will be provided with a copy of the informed consent to review. If a subject requires more time to consider the study, the staff member will give them a copy of the informed consent along with the staff member's contact information, so that subjects may take the documents home for further review. After questions related to the study and the informed consent has been answered to the subject's satisfaction, subjects will be asked to sign the IRB-approved consent form.

4.3 Subject Inclusion Criteria

EC Arm

1. Age ≥18 years.
2. Documented HIV-1 infection confirmed by enzyme-linked immunosorbent assay (ELISA) and Western blot tests (will not be repeated if performed previously at NIH).
3. Categorized as a long term non-progressor EC as defined by viral loads typically less than the LLD of commercially available assays and clinical and laboratory criteria (no OIs, no ART, stable CD4 T cell counts for more than 3 years). Viral load "blips" are allowed as long as they are <500 copies/mL and flanked by viral

load measurements less than limit of detection of the commercially available assay. Viral load <100c/mL will be acceptable for eligibility at screening.
4. In women of childbearing potential, with no plans for pregnancy for the next 15 months and willing to use 2 investigator approved highly reliable methods of birth control consistently while on the study or in 3 month follow up.
5. Willingness to have samples stored for future research.
6. Not on a statin or ASA for the past 6 months.

ART <50 Arm

1. Age ≥18 years.
2. Documented HIV-1 infection confirmed by enzyme-linked immunosorbent assay (ELISA) and Western blot tests.
3. In women of childbearing potential, with no plans for pregnancy for the next 15 months and willing to use 2 investigator approved highly reliable methods of birth control consistently while on the study or in 3 month follow up.
4. On continuous combination ART >4years.
5. HIV RNA <50 copies/mL (or <40 or <48 copies/mL, depending on the lower limit of detection of the assay used; transient periods of low level (<300) detectable virus, "blips," acceptable if isolated and followed by <50 copies/mL values) >3 years and current HIV-RNA less than the LLD of the commercially available assay used. Subject will be rescreened if HIV detectable at screening visit.
6. Willingness to have samples stored for future research.
7. Not on a statin or ASA for the past 6 months.

4.4 Participation of Women:

Decreased cholesterol synthesis caused by ATV may cause fetal harm when administered to women who are pregnant; ATV has been listed as a pregnancy category X drug. ASA has been listed as a pregnancy category D drug by the Food and Drug Administration (FDA) due to the potential for known teratogenic or abortifacient effects on the developing fetus. Subjects must agree not to become pregnant. Females of childbearing potential must have a pregnancy test before initiating the study agent and at each study visit. Because of the risk involved, sexually active subjects and their partners must use 2 methods of birth control, one of which must be a barrier method. They must continue to use both methods until the end of study visit (Month 15). The methods of birth control may be selected from the list included below:

- Hormonal contraception
- Male or female condoms with or without a spermicide
- Diaphragm or cervical cap with a spermicide
- Intrauterine device (IUD)

- Male partner with a vasectomy

If pregnancy is suspected or should occur, subjects must notify the study staff immediately.

4.5 Subject Exclusion Criteria

1. Diagnosis of cardiovascular disease or hypercholesterolemia (LDL cholesterol ≥.190 mg/dL).
2. Known hypersensitivity or allergy to ATV or ASA, including a history of myositis or rhabdomyolysis with statin or ASA use.
3. Other contraindication for ASA or statin therapy (active liver disease, peptic ulcer disease, etc.).
4. Women who are lactating, pregnant, or actively trying to become pregnant or considering pregnancy over the likely span of the study (including women of childbearing potential who are unwilling to use adequate contraception throughout the study).
5. Any chronic inflammatory condition either requiring anti-inflammatory medication (systemic corticosteroids, daily NSAID use,immunomodulating medications) which may, in the opinion of the investigator, confound the interpretation of soluble inflammatory biomarkers. While on study, short term (less than 5 days) NSAID use will be allowed at the discretion of the investigator.
6. Active drug use or alcohol abuse that, in the opinion of the investigator, may interfere with the ability of the subject to participate in the study or that may unacceptably increase the risk of the study intervention..
7. Safety laboratory cut offs: coagulation (INR >2 upper limit of normal [ULN], PLT<75K), renal function (GFR<60), liver function (ALT or Alkaline phosphatase or direct bilirubin >2x ULN), aldolase <1.5 ULN and anemia (Hg <9 mg/dL).
8. Antiretroviral therapy with tipranivir, or any therapy which combines non-nucleoside reverse transcriptase inhibitors with protease inhibitors.
9. Chronic hepatitis C co-infection. However, if a subject has more than 24 weeks of sustained virologic response (SVR), the subject can be considered for eligibility.
10. If either MR or apheresis is contraindicated, subject may still participate without this procedure. In the case of missed apheresis, a 30 mL research blood draw will be substituted (see Appendices B and C).
11. If statin initiation is indicated per current guidelines, subject will be counseled to consult with their PMD. If the subject then chooses to take part in the study, we will provide their PMD with all pertinent lab results during the course of the study, if requested.

Co-enrollment Guidelines: Co-enrollment in other trials will be restricted, other than enrollment on observational studies. Study staff should be notified of co-enrollment as it may require the approval of the Investigator.

4.6 Justification for Exclusion of Women and Children (Special Populations)

4.6.1 Exclusion of Women

- **Pregnancy:** Pregnant women are excluded from this study because there are known adverse effects of ATV, a pregnancy category X drug, on the developing human fetus.

ASA has been listed as a pregnancy category D drug by the FDA due to the potential for known teratogenic or abortifacient effects on the developing fetus.

- **Breast-feeding:** Because there is an unknown but potential risk for adverse events (AEs) in nursing infants secondary to treatment of the mother with ATV, breastfeeding should be discontinued if the mother will be treated with ATV. There is a known risk for AEs in nursing infants secondary to treatment of the mother with ASA, therefore breastfeeding should be discontinued if the mother will be treated with ASA.

4.6.2 Exclusion of Children

Because there are insufficient data regarding dosing or AEs available in HIV-infected adults to judge the potential risk in HIV-infected children, children are excluded from this study.

5 STUDY AGENT/INTERVENTIONS

5.1 Disposition and Dispensation

Study agents will be distributed via the NIH Central Pharmacy according to standard pharmacy procedures.

5.1.1 Formulation, Packaging, and Labeling

Each bottle will be individually labeled with the participant ID number, dosing instructions, recommended storage conditions, the name and address of the manufacturer, randomization number, and that the agent should be kept out of reach of children.

5.2 Study Agent Storage and Stability

Both ATV and ASA should be stored at room temperature, 20-25°C (68-77°F).

5.3 Preparation, Administration, and Dosage of Study Agent/Intervention(s)

5.3.1 Study Agent : atorvastatin

Description

Dosing and Administration: 40 mg tablet, daily. In subjects on certain antiretroviral medications, ATV dosing will be adjusted in accordance with DHHS guidelines [84]. See Table 1 below for list of antiretroviral agents requiring adjustment. Briefly, in subjects on cobicistat -or ritonavir- boosted protease inhibitor or elvitegravir-based regimens, the atorvastatin AUC can increase by 3-6 fold [87]. In subjects on protease inhibitor (other than tipranavir) or elvitegravir-based regimens, the atorvastatin dose will be decreased to 20mg daily. In subjects on efavirenz or etravirine-based regimens, atorvastatin AUC can decrease from 32 to 43%. Therefore, in subjects on efavirenz or etravirine-based regimens, the dose of atorvastatin will be increased to 80mg daily. Dosing of ATV with other ART regimens will also be made in accordance with DHHS guidelines [84].

Table 1. Atorvastatin Interactions with Selected Antiretrovirals and Dosing Recommendations

Antiretroviral Medication	Effect on Atorvastatin	Adjusted Atorvastatin
Atazanavir, Atazanavir with Ritonavir or Cobicistat	Increased Atorvastatin possible	20mg,daily
Darunavir with Ritonavir or Cobicistat	DRV/r + Atorvastatin 10mg similar to Atorvastatin 40mg administered alone	20mg daily
Elvitegravir with Cobicistat (or Ritonavir)	Increased Atorvastatin possible	20mg, daily
Lopinavir with ritonavir	Increased AtorvastatinAUC 488%	20mg daily
Efavirenz, Etravirine	Decreased Atorvastatin AUC 32-43%	80mg daily
Rilpivirine	Atorvastatin AUC unchanged	40mg daily

Route of Administration: PO

Duration of Therapy: 9 months

Tracking of Dose: pill count and participant stated compliance.

Limitations on Prior Therapy: Prior statin therapy allowable if therapy ceased at least 6 months prior to the screening visit.

Subject Access to Study Agent at Study Closure: ATV is only available by prescription, and subjects will be counseled to consult with their primary physician before considering chronic therapy.

5.3.2 Study Agent: aspirin

Description

Dosing and Administration: 81 mg tablet, daily

Route of Administration: PO

Duration of Therapy: 9 months

Tracking of Dose: pill count and participant stated compliance.

Limitations on Prior Therapy: Prior chronic asprin use allowable if therapy ceased at least 6 months prior to the screening visit.

Use of Ancillary Medications/OTC Products/Foods: Use of systemic corticosteroids, daily NSAID use or immunomodulating medications prohibited at the discretion of the principal investigator (PI)

Subject Access to Study Agent at Study Closure: While ASA is available over-the-counter, subjects will be counseled to consult with their primary physician before considering chronic ASA therapy.

5.4 Study Product Accountability Procedures

We will follow the NIH Central Pharmacy study product accountability procedures.

5.5 Assessment of Subject Compliance with Study Agent/Intervention(s)

Particpants will be asked about missing pills at each visit and a pill count will be performed.

5.6 Concomitant Medications and Procedures

All concomitant prescription medications taken during study participation will be documented in the Clinical Research Information Management System of NIAID (CRIMSON). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in CRIMSON are concomitant prescription medications, over-the-counter medications and non-prescription medications taken at the time of AEs (all grades except grade 1).

5.7 Prohibited Medications and Procedures

Treatment with immunomodulating agents, systemic corticosteroids and daily NSAIDs will not be permitted unless discussed with and approved by the study investigator. Subjects treated with a statin or ASA daily up to 6 months prior to the screening visit will also be excluded. Treatment with tipranavir will be prohibited because ATV is contraindicated in these patients. Treatment with any ART regimen combining a non-nucleoside reverse transcriptase inhibitor with a protease inhibitor will be prohibited because of the lack of data concerning drug interactions with ATV.

6 STUDY SCHEDULE

For the purposes of this study, a month is a calendar month. A window of up to ± 2 weeks will be acceptable for all visits after the baseline visit. Visits that include procedures (MRI or pheresis) may be completed in more than one day.

6.1 Screening

Subjects will be screened at either the NIH Clinical Center or Hennepin County Medical Center and undergo the following procedures subsequent to signing informed consent:

- Review patient eligibility
- Physical examination, medical history and medication history (including herbal supplements)
- HIV RNA, CD4
- Pregnancy testing (urine or serum) in women of child-bearing potential
- Safety labs (Hematology, PT/PTT, Chemistry, Liver Function Tests, Urinalysis, Creatine Kinase, Aldolase)

- Hepatitis serology (HBsAg, anti-HBcAb and anti-HBsAb, anti-HAV IgG, HCV Ab and HCV PCR) HCV Ab testing accepted from outside lab if performed within 2 months of Baseline Month 0 visit.
- D-dimer, fibrinogen, Protein C and S, antithrombin III,
- Fasting lipid profile
- Documentation of HIV infection status

6.2 Enrollment/Baseline (Month 0)

This visit, and all subsequent visits, will take place at the NIH Clinical Center only. This Enrollment/Baseline Month 0 Visit will occur between 2 days and 2 months of screening, At Month 0, enrolled subjects will undergo the following procedures:

- Physical examination, medical history and medication history (including herbal supplements)
- Laboratory data for HIV RNA, CD4
- Research flow cytometry
- PBMCs, serum and plasma for research and storage
- Safety labs (Hematology, PT/PTT/D-dimer, Chemistry/CRP, Liver Function Tests, Urinalysis, Pregnancy Testing, Creatine Kinase, Aldolase)
- D-dimer, fibrinogen, Protein C and S, antithrombin III
- Fasting lipid profile
- Hemoglobin A1c
- HLA typing (if not previously performed at NIH)
- Carotid MRI
- ELISA and Western Blot (if not previously performed at NIH)
- Rectal swab and dietary questionnaire for microbiome studies
- Framingham Risk Score Calculation

6.3 Randomization

The NIH Pharmacy Department will carry out blocked, open-label, randomization using a random number generator. At the Month 3 study visit, ECs and Treated Progressors will be separately randomized 1:1 to open label ASA or ATV arms.

6.4 Study Phase – Month 3 (± 2 weeks)

Following randomization, study participants will initiate study drug and the following procedures at this vist:

- Initiation of open label ATV 40 mg (dose adjusted for subjects on antiretroviral regimens with significant interactions, see Section 5.3.1) or ASA 81 mg PO daily,

- Targeted physical examination, medical history and medication history (including over the counter medications and herbal supplements)
- HIV RNA, CD4
- Research flow cytometry
- PBMCs, serum and plasma for research and storage
- Safety labs (Hematology, PT/PTT/D-dimer, Chemistry/CRP, Liver Function Tests, Urinalysis, Pregnancy Testing (for females of childbearing potential), Creatine Kinase, Aldolase)
- D-dimer, fibrinogen, Protein C and S, antithrombin III
- Fasting lipid profile
- Hemoglobin A1c
- 1 L leukapheresis (prior to drug initiation)

6.5 Study Phase – Month 6 and Month 9 (± 2 weeks)

Study participants will continue study drug and will undergo the following procedures at this visit:

- Targeted physical examination, medical history and medication history (including over the counter medications and herbal supplements)
- HIV RNA, CD4
- Research flow cytometry
- PBMCs, serum and plasma for research and storage
- Safety labs (Hematology, PT/PTT/D-dimer, Chemistry/CRP, Liver Function Tests, Urinalysis, Pregnancy Testing (for females of childbearing potential), Creatine Kinase, Aldolase)
- D-dimer, fibrinogen, Protein C and S, antithrombin III
- Fasting lipid profile
- Hemoglobin A1c

6.6 Washout Phase – Month 12 (± 2 weeks)

The follow procedures will be completed at Month 12:

- Discontinuation of ATV and ASA therapy
- Targeted physical examination, medical history and medication history (including over the counter medications and herbal supplements)
- HIV RNA, CD4
- Research flow cytometry
- PBMCs, serum and plasma for research and storage

- Safety labs (Hematology, PT/PTT/D-dimer, Chemistry/CRP, Liver Function Tests, Urinalysis, Pregnancy Testing (for females of childbearing potential), Creatine Kinase, Aldolase)
- D-dimer, fibrinogen, Protein C and S, antithrombin III
- Fasting lipid profile
- Hemoglobin A1c
- Carotid MRI
- 1 L leukapheresis
- Rectal swab

6.7 End of Study Visit – Month 15 (± 2 weeks)

- Targeted physical examination, medical history and medication history (including over the counter medications and herbal supplements)
- HIV RNA, CD4
- Research flow cytometry
- PBMCs, serum and plasma for research and storage
- Safety labs (Hematology, PT/PTT/D-dimer, Chemistry/CRP, Liver Function Tests, Urinalysis, Pregnancy Testing (for females of childbearing potential), Creatine Kinase, Aldolase)
- D-dimer, fibrinogen, Protein C and S, antithrombin III
- Fasting lipid profile
- Hemoglobin A1c

6.8 Early Termination Visit

If a subject becomes pregnant (see section 6.9) or experiences a life-threatening adverse reaction related to either ATV or ASA and is forced to terminate study drug, the subject will continue to be followed at the established study time points until Month 15, with only safety laboratory tests drawn.

6.9 Pregnancy and Follow-up Visit

Urine or serum pregnancy tests will be performed for all female participants of childbearing potential at each study visit. All pregnancy tests must be negative in order to continue participating in the protocol. The following actions will be taken if the PI is notified that a female participant becomes pregnant while on study:

- Withdrawal of the participant from the study if the pregnancy occurs before drug administration.
- Discontinuation of study drug (both ATV and ASA) immediately if the pregnancy occurs during the treatment phase. The patient will be referred to a maternal fetal medicine specialist. The patient will be followed as necessary by the study team

throughout the remainder of the study period or until the time of birth (whichever occurs later), for safety assessments and labs.

6.10 Recontact of Subjects After Trial Termination

Subjects may be recontacted after trial termination to be informed about study results and possibly to be notified about potential similar follow-up studies.

7 STUDY PROCEDURES/EVALUATIONS

7.1 Clinical Evaluations

- Medical/medication/social history with complete or targeted physical examination. Physical examination will include:
    - Vital signs (temperature, pulse, resting blood pressure, respiratory rate, oxygen saturation)
    - Skin
    - Head, ears, eyes, nose, and throat
    - Oral mucosa
    - Lymph nodes (including cervical, axillary, clavicular, and inguinal)
    - Respiratory system
    - Cardiovascular system
    - Abdominal area
    - Neurological system
    - Musculoskeletal system

- Targeted examination will take place at study time points after screening and Month 0 visits.

- Participants with a contraindication for MR will not be required to undergo the procedure.

7.2 Laboratory Evaluations

- Apheresis: Participants with inadequate venous access will only undergo an additional 30 mL blood draw (see Appendices B and C).
- Phlebotomy: Collection of blood for safety lab tests, fasting lipid prolife, hepatitis serology, hemoglobin A1c, coagulation studies, HIV-1 serology and storage.
- Research flow cytometry: activation of T cells and monocytes at study time points
- CD4, HIV-RNA levels, HLA typing
- Microbiome studies which consists of a rectal swab and dietary history questionnaire.

7.2.1 Clinical and Research Laboratory Evaluations and Specimen Collection

All safety labs will be performed at the NIH Clinical Center, as well as hsCRP and D-dimer. Testing for research chemokines (such as IP-10), cytokines (ie IL-6,

TNA-α, and IL-10), soluble biomarkers (including sCD14, IL-6, and sTF) and flow cytometry will be batched and performed at Leidos Biomedical Research, Inc. Leidos Biomedical Research, Inc. will also process and organize research stored samples.

7.3 MRI Evaluations

All MRIs will be reviewed by the NIH Clinical Center radiologist according to standard clinical protocols and the read entered into the patient chart. If an individual participant is found to have clinically significant abnormalities as a result of participation in this study, the findings will be reviewed with the patient in detail by the study team. This will include any clinical recommendations for future care or follow-up testing, and this information will also be provided to the subject's doctor(s) when indicated.

In order to answer the research objective, an MR reading for research with IMT measurement will be performed by Dr Gharib or Dr Patronas (study collaborator) who will not be involved in he clinical care of the patients.

8 POTENTIAL RISKS AND BENEFITS

8.1 Potential Risks

Atorvastatin:

Per the package insert (Appendix D), the following warnings and precautions should be considered:

- **Skeletal Muscle Effects**: Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin calcium tablets and with other drugs in this class. Atorvastatin, like other statins, occasionally causes myopathy,, defined as muscle aches or weakness in conjunction with increases in CPK values >10 times ULN.The comcomitant use of higher doses of atorvastatin with certain drugs such as cyclosporine and strong CYP3A4 inhibitors (e.g. clarithromycin, itraconazole, and HIV protease inhibitors) increases the risk of myopathy/rahbdomyolysis.
- **Liver Dysfunction:** Persistent elevations (<3 time ULN occurring on 2 or more occasions in serum transaminases occurred in 0.7% of patients who received atorvastatin calcium tablets in clinical trails.
- **Endocrine Effects:** "Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors," including ATV.

Aspirin:

According to the ASA package insert (Appendix E), the following warnings and precautions should be considered in patients with the following morbidities:

- **Alcohol Warning:** Increased bleeding risks may occur in patients who consume 3 or more alcoholic drinks a day.
- **Coagulation Abnormalities:** "Even low doses of ASA can inhibit platelet function leading to an increase in bleeding time. This can adversely affect patients with inherited (hemophilia) or acquired (liver disease or vitamin K deficiency) bleeding disorders."
- **GI Side Effects:** "GI side effects include stomach pain, heartburn, nausea, vomiting, and gross GI bleeding."
- **Peptic Ulcer Disease:** ASA can cause gastric mucosal irriation and bleeding so patients with a history of active peptic ulcer disease should avoid use.
- **Renal Failure:** Patients with glomerular filtration rates less that 10 mL/minute should avoid use.
- **Hepatic Insufficiency:** Avoid use in patients with hepatic insufficiency.
- **Sodium Restricted Diet:** The high sodium content in buffered ASA preparations should be avoided in patients with sodium retaining states (ie congestive heart failure or renal failure).

Phlebotomy

The risks associated with phlebotomy include discomfort, bruising, local hematoma formation and, on rare occasions, infections, lightheadedness, and fainting. The amount of blood drawn for research purposes will be within the limits allowed for adult subjects at the NIH Clinical Center (Medical Administrative Policy 95-9: Guidelines for Limits of Blood Drawn for Research Purposes in the Clinical Center: http://cc-internal.cc.nih.gov/policies/PDF/M95-9.pdf).

Apheresis

The potential risks associated with apheresis include lightheadedness, dizziness, possible fainting, tingling around the mouth and in the fingers and toes, nausea, chills, vomiting, mild muscle cramps, loss of <1 pint of blood, or pain, bruising, or discomfort at the needle insertion sites. More serious, but rare, complications include nerve damage at the needle insertion site, seizures and air embolism. Most procedures are performed without an incident. Blood components removed during apheresis are generally replaced by the body within a few hours or a few days. No infections associated with this procedure have been reported in thousands of cases performed over the last 10 years at the NIH.

Magnetic Resonance Imaging

Patients with pacemakers, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including heart valves and cochlear implants), or shrapnel fragments in critical sites, such as the orbit or the brain are at risk of injury from MR imaging. Welders and metal workers are also at risk for injury because of possible metallic foreign bodies in

the eye. The patient will lie flat in a long metal cylinder. No pain will be felt, but this may be uncomfortable if the patient fears closed spaces. An operator will be present at all times for observation and assistance if necessary. If requested, removal from the machine can occur at any time.

Rectal Swabs
Participant may experience pressure as the swab is inserted into the rectum, but the test is usually not painful.

8.2 Potential Benefits
Participation in the study provides no direct benefit to volunteer participants, although similar treatments have been of benefit in other patients with increased cardiovascular risk. Currently, no treatment exists that addresses increased immune activation and cardiovascular disease in HIV-infected individuals; therefore this study may benefit future populations of HIV-infected persons with risk of cardiovascular events.

9 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS, OR DATA

- **Intended Use:** Samples and data collected under this protocol may be used to study biomarkers and cellular markers of activation or other immune measurements that are relevant to HIV infection or similar immunodeficiencies as well as cardiovascular disease. Any other research or experimental treatments will be done under this or other protocols for which separate signed informed consent documents will be obtained.
- **Storage:** Access to stored samples will be limited using either a locked room or a locked freezer. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
- **Tracking:** Samples will be tracked utilizing the NCI at Frederick Central repository operated by Leidos Biomedical Research, Inc. Data will be stored and maintained in the CRIMSON database.

- **Disposition at the Completion of the Protocol:**
  - In the future, other investigators (both at NIH and outside) may wish to study these samples and/or data. In that case, IRB approval must be sought prior to any sharing of samples and/or data. Any clinical information shared about the sample would similarly require prior IRB approval.
  - At the completion of the protocol (termination), samples and data will either be destroyed, or after IRB approval, transferred to another existing protocol.

- **Reporting the Loss or Destruction of Samples/Specimens/Data to the IRB:**
  Any loss or unanticipated destruction of samples (for example, due to freezer malfunction) or data (for example, misplacing a printout of data with identifiers) that meets the definition of a Protocol Deviation, Unanticipated Problem, and/or compromises the scientific integrity of the data collected for the study, will be reported to the NIAID IRB.

- Additionally, subjects may decide at any point not to have their samples stored. In this case, the principal investigator will destroy all known remaining samples and report what was done to both the subject and to the IRB. This decision will not affect the subject's participation in this protocol or any other protocols at NIH. *(If applicable).*

10 REMUNERATION PLAN FOR SUBJECTS

Eligible subjects will be compensated for travel according to the NIAID/NIH travel policy. Compensation for time inconvenience will be provided for participants who attempt or complete leukapheresis procedures ($150); carotid MRI ($150); dietary questionnaire ($70), rectal swab ($30); phlebotomy $40 and clinic visit $20 . If a subject does not qualify for leukapheresis, an additional research blood draw of 30 mL will be added (see Appendix C), and in that case, compensation for time and inconvenience will be provided for this procedure ($40). If a subject completes all study visits, the subject will receive a study completion compensation of $200 at the end of the study for their time and inconvenience.

11 ASSESSMENT OF SAFETY

11.1 Toxicity Scale

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Toxicity (Version 1.0 - December 2004 (Clarification dated August 2009)) will be used to grade each AE:

http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx
All AEs will be recorded regardless of grade. Only grade 2 and above AEs will be reported.

11.2 Specification of Safety Parameters

Atorvastatin:

The following most common adverse reactions have been reported with ATV use, according to the package insert:

- Nasopharyngitis (8.3%)
- Arthralgia (6.9%)
- Diarrhea (6.8%)
- Pain in extremity (6.0%)
- Urinary tract infection (5.7%)

These events, should they occur, would constitute expected adverse events.

Aspirin

Abormalities in the following laboratory tests have been associated with ASA use:

- "Elevated hepatic enzymes, blood nitrogen, urea nitrogen, serum creatinine, hyperkalemia, proteinuria, and prolonged bleeding time."

The following adverse reactions have been noted to occur with ASA use (note that these adverse reactions are usually dose related and more frequently occur at higher doses compared to the 81 mg dose used in this study):

- "**Body as a Whole:** Fever, hypothermia, thirst.
- **Cardiovascular:** Dysrhythmias, hypotension, tachycardia.
- **Central Nervous System:** Agitation, cerebral edema, coma, confusion, dizziness, headache, subdural or intracranial hemorrhage, lethargy, seizures.
- **Fluid and Electrolyte:** Dehydration, hyperkalemia, metabolic acidosis, repiratory alkalosis.
- **Gastrointestinal:** Dyspepsia, GI bleeding, ulceration and perforation, nausea, vomiting, transient elevations of hepatic enzymes, hepatitis, Reye's syndrome, pancreatitis.
- **Hematologic:** Prolongation of the prothrombin time, disseminated intravascular coagulation, coagulopathy, thrombocytopenia.
- **Hypersensitivity:** Acute anaphylaxis, angioedema, asthma, bronchospasm, laryngeal edema, urticarial.
- **Musculoskeletal:** Rhabdomyolysis.
- **Metabolism:** Hypoglycemia (in children), hyperglycemia.
- **Reproductive:** Prolonged pregnancy and labor, stillbirths, lower birth weight infants, antepartum and postpartum bleeding.
- **Respiratory:** Hyperpnea, pulmonary edema, tachypnea.
- **Special Senses:** Hearing loss, tinnitus. Patients with higher frequency hearing loss may have difficulty perceiving tinnitus. In these patients, tinnitus cannot be used as a clinical indicator of salicylism.
- **Urogential:** Interstitial nephritis, papillary necrosis, proteinuria, renal insufficiency and failure."

These events, should they occur, would constitute expected adverse events.

11.3 Recording/Documentation

At each contact with the subject, information regarding adverse events will be elicited by appropriate questioning and examinations. All events, both expected/unexpected and related/unrelated will be recorded on a source document. Source documents will include: progress notes, laboratory reports, consult notes, phone call summaries, survey tools and

data collection tools. Source documents will be reviewed in a timely manner by the research team. All reportable adverse events that are identified will be recorded in CRIMSON. The start date, the stop date, the severity of each reportable event, and the PI's judgment of the AEs relationship and expectedness to the study agent/intervention will also be recorded in CRIMSON.

11.4 Definitions

Adverse Event: Any untoward medical occurrence in a human subject, that includes any abnormal sign symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the research.

Serious adverse event: Any AE that

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- results in inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- results in a congenital anomaly/birth defect; or
- based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition. *(examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse)*

Protocol Deviation: Any change, divergence, or departure from the IRB approved study procedures in a research protocol. Protocol deviations are designated as serious or non-serious and further characterized as

1. Those that occur because a member of the research team deviates from the protocol.
2. Those that are identified before they occur, but cannot be prevented.
3. Those that are discovered after they occur

Serious Protocol Deviation: A deviation that meets the definition of a Serious Adverse Event or compromises the safety, welfare or rights of subjects or others.

Non-compliance: The failure to comply with applicable NIH HRPP policies, IRB requirements, or regulatory requirements for the protection of human subjects. Non-compliance is further characterized as

1. Serious: Non-compliance that
    a. Increases risks, or causes harm, to participants
    b. Decreases potential benefits to participants
    c. Compromises the integrity of the NIH-HRPP
    d. Invalidates the study data
2. Continuing: Non-compliance that is recurring

3. Minor: Non-compliance that, is neither serious nor continuing.

Unanticipated Problem: (UP)Any incident, experience, or outcome that meets all three of the following criteria would be considered a serious UP:

1. unexpected in terms of nature, severity, or frequency in relation to
   a. the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure (IB) or other study documents; and
   b. the characteristics of the subject population being studied; and
2. related or possibly related to participation in the research; and
3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unanticipated problem that is not an Adverse Event (UPnonAE): An unanticipated problem that does not fit the definition of an adverse event, but which may, in the opinion of the investigator, involve risk to the subject, affect others in the research study, or significantly impact the integrity of research data. Such events would be considered a non-serious UP. For example, we will report occurrences of breaches of confidentiality, accidental destruction of study records, or unaccounted-for study drug.

11.5 Reporting Procedures

11.5.1 Expedited Reporting to the NIAID IRB

Serious and non-serious Unanticipated Problems, deaths, serious deviations, and serious or continuing non-compliance will be reported within 7 calendar days of investigator awareness. Serious Adverse Events that are possibly, probably, or definitely related to the research will be reported to the NIAID IRB within 7 calendar days of investigator's awareness, regardless of expectedness.

11.5.2 Annual Reporting to the NIAID IRB

The following items will be reported to the NIAID IRB in summary at the time of Continuing Review:

- Serious and non-serious unanticipated
- Expected SAEs that are possibly, probably, or definitely related to the research
- SAEs that are not related to the research
- All adverse events, except expected AEs and deaths granted a waiver of reporting
- Serious and non-serious protocol deviations
- Serious, continuing, and minor non-compliance
- Any trends or events which in the opinion of the investigator should be reported
- Grade 1 AEs will not be reported.

11.6 Reporting of Pregnancy

Pregnancy itself is not an AE. Pregnancies and complications of pregnancies will be reported as information items and in summary at the time of CR.

11.7 Type and Duration of the Follow-up of Subjects after Adverse Events

- The participant will be withdrawn from the study if the AE occurs before drug administration, at the discretion of the principal investigator.
- The study drug (both ATV and ASA) will be discontinued immediately if the AE occurs during the treatment phase at the discretion of the investigator. The participant will be followed as necessary throughout the remainder of the study period for safety assessments and labs.

11.8 Modification of Study Agent(s)/Intervention(s) for a Subject

If a participant is unable to tolerate ATV or ASA, they will discontinue study drug and will be withdrawn from study. No dose adjustment will occur during the course of this study. See 11.7 for AEs.

11.9 Pausing Rules for the Protocol

The study drugs are very commonly used medications with wide experience and ASA is also an over the counter medication. The study will be monitored by the study team and if an unusual number of SAEs or grade 3 or 4 events occur related to participation in the research, the study will be paused in consultation with the IRB until the events are better evaluated.

11.10 Stopping Rules for an Individual Subject/Cohort

A study subject will be discontinued from further Study Agent(s)/Intervention(s) administration for:

- Any clinical AE, laboratory abnormality, intercurrent illness, other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- Development of any exclusion criteria may be cause for discontinuation.
- Grade 3 or 4 adverse reactions to the study drug, including myalgia, abdominal pain, and nausea.
- Grade 3 elevation of hepatic transaminases that is confirmed by repeated testing and is considered related to study drug.
- New pregnancy (see Section 6.9).
- Development of allergy or hypersensitivity to study drug.
- Request by participant to withdraw from study.
- Development of a medical condition that requires administration of the following prohibited concomittent medications:
    - Systemic corticosteroids
    - Daily NSAIDs

  - Immunomodulating medication
- Subject is judged to be at risk of failing to adhere to the study provisions to such a degree that, in the opinion of the investigator, the integrity of the study results might become compromised.

For all subjects withdrawn from study, the PI will evaluate on an individual basis if it is in the best interest of the participant to be followed by the protocol team with follow-up visits that include safety laboratory tests.

11.11 Premature Withdrawal of a Subject

If a subject elects to withdraw, end of study evaluations will be performed at the time of their withdrawal. Leukapheresis and MR carotid imaging may be performed if the study participation is nearing completion.

11.12 Replacement of a Subject Who Discontinues Study Treatment

Subjects who receive less than 6 months of study drug will be replaced.

12 CLINICAL MONITORING STRUCTURE

12.1 Safety Monitoring Plan

Study staff will review laboratory and study test results as they become available. Review of test results and communication of findings will be in accordance with OP8 Clinic Operations Standard Operating Procedure for review and assessment of test results. When medically indicated, appropriate follow-up testing and treatment will be offered to participants utilizing the resources and expertise available at the NIH Clinical Center.

13 STATISTICAL CONSIDERATIONS

13.1 Study Hypotheses

Based on the evidence presented above on the impact of statins and ASA on the biomarkers related to inflammation, the coagulation cascade and on cellular markers of activation, we hypothesize that both EC and ART <50 will exhibit reductions in biomarkers and cellular markers of activation and could be grouped for the purposes of the primary end point analysis.

13.2 Sample Size Justification

Those who died in the SMART study had a baseline median sCD14 level of 2.47 µg/mL (IQR 2.19 – 2.91), while matched controls had lower levels at 2.23 µg/mL (IQR 2.01 - 2.63). We powered our study to exhibit a similar effect size.

Assuming a mean of 2.45 µg/mL and a standard deviation of 0.45 µg/mL observed in ART treated subjects in the SMART study (personal communication Dr. Sandler) and a correlation coefficient of 0.71 (personal communication Dr. Sandler and Dr. Funderburg), a trial with a total of 40 patients (per treatment arm) has a power of 95% (with type I error of 0.05 based on a one-sample paired difference t test, two-sided) for detecting a 0.20 difference in sCD14 levels between Month 3 and Month 12 visits. This power reduces to

74% when N = 20 and we consider each randomization arm within each group separately (a secondary end point).

13.3 Safety Analysis
Descriptive statistics with a summary of AEs will be completed at the end of study.

13.4 Planned Interim Analyses
There will be no interim analysis.

13.5 Efficacy Analysis
The primary endpoint will be set as a change in sCD14 after 9 months of treatment with ASA or ATV, in ECs and in Treated Progressors (ART <50) combined. Assuming 40 patients enroll in each treatment arm, with a mean sCD14 of 2.45 μg/mL and a standard deviation of 0.45 μg/mL, the study has 95% power to detect a reduction of 0.20 in sCD14 levels (See Section 13.2) after 9 months of treatment. The significance of paired differences within each group will be evaluated using two-sided nonparametric (one-sample signed rank) test. As discussed above, this power decreases to 74% when treatment arms are compared individually within each group (as a secondary endpoint, see below). Adjustment for differences in CD4, age and smoking status will be done in any between group (EC vs ART<50) comparisons.

Secondary endpoints, including group comparisons (ASA vs statin and EC vs ART<50) of changes in biomarkers and T cell activation, cardiovascular disease prevalence, and changes in plasma viremia will be evaluated using two-sided nonparametric (Wilcoxon rank-sum) tests. Exploratory analyses comparing paired differences of carotid IMT thickness at Month 0 and Month 12 within each group will be assessed by two-sided nonparametric (one-sample signed rank) tests. Associations between continuous variables (MR measurements and biomarks and cellular activation markers) will be assessed using Spearman rank order correlation coefficients. Linear regression models will be used to control for factors such as age, smoking, and inflammatory biomarkers. For all evaluations, type I error will be set at 0.05.

14 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Informed Consent Process
Informed consent is a process where information is presented to enable persons to voluntarily decide whether or not to participate as a research subject. It is an on-going conversation between the human research subject and the researchers which begins before consent is given and continues until the end of the subject's involvement in the research. Discussions about the research will provide essential information about the study and include: purpose, duration, experimental procedures, alternatives, risks and benefits. Subjects will be given the opportunity to ask questions and have them answered.

The subjects will sign the informed consent document prior to undergoing any research procedures. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The researcher will document the signing of the consent form in the subject’s medical record. The rights and welfare of the subjects will be protected by emphasizing to

them that the quality of their medical care will not be adversely affected if they decline to participate in this study. For Non-English–Speaking Participants the Investigator obtaining consent will document the consent process in the participant's electronic medical record, including the name of the interpreter. Further, all instances of use of the CC Short Written Consent Form will be reported to the IRB at the time of annual review. If the CC Short Written Consent Form is used three times or more for the same language, this will be reported to the IRB immediately, and the consent will need to be translated into that language.

14.1.1 Remote Site Consent Process

Screening may take place at either the NIH Clinical Center or the Hennepin County Medical Center (HCMC). For patients recruited from HCMC, the following consent process will be followed:

a) The signed, witnessed, and dated consent must be completed by the Associate Investigator at Hennepin County prior to any screening labs. The original document will be maintained at the site and a copy sent to NIH.
b) The consent will be checked for accuracy. The copy of the signed consent will be filed in the medical record.
c) Participants recruited from HCMC will sign the NIH consent document separately upon arrival at the NIH Clinical Center and this signed consent will be filed in the medical record as well.

14.2 Subject Confidentiality

All records will be kept confidential to the extent provided by federal, state and local law. The study monitors and other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records. Records will be kept locked and all computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, NIAID, or the Office for Human Research Protections (OHRP).

15 DATA HANDLING AND RECORD KEEPING

15.1 Data Capture and Management

Study data will be maintained in CRIMSON and collected directly from subjects during study visits and telephone calls, or will be abstracted from subjects' medical records. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary to confirm the data abstracted for this study. Source documentation (the point of initial recording of information) should support the data collected and must be signed and dated by the person recording and/or reviewing the data. Data entry into CRIMSON will be performed by authorized individuals. The Investigator is responsible for assuring that the data collected are complete, accurate, and recorded in a timely manner. Corrections to electronic data systems shall be tracked electronically (password protected) with time, date, individual making the correction, and what was changed.

15.2 Record Retention

The investigator is responsible for retaining all essential documents listed in the ICH Good Clinical Practice (GCP) Guideline. Study records will be maintained by the PI for a minimum of 3 years and in compliance with institutional, IRB, state, and federal medical records retention requirements, whichever is longest. All stored records will be kept confidential to the extent required by federal, state, and local law.

Should the investigator wish to assign the study records to another party and/or move them to another location, the investigator will provide written notification of such intent to Regulatory Compliance and Human Subjects Protection Branch (RCHSPB)/NIAID with the name of the person who will accept responsibility for the transferred records and/or their new location. Destruction or relocation of research records will not proceed without written permission from RCHSPB/NAID.

APPENDIX A: SCIENTIFIC REFERENCES

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APPENDIX B: SCHEDULE OF PROCEDURES/EVALUATIONS

(After baseline, all visit windows ± 2 weeks)

Evaluation	Screening (0 days– -2 months)	Baseline (Month 0)	Month 3	Month 6	Month 9	Month 12	Month 15
Medical/Medication History	X	X	X	X	X	X	X
Clinical Assessment	X	X	X	X	X	X	X
Physical Exam[1]	X	X	X	X	X	X	X
Carotid MRI[2]		X				X	
Rectal swab & dietary questionnaire		X				X (swab only)	
Apheresis (2-Pass)[3]			X			X	
CBC, differential, platelets	X	X	X	X	X	X	X
PT/PTT/D-dimer	X	X	X	X	X	X	X
Acute Care/Hepatic Panel/Mineral Panel/hsCRP/CK/Aldolase	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X
Pregnancy Testing	X	X	X	X	X	X	X
CD4/HIV-1 RNA	X	X	X	X	X	X	X
Hemoglobin A1c		X	X	X	X	X	X
Lipid Panel (fasting)	X	X	X	X	X	X	X
Hepatitis Serology	X						
ELISA/Western Blot	X[4]						
Research Storage (Plasma, PBMC, Serum)		X	X	X	X	X	X
Research Flow Cytometry		X	X	X	X	X	X
Atorvastatin or Aspirin Dispensed			X	X	X		
Pill Count			X	X	X	X	

[1] Targeted physical exam for acute presentations following screening visit.
[2] Can occur any time on or between the M0 and M3 visits, based on MR availability.
[3] If adequate venous access and Hg>9g/dL and PLT>50,000. If inadequate venous access, 30mL of additional blood will be drawn in lieu of apheresis (3-10mL green tops
[4] If not previously performed at NIH

APPENDIX C: BLOOD VOLUMES FOR SPECIMEN COLLECTION

[1] Visit	Tube Type	Screening	[6]Baseline					End of Study
Month (M) of Study			M 0	M 3	M 6	M 9	M 12	M 15
Clinical								
CBC, differential, platelets	3mL Light lavender top	3	3	3	3	3	3	3
PT, aPTT, D-dimer, fibrinogen, protein C and S, antithrombin III	4.5 mL Light blue top	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Pregnancy test: urine								
Acute Care, Hepatic and Mineral Panel	8mL Green top(lithium heparin)	8	8	8	8	8	8	8
Creatine Kinase, Aldolase, hsCRP	Same tube	X	X	X	X	X	X	X
HBsAg, anti-HBcAb, anti-HBsAb, anti-HAV IgG, HCV Ab and HCV PCR[2]	8mL SST	8						
ELISA/Western Blot [3]	4mL SST	4						
Lipid Panel	4 mL Green top (lithium heparin)	4	4	4	4	4	4	4
HIV-1 RNA	6mL Purple top	6	6	6	6	6	6	6
Hemoglobin A1c	3mL Light lavender top		3	3	3	3	3	3
HLA typ[3]	10ml Purple top		10					
Research								
PBMC Storage[4]	6mL Green top		55	60	60	60	60	60
Plasma Storage	6mL Dark lavender top		12	12	12	12	12	12
Serum Storage	8mL SST		8	8	8	8	8	8
Single Copy Assay	(3) 9ml Purple top		27	27			27	
Flow Cytometry	6mL Purple top	6	6	6	6	6	6	6
Daily Volume (mL)		**43.5**	**146.5**	**141.5**	**114.5**	**114.5**	**141.5**	**114.5**
[4]Cumulative Volume (mL)			**190**	**331.5**	**446**	**560.5**	**702**	**816.5**

[1] Visit Windows: All visit windows ± 2 weeks after baseline

2 HCV Ab will be accepted from an outside lab if performed within 2 months of of Month 0

[3] Only if not previously done at NIH

4 An additional 30mL(3-10mL green tops) of PBMC storage will be collected if patient is unable to undergo apheresis at the designated study visits .

[5]Per NIH MEC Policy M95-9, maximum blood volumes drawn for *research purposes* for an *adult* subject (aged 18 years or older) may not exceed: 10.5 mL/kg or 550 mL, whichever is smaller, over any eight week period. Exceptions to this policy shall be approved by the IRB.

[6] M 0 evaluations are the baseline for subsequent safety assessments. Visit must occur 0 days – 2 months after screening.

APPENDIX D: ATORVASTATIN PACKAGE INSERT

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use atorvastatin calcium tablets safely and effectively. See full prescribing information for atorvastatin calcium tablets.

Atorvastatin Calcium Tablets for oral administration
Initial U.S. Approval: 1996

---------- RECENT MAJOR CHANGES----------

Dosage and Administration (2.6)	11/2012
Warnings and Precautions (5.1)	11/2012
Drug Interactions (7)	02/2012

----------INDICATIONS AND USAGE----------

Atorvastatin calcium is an inhibitor of HMG-CoA reductase (statin) indicated as an adjunct therapy to diet to:

- Reduce the risk of MI, stroke, revascularization procedures, and angina in patients without CHD, but with multiple risk factors (1.1).
- Reduce the risk of MI and stroke in patients with type 2 diabetes without CHD, but with multiple risk factors (1.1).
- Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF, and angina in patients with CHD (1.1).
- Reduce elevated total-C, LDL-C, apo B, and TG levels and increase HDL-C in adult patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (1.2).
- Reduce elevated TG in patients with hypertriglyceridemia and primary dysbetalipoproteinemia (1.2).
- Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH) (1.2).
- Reduce elevated total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy (1.2).

Limitations of Use
Atorvastatin calcium tablets have not been studied in *Fredrickson* Types I and V dyslipidemias.

----------DOSAGE AND ADMINISTRATION----------

Dose range: 10 to 80 mg once daily (2.1).
Recommended start dose: 10 or 20 mg once daily (2.1).
Patients requiring large LDL-C reduction (>45%) may start at 40 mg once daily (2.1).
Pediatric starting dose: 10 mg once daily; maximum recommended dose: 20 mg once daily (2.2).

----------DOSAGE FORMS AND STRENGTHS----------

10, 20, 40, and 80 mg tablets (3).

----------CONTRAINDICATIONS----------

Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels (4.1).
Women who are pregnant or may become pregnant (4.3).
Nursing mothers (4.4).
Hypersensitivity to any component of this medication (4.2).

----------WARNINGS AND PRECAUTIONS----------

Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): Risks increase when higher doses are used concomitantly with cyclosporine and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, HIV protease inhibitors). Predisposing factors include advanced age (> 65), uncontrolled hypothyroidism, and renal impairment. Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported. Advise patients to promptly report to their physician unexplained and/or persistent muscle pain, tenderness, or weakness. Atorvastatin therapy should be discontinued if myopathy is diagnosed or suspected (5.1, 8.5).

Liver enzyme abnormalities: Persistent elevations in hepatic transaminases can occur. Check liver enzyme tests before initiating therapy and as clinically indicated thereafter (5.2).

A higher incidence of hemorrhagic stroke was seen in patients without CHD but with stroke or TIA within the previous 6 months in the atorvastatin calcium tablets 80 mg group vs. placebo (5.5).

----------ADVERSE REACTIONS----------

The most commonly reported adverse reactions (incidence ≥ 2%) in patients treated with atorvastatin calcium tablets in placebo-controlled trials regardless of causality were: nasopharyngitis, arthralgia, diarrhea, pain in extremity, and urinary tract infection (6.1).
To report SUSPECTED ADVERSE REACTIONS, contact Greenstone LLC at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis (2.6, 5.1, 7, 12.3)

Interacting Agents	Prescribing Recommendations
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir) Hepatitis C protease inhibitor (boceprevir)	Do not exceed 40 mg atorvastatin daily

- Other Lipid-Lowering Medications: Use with fibrate products or lipid-modifying doses (≥1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with atorvastatin calcium tablets (7).
- Digoxin: Patients should be monitored appropriately (7.8).
- Oral Contraceptives: Values for norethindrone and ethinyl estradiol may be increased (7.9).
- Rifampin should be simultaneously co-administered with atorvastatin calcium tablets (7.7).

----------USE IN SPECIFIC POPULATIONS----------

- Hepatic impairment: Plasma concentrations markedly increased in patients with chronic alcoholic liver disease (12.3).

See 17 for PATIENT COUNSELING INFORMATION
Revised: [11/2012]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Drug therapy is recommended as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate. In patients with CHD or multiple risk factors for CHD, atorvastatin calcium tablets can be started simultaneously with diet.

1.1 Prevention of Cardiovascular Disease

In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, atorvastatin calcium tablets are indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke
- Reduce the risk for revascularization procedures and angina

In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, atorvastatin calcium tablets are indicated to:

- Reduce the risk of myocardial infarction
- Reduce the risk of stroke

In patients with clinically evident coronary heart disease, atorvastatin calcium tablets are indicated to:

- Reduce the risk of non-fatal myocardial infarction
- Reduce the risk of fatal and non-fatal stroke
- Reduce the risk for revascularization procedures
- Reduce the risk of hospitalization for CHF
- Reduce the risk of angina

1.2 Hyperlipidemia

Atorvastatin calcium tablets are indicated:

- As an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia *(Fredrickson* Types IIa and IIb);
- As an adjunct to diet for the treatment of patients with elevated serum TG levels *(Fredrickson* Type IV);
- For the treatment of patients with primary dysbetalipoproteinemia *(Fredrickson* Type III) who do not respond adequately to diet;
- To reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable;
- As an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:
  a. LDL-C remains ≥ 190 mg/dL or
  b. LDL-C remains ≥ 160 mg/dL and:
    - there is a positive family history of premature cardiovascular disease or
    - two or more other CVD risk factors are present in the pediatric patient

1.3 Limitations of Use

Atorvastatin calcium tablets have not been studied in conditions where the major lipoprotein abnormality is elevation of chylomicrons *(Fredrickson* Types I and V).

2 DOSAGE AND ADMINISTRATION

2.1 Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia *(Fredrickson* Types IIa and IIb)

The recommended starting dose of atorvastatin calcium tablets is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of atorvastatin calcium tablets is 10 to 80 mg once daily. Atorvastatin calcium tablets can be administered as a single dose at any time of the day, with or without food. The starting dose and maintenance doses of atorvastatin calcium tablets should be individualized according to patient characteristics such as goal of therapy and response (see current *NCEP Guidelines*). After initiation and/or upon titration of atorvastatin calcium tablets, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

2.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age)

The recommended starting dose of atorvastatin calcium tablets is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy [see current *NCEP Pediatric Panel Guidelines*, *Clinical Pharmacology (12)*, and *Indications and Usage (1.2)*]. Adjustments should be made at intervals of 4 weeks or more.

2.3 Homozygous Familial Hypercholesterolemia

The dosage of atorvastatin calcium tablets in patients with homozygous FH is 10 to 80 mg daily. Atorvastatin calcium tablets should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

2.4 Concomitant Lipid-Lowering Therapy

Atorvastatin calcium tablets may be used with bile acid resins. The combination of HMG-CoA reductase inhibitors (statins) and fibrates should generally be used with caution [see *Warnings and Precautions*, *Skeletal Muscle (5.1), Drug Interactions (7)*].

2.5 Dosage in Patients With Renal Impairment

Renal disease does not affect the plasma concentrations nor LDL-C reduction of atorvastatin calcium tablets; thus, dosage adjustment in patients with renal dysfunction is not necessary [see *Warnings and Precautions, Skeletal Muscle (5.1), Clinical Pharmacology, Pharmacokinetics (12.3)*].

2.6 Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors

In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), therapy with atorvastatin calcium tablets should be avoided. In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing atorvastatin calcium tablets and the lowest dose necessary employed. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, therapy with atorvastatin calcium tablets should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin calcium tablets is employed. In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, therapy with atorvastatin calcium tablets should be limited to 40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin calcium tablets is employed [see *Warnings and Precautions, Skeletal Muscle (5.1), Drug Interactions (7)*].

3 DOSAGE FORMS AND STRENGTHS

White, elliptical, film-coated tablets containing 10, 20, 40, and 80 mg atorvastatin calcium.

4 CONTRAINDICATIONS

4.1 Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels

4.2 Hypersensitivity to any component of this medication

4.3 Pregnancy

Women who are pregnant or may become pregnant. Atorvastatin calcium tablets may cause fetal harm when administered to a pregnant woman. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. There are no adequate and well-

controlled studies of atorvastatin calcium tablets use during pregnancy; however in rare reports, congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal reproduction studies, atorvastatin revealed no evidence of teratogenicity. ATORVASTATIN CALCIUM TABLETS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, atorvastatin calcium tablets should be discontinued immediately and the patient apprised of the potential hazard to the fetus [see *Use in Specific Populations (8.1)*].

4.4 Nursing mothers

It is not known whether atorvastatin is excreted into human milk; however a small amount of another drug in this class does pass into breast milk. Because statins have the potential for serious adverse reactions in nursing infants, women who require atorvastatin calcium tablets treatment should not breastfeed their infants [see *Use in Specific Populations (8.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin calcium tablets and with other drugs in this class. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

Atorvastatin, like other statins, occasionally causes myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN. The concomitant use of higher doses of atorvastatin with certain drugs such as cyclosporine and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, and HIV protease inhibitors) increases the risk of myopathy/rhabdomyolysis.

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing atorvastatin calcium tablets. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, clarithromycin, the hepatitis C protease inhibitor telaprevir, combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, clarithromycin, a combination of saquinavir plus ritonavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance doses of atorvastatin should be considered when taken concomitantly with the aforementioned drugs (see *Drug Interactions (7)*). Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Prescribing recommendations for interacting agents are summarized in Table 1 [see also *Dosage and Administration (2.6), Drug Interactions (7), Clinical Pharmacology (12.3)*].

Table 1. Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir*, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir) Hepatitis C protease inhibitor (boceprevir)	Do not exceed 40 mg atorvastatin daily

*Use with caution and with the lowest dose necessary (12.3)

Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine [see *Drug Interactions (7.11)*].

Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

5.2 Liver Dysfunction

Statins, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin calcium tablets in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.**

One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin calcium tablets.

It is recommended that liver enzyme tests be obtained prior to initiating therapy with atorvastatin calcium tablets and repeated as clinically indicated. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including atorvastatin. If serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment with atorvastatin calcium tablets, promptly interrupt therapy. If an alternate etiology is not found, do not restart atorvastatin calcium tablets.

Atorvastatin calcium tablets should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin calcium tablets [see *Contraindications (4.1)*].

5.3 Endocrine Function

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin calcium tablets.

Statins interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of statins on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if a statin is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

5.4 CNS Toxicity

Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose.

5.5 Use in Patients with Recent Stroke or TIA

In a post-hoc analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study where atorvastatin calcium tablets 80 mg vs. placebo was administered in 4,731 subjects without CHD who had a stroke or TIA within the preceding 6 months, a higher incidence of hemorrhagic stroke was seen in the atorvastatin calcium tablets 80 mg group compared to placebo (55, 2.3% atorvastatin vs. 33, 1.4% placebo; HR: 1.68, 95% CI: 1.09, 2.59; p=0.0168). The incidence of fatal hemorrhagic stroke was similar across treatment groups (17 vs. 18 for the atorvastatin and placebo groups, respectively). The incidence of nonfatal hemorrhagic stroke was significantly higher in the atorvastatin group (38, 1.6%) as compared to the placebo group (16, 0.7%). Some baseline characteristics, including hemorrhagic and lacunar stroke on study entry, were associated with a higher incidence of hemorrhagic stroke in the atorvastatin group [see *Adverse Reactions (6.1)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:
Rhabdomyolysis and myopathy [see *Warnings and Precautions (5.1)*]
Liver enzyme abnormalities [see *Warnings and Precautions (5.2)*]

6.1 Clinical Trial Adverse Experiences

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In the atorvastatin calcium tablets placebo-controlled clinical trial database of 16,066 patients (8755 atorvastatin calcium tablets vs. 7311 placebo; age range 10–93 years, 39% women, 91% Caucasians, 3% Blacks, 2% Asians, 4% other) with a median treatment duration of 53 weeks, 9.7% of patients on atorvastatin calcium tablets and 9.5% of the patients on placebo discontinued due to adverse reactions regardless of causality. The five most common adverse reactions in patients treated with atorvastatin calcium tablets that led to treatment discontinuation and occurred at a rate greater than placebo were: myalgia (0.7%), diarrhea (0.5%), nausea (0.4%), alanine aminotransferase increase (0.4%), and hepatic enzyme increase (0.4%).

The most commonly reported adverse reactions (incidence ≥ 2% and greater than placebo) regardless of causality, in patients treated with atorvastatin calcium tablets in placebo controlled trials (n=8755) were: nasopharyngitis (8.3%), arthralgia (6.9%), diarrhea (6.8%), pain in extremity (6.0%), and urinary tract infection (5.7%).

Table 2 summarizes the frequency of clinical adverse reactions, regardless of causality, reported in ≥ 2% and at a rate greater than placebo in patients treated with atorvastatin calcium tablets (n=8755), from seventeen placebo-controlled trials.

Table 2. Clinical adverse reactions occurring in ≥ 2% in patients treated with any dose of atorvastatin calcium tablets and at an incidence greater than placebo regardless of causality (% of patients).

Adverse Reaction*	Any dose N=8755	10 mg N=3908	20 mg N=188	40 mg N=604	80 mg N=4055	Placebo N=7311
Nasopharyngitis	8.3	12.9	5.3	7.0	4.2	8.2
Arthralgia	6.9	8.9	11.7	10.6	4.3	6.5

Diarrhea	6.8	7.3	6.4	14.1	5.2	6.3
Pain in extremity	6.0	8.5	3.7	9.3	3.1	5.9
Urinary tract infection	5.7	6.9	6.4	8.0	4.1	5.6
Dyspepsia	4.7	5.9	3.2	6.0	3.3	4.3
Nausea	4.0	3.7	3.7	7.1	3.8	3.5
Musculoskeletal pain	3.8	5.2	3.2	5.1	2.3	3.6
Muscle Spasms	3.6	4.6	4.8	5.1	2.4	3.0
Myalgia	3.5	3.6	5.9	8.4	2.7	3.1
Insomnia	3.0	2.8	1.1	5.3	2.8	2.9
Pharyngolaryngeal pain	2.3	3.9	1.6	2.8	0.7	2.1
* Adverse Reaction ≥ 2% in any dose greater than placebo						

Other adverse reactions reported in placebo-controlled studies include:
Body as a whole: malaise, pyrexia; *Digestive system:* abdominal discomfort, eructation, flatulence, hepatitis, cholestasis; *Musculoskeletal system*: musculoskeletal pain, muscle fatigue, neck pain, joint swelling; *Metabolic and nutritional system*: transaminases increase, liver function test abnormal, blood alkaline phosphatase increase, creatine phosphokinase increase, hyperglycemia; *Nervous system*: nightmare; *Respiratory system:* epistaxis; *Skin and appendages*: urticaria; *Special senses*: vision blurred, tinnitus; *Urogenital system:* white blood cells urine positive.

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)
In ASCOT [see *Clinical Studies (14.1)*] involving 10,305 participants (age range 40–80 years, 19% women; 94.6% Caucasians, 2.6% Africans, 1.5% South Asians, 1.3% mixed/other) treated with atorvastatin calcium tablets 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with atorvastatin calcium tablets was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.

Collaborative Atorvastatin Diabetes Study (CARDS)
In CARDS [see *Clinical Studies (14.1)*] involving 2,838 subjects (age range 39–77 years, 32% women; 94.3% Caucasians, 2.4% South Asians, 2.3% Afro-Caribbean, 1.0% other) with type 2 diabetes treated with atorvastatin calcium tablets 10 mg daily (n=1,428) or placebo (n=1,410), there was no difference in the overall frequency of adverse reactions or serious adverse reactions between the treatment groups during a median follow-up of 3.9 years. No cases of rhabdomyolysis were reported.

Treating to New Targets Study (TNT)
In TNT [see *Clinical Studies (14.1)*] involving 10,001 subjects (age range 29–78 years, 19% women; 94.1% Caucasians, 2.9% Blacks, 1.0% Asians, 2.0% other) with clinically evident CHD treated with atorvastatin calcium tablets 10 mg daily (n=5006) or atorvastatin calcium tablets 80 mg daily (n=4995), there were more serious adverse reactions and discontinuations due to adverse reactions in the high-dose atorvastatin group (92, 1.8%; 497, 9.9%, respectively) as compared to the low-dose group (69, 1.4%; 404, 8.1%, respectively) during a median follow-up of 4.9 years. Persistent transaminase elevations (≥3 x ULN twice within 4–10 days) occurred in 62 (1.3%) individuals with atorvastatin 80 mg and in nine (0.2%) individuals with atorvastatin 10 mg. Elevations of CK (≥ 10 x ULN) were low overall, but were higher in the high-dose atorvastatin treatment group (13, 0.3%) compared to the low-dose atorvastatin group (6, 0.1%).

Incremental Decrease in Endpoints through Aggressive Lipid Lowering Study (IDEAL)
In IDEAL [see *Clinical Studies (14.1)*] involving 8,888 subjects (age range 26–80 years, 19% women; 99.3% Caucasians, 0.4% Asians, 0.3% Blacks, 0.04% other) treated with atorvastatin calcium tablets 80 mg/day (n=4439) or simvastatin 20–40 mg daily (n=4449), there was no difference in the overall frequency of adverse reactions or serious adverse reactions between the treatment groups during a median follow-up of 4.8 years.

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)
In SPARCL involving 4731 subjects (age range 21–92 years, 40% women; 93.3% Caucasians, 3.0% Blacks, 0.6% Asians, 3.1% other) without clinically evident CHD but with a stroke or transient ischemic attack (TIA) within the previous 6 months treated with atorvastatin calcium tablets 80 mg (n=2365) or placebo (n=2366) for a median follow-up of 4.9 years, there was a higher incidence of persistent hepatic transaminase elevations (≥ 3 x ULN twice within 4–10 days) in the atorvastatin group (0.9%) compared to placebo (0.1%). Elevations of CK (>10 x ULN) were rare, but were higher in the atorvastatin group (0.1%) compared to placebo (0.0%). Diabetes was reported as an adverse reaction in 144 subjects (6.1%) in the atorvastatin group and 89 subjects (3.8%) in the placebo group [see *Warnings and Precautions (5.5)*].

In a post-hoc analysis, atorvastatin calcium tablets 80 mg reduced the incidence of ischemic stroke (218/2365, 9.2% vs. 274/2366, 11.6%) and increased the incidence of hemorrhagic stroke (55/2365, 2.3% vs. 33/2366, 1.4%) compared to placebo. The incidence of

fatal hemorrhagic stroke was similar between groups (17 atorvastatin calcium tablets vs. 18 placebo). The incidence of non-fatal hemorrhagic strokes was significantly greater in the atorvastatin group (38 non-fatal hemorrhagic strokes) as compared to the placebo group (16 non-fatal hemorrhagic strokes). Subjects who entered the study with a hemorrhagic stroke appeared to be at increased risk for hemorrhagic stroke [7 (16%) atorvastatin calcium tablets vs. 2 (4%) placebo].

There were no significant differences between the treatment groups for all-cause mortality: 216 (9.1%) in the atorvastatin calcium tablets 80 mg/day group vs. 211 (8.9%) in the placebo group. The proportions of subjects who experienced cardiovascular death were numerically smaller in the atorvastatin calcium tablets 80 mg group (3.3%) than in the placebo group (4.1%). The proportions of subjects who experienced non-cardiovascular death were numerically larger in the atorvastatin calcium tablets 80 mg group (5.0%) than in the placebo group (4.0%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of atorvastatin calcium tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions 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), rhabdomyolysis, fatigue, tendon rupture, fatal and non-fatal hepatic failure, dizziness, depression, peripheral neuropathy, and pancreatitis.

There have been rare reports of immune-mediated necrotizing myopathy associated with statin use [see *Warnings and Precautions (5.1)*].

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

6.3 Pediatric Patients (ages 10-17 years)

In a 26-week controlled study in boys and postmenarchal girls (n=140, 31% female; 92% Caucasians, 1.6% Blacks, 1.6% Asians, 4.8% other), the safety and tolerability profile of atorvastatin calcium tablets 10 to 20 mg daily was generally similar to that of placebo [see *Clinical Studies (14.6)* and *Use in Special Populations, Pediatric Use (8.4)*].

7 DRUG INTERACTIONS

The risk of myopathy during treatment with statins is increased with concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin, cyclosporine, or strong CYP 3A4 inhibitors (e.g., clarithromycin, HIV protease inhibitors, and itraconazole) [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Clinical Pharmacology (12.3)*].

7.1 Strong Inhibitors of CYP 3A4: Atorvastatin is metabolized by cytochrome P450 3A4. Concomitant administration of atorvastatin calcium tablets with strong inhibitors of CYP 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depend on the variability of effect on CYP 3A4.

Clarithromycin: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin calcium tablets 80 mg with clarithromycin (500 mg twice daily) compared to that of atorvastatin calcium tablets alone [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking clarithromycin, caution should be used when the atorvastatin dose exceeds 20 mg [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*].

Combination of Protease Inhibitors: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin calcium tablets with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor telaprevir, compared to that of atorvastatin calcium tablets alone [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of atorvastatin calcium tablets should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing atorvastatin calcium tablets and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the dose of atorvastatin calcium tablets should not exceed 20 mg and should be used with caution [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*]. In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, the dose of atorvastatin calcium tablets should not exceed 40 mg and close clinical monitoring is recommended.

Itraconazole: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin calcium tablets 40 mg and itraconazole 200 mg [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking itraconazole, caution should be used when the atorvastatin dose exceeds 20 mg [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*].

7.2 Grapefruit Juice: Contains one or more components that inhibit CYP 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 liters per day).

7.3 Cyclosporine: Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g., cyclosporine) can increase the bioavailability of atorvastatin. Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin calcium tablets 10 mg and cyclosporine 5.2 mg/kg/day compared to that of atorvastatin calcium tablets alone [see *Clinical Pharmacology (12.3)*]. The co-administration of atorvastatin calcium tablets with cyclosporine should be avoided [see *Warnings and Precautions, Skeletal Muscle (5.1)*].

7.4 Gemfibrozil: Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are co-administered with gemfibrozil, concomitant administration of atorvastatin calcium tablets with gemfibrozil should be avoided [see *Warnings and Precautions (5.1)*].

7.5 Other Fibrates: Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of other fibrates, atorvastatin calcium tablets should be administered with caution when used concomitantly with other fibrates [see *Warnings and Precautions (5.1)*].

7.6 Niacin: The risk of skeletal muscle effects may be enhanced when atorvastatin calcium tablets are used in combination with niacin; a reduction in atorvastatin calcium tablets dosage should be considered in this setting [see *Warnings and Precautions (5.1)*].

7.7 Rifampin or other Inducers of Cytochrome P450 3A4: Concomitant administration of atorvastatin calcium tablets with inducers of cytochrome P450 3A4 (e.g., efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin calcium tablets with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

7.8 Digoxin: When multiple doses of atorvastatin calcium tablets and digoxin were coadministered, steady state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately.

7.9 Oral Contraceptives: Co-administration of atorvastatin calcium tablets and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol [see *Clinical Pharmacology (12.3)*]. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

7.10 Warfarin: Atorvastatin calcium tablets had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

7.11 Colchicine: Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

Atorvastatin calcium tablets are contraindicated in women who are or may become pregnant. Serum cholesterol and triglycerides increase during normal pregnancy. Lipid lowering drugs offer no benefit during pregnancy because cholesterol and cholesterol derivatives are needed for normal fetal development. Atherosclerosis is a chronic process, and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hypercholesterolemia therapy.

There are no adequate and well-controlled studies of atorvastatin use during pregnancy. There have been rare reports of congenital anomalies following intrauterine exposure to statins. In a review of about 100 prospectively followed pregnancies in women exposed to other statins, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed the rate expected in the general population. However, this study was only able to exclude a three-to-four-fold increased risk of congenital anomalies over background incidence. In 89% of these cases, drug treatment started before pregnancy and stopped during the first trimester when pregnancy was identified.

Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m^2) [see *Contraindications, Pregnancy (4.3)*].

In a study in rats given 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye-opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day.

Statins may cause fetal harm when administered to a pregnant woman. Atorvastatin calcium tablets should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking atorvastatin, it should be discontinued immediately and the patient advised again as to the potential hazards to the fetus and the lack of known clinical benefit with continued use during pregnancy.

8.3 Nursing Mothers

It is not known whether atorvastatin is excreted in human milk, but a small amount of another drug in this class does pass into breast milk. Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Animal breast milk drug levels may not accurately reflect human breast milk levels. Because another drug in this class passes into human milk and because statins have a potential to cause serious adverse reactions in nursing infants, women requiring atorvastatin treatment should be advised not to nurse their infants [see *Contraindications (4)*].

8.4 Pediatric Use

Safety and effectiveness in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial of 6 months' duration in adolescent boys and postmenarchal girls. Patients treated with atorvastatin calcium tablets had an adverse experience profile generally similar to that of patients treated with placebo. The most common adverse experiences observed in both groups, regardless of causality assessment, were infections. **Doses greater than 20 mg have not been studied in this patient population.** In this limited controlled study, there was no significant effect on growth or sexual maturation in boys or on menstrual cycle length in girls [see *Clinical Studies (14.6); Adverse Reactions, Pediatric Patients (ages 10-17 years) (6.3)*; and *Dosage and Administration, Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age) (2.2)*]. Adolescent females should be counseled on appropriate contraceptive methods while on atorvastatin therapy [see *Contraindications, Pregnancy (4.3)* and *Use in Specific Populations, Pregnancy (8.1)*]. **Atorvastatin calcium tablets have not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.**

Clinical efficacy with doses up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients [see *Clinical Studies, Homozygous Familial Hypercholesterolemia (14.5)*].

8.5 Geriatric Use

Of the 39,828 patients who received atorvastatin calcium tablets in clinical studies, 15,813 (40%) were ≥65 years old and 2,800 (7%) were ≥75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older adults cannot be ruled out. Since advanced age (≥65 years) is a predisposing factor for myopathy, atorvastatin should be prescribed with caution in the elderly.

8.6 Hepatic Impairment

Atorvastatin calcium tablets are contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels [see *Contraindications (4)* and *Pharmacokinetics (12.3)*].

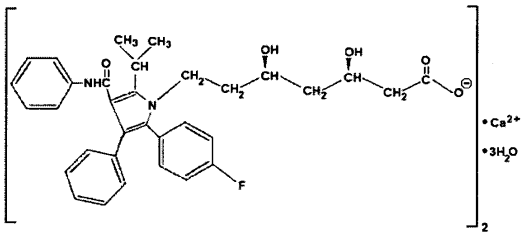
10 OVERDOSAGE

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.

11 DESCRIPTION

Atorvastatin calcium is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca \cdot 3H_2O$ and its molecular weight is 1209.42. Its structural formula is:



Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile; slightly soluble in ethanol; and freely soluble in methanol.

Atorvastatin calcium tablets for oral administration contain 10, 20, 40, or 80 mg atorvastatin and the following inactive ingredients: calcium carbonate, USP; candelilla wax, FCC; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1-7040 (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80, NF; simethicone emulsion.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Atorvastatin calcium is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into HDL (high-density lipoprotein), IDL (intermediate-density lipoprotein), LDL (low-density lipoprotein), and VLDL (very-low-density lipoprotein) fractions. Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. LDL is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total cholesterol (total-C), LDL-cholesterol (LDL-C), and apolipoprotein B (apo B) promote human atherosclerosis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated with a decreased cardiovascular risk.

In animal models, atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell surface to enhance uptake and catabolism of LDL; atorvastatin also reduces LDL production and the number of LDL particles. Atorvastatin reduces LDL-C in some patients with homozygous familial hypercholesterolemia (FH), a population that rarely responds to other lipid-lowering medication(s).

A variety of clinical studies have demonstrated that elevated levels of total-C, LDL-C, and apo B (a membrane complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-C (and its transport complex, apo A) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C, and inversely with the level of HDL-C.

Atorvastatin reduces total-C, LDL-C, and apo B in patients with homozygous and heterozygous FH, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Atorvastatin also reduces VLDL-C and TG and produces variable increases in HDL-C and apolipoprotein A-1. Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not

consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

12.2 Pharmacodynamics

Atorvastatin calcium, as well as some of its metabolites, is pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dosage, rather than systemic drug concentration, correlates better with LDL-C reduction. Individualization of drug dosage should be based on therapeutic response [see *Dosage and Administration (2)*].

12.3 Pharmacokinetics

Absorption: Atorvastatin calcium tablets are rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin calcium dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether atorvastatin calcium tablets are given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration [see *Dosage and Administration (2)*].

Distribution: Mean volume of distribution of atorvastatin is approximately 381 liters. Atorvastatin is ≥98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk [see *Contraindications, Nursing Mothers (4.4)* and *Use in Specific Populations, Nursing Mothers (8.3)*].

Metabolism: Atorvastatin is extensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following co-administration with erythromycin, a known inhibitor of this isozyme [see *Drug Interactions (7.1)*]. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion: Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin calcium tablets is recovered in urine following oral administration.

Specific Populations

Geriatric: Plasma concentrations of atorvastatin are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults [see *Use in Specific Populations, Geriatric Use (8.5)*].

Pediatric: Pharmacokinetic data in the pediatric population are not available.

Gender: Plasma concentrations of atorvastatin in women differ from those in men (approximately 20% higher for Cmax and 10% lower for AUC); however, there is no clinically significant difference in LDL-C reduction with atorvastatin between men and women.

Renal Impairment: Renal disease has no influence on the plasma concentrations or LDL-C reduction of atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary [see *Dosage and Administration, Dosage in Patients with Renal Impairment (2.5)*, *Warnings and Precautions, Skeletal Muscle (5.1)*].

Hemodialysis: While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin since the drug is extensively bound to plasma proteins.

Hepatic Impairment: In patients with chronic alcoholic liver disease, plasma concentrations of atorvastatin are markedly increased. Cmax and AUC are each 4-fold greater in patients with Childs-Pugh A disease. Cmax and AUC are approximately 16-fold and 11-fold increased, respectively, in patients with Childs-Pugh B disease [see *Contraindications (4.1)*].

TABLE 3. Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC[&]	Change in Cmax[&]
#Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD for 28 days	↑ 8.7 fold	↑10.7 fold
#Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	10 mg, SD	↑ 9.4 fold	↑ 8.6 fold
#Telaprevir 750 mg q8h, 10 days	20 mg, SD	↑ 7.88 fold	↑ 10.6 fold
#,‡Saquinavir 400 mg BID/ ritonavir 400 mg BID, 15 days	40 mg QD for 4 days	↑ 3.9 fold	↑ 4.3 fold
#Clarithromycin 500 mg BID, 9 days	80 mg QD for 8 days	↑ 4.4 fold	↑ 5.4 fold
#Darunavir 300 mg BID/ritonavir 100 mg BID, 9 days	10 mg QD for 4 days	↑ 3.4 fold	↑ 2.25 fold
#Itraconazole 200 mg QD, 4 days	40 mg SD	↑ 3.3 fold	↑ 20%
#Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	10 mg QD for 4 days	↑ 2.53 fold	↑ 2.84 fold
#Fosamprenavir 1400 mg BID, 14 days	10 mg QD for 4 days	↑ 2.3 fold	↑ 4.04 fold
#Nelfinavir 1250 mg BID, 14 days	10 mg QD for 28 days	↑ 74%	↑ 2.2 fold
#Grapefruit Juice, 240 mL QD *	40 mg, SD	↑ 37%	↑ 16%
Diltiazem 240 mg QD, 28 days	40 mg, SD	↑ 51%	No change
Erythromycin 500 mg QID, 7 days	10 mg, SD	↑ 33%	↑ 38%
Amlodipine 10 mg, single dose	80 mg, SD	↑ 15%	↓ 12 %
Cimetidine 300 mg QD, 4 weeks	10 mg QD for 2 weeks	↓ Less than 1%	↓ 11%
Colestipol 10 mg BID, 28 weeks	40 mg QD for 28 weeks	Not determined	↓ 26%**
Maalox TC® 30 mL QD, 17 days	10 mg QD for 15 days	↓ 33%	↓ 34%
Efavirenz 600 mg QD, 14 days	10 mg for 3 days	↓ 41%	↓ 1%
#Rifampin 600 mg QD, 7 days (co-administered)†	40 mg SD	↑ 30%	↑ 2.7 fold
#Rifampin 600 mg QD, 5 days (doses separated)†	40 mg SD	↓ 80%	↓ 40%
#Gemfibrozil 600mg BID, 7 days	40mg SD	↑ 35%	↓ Less than 1%
#Fenofibrate 160mg QD, 7 days	40mg SD	↑ 3%	↑ 2%
Boceprevir 800 mg TID, 7 days	40 mg SD	↑2.30 fold	↑2.66 fold

[&] Data given as x-fold change represent a simple ratio between co-administration and atorvastatin alone (i.e., 1-fold = no change). Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change).

See Sections 5.1 and 7 for clinical significance.

* Greater increases in AUC (up to 2.5 fold) and/or Cmax (up to 71%) have been reported with excessive grapefruit consumption (≥ 750 mL - 1.2 liters per day).

** Single sample taken 8-16 h post dose.

† Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

‡ The dose of saquinavir plus ritonavir in this study is not the clinically used dose. The increase in atorvastatin exposure when used clinically is likely to be higher than what was observed in this study. Therefore, caution should be applied and the lowest dose necessary should be used.

TABLE 4. Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs

Atorvastatin	Co-administered drug and dosing regimen		
	Drug/Dose (mg)	Change in AUC	Change in Cmax
80 mg QD for 15 days	Antipyrine, 600 mg SD	↑ 3%	↓ 11%
80 mg QD for 14 days	#Digoxin 0.25 mg QD, 20 days	↑ 15%	↑ 20 %
40 mg QD for 22 days	Oral contraceptive QD, 2 months - norethindrone 1mg	↑ 28%	↑ 23%

	- ethinyl estradiol 35µg	↑ 19%	↑ 30%
10 mg, SD	Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	No change	No change
10 mg QD for 4 days	Fosamprenavir 1400 mg BID, 14 days	↓ 27%	↓ 18%
10 mg QD for 4 days	Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	No change	No change

[#] See Section 7 for clinical significance.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0–24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli,* the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test.

Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

14 CLINICAL STUDIES

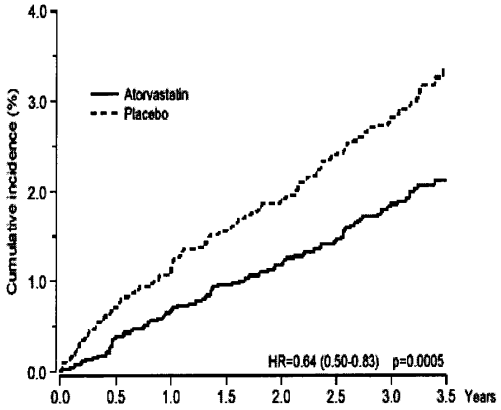
14.1 Prevention of Cardiovascular Disease

In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40–80 years of age (mean of 63 years), without a previous myocardial infarction and with TC levels ≤251 mg/dL (6.5 mmol/L). Additionally, all patients had at least 3 of the following cardiovascular risk factors: male gender (81.1%), age >55 years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), TC:HDL >6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypertrophy (14.4%), prior cerebrovascular event (9.8%), specific ECG abnormality (14.3%), proteinuria/albuminuria (62.4%). In this double-blind, placebo-controlled study, patients were treated with anti-hypertensive therapy (Goal BP <140/90 mm Hg for non-diabetic patients; <130/80 mm Hg for diabetic patients) and allocated to either atorvastatin calcium tablets 10 mg daily (n=5168) or placebo (n=5137), using a covariate adaptive method which took into account the distribution of nine baseline characteristics of patients already enrolled and minimized the imbalance of those characteristics across the groups. Patients were followed for a median duration of 3.3 years.

The effect of 10 mg/day of atorvastatin calcium tablets on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin significantly reduced the rate of coronary events [either fatal coronary heart disease (46 events in the placebo group vs. 40 events in the atorvastatin calcium tablets group) or non-fatal MI (108 events in the placebo group vs. 60 events in the atorvastatin calcium tablets group)] with a relative risk reduction of 36% [(based on incidences of 1.9% for atorvastatin calcium tablets vs. 3.0% for placebo), p=0.0005 (see Figure 1)]. The risk reduction was consistent regardless of age, smoking status, obesity, or presence of renal dysfunction. The effect of atorvastatin was seen regardless of baseline LDL levels. Due to the small number of events, results for women were inconclusive.

Figure 1: Effect of Atorvastatin 10 mg/day on Cumulative Incidence of Non-Fatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)



Atorvastatin also significantly decreased the relative risk for revascularization procedures by 42%. Although the reduction of fatal and non-fatal strokes did not reach a pre-defined significance level (p=0.01), a favorable trend was observed with a 26% relative risk reduction (incidences of 1.7% for atorvastatin calcium tablets and 2.3% for placebo). There was no significant difference between the treatment groups for death due to cardiovascular causes (p=0.51) or noncardiovascular causes (p=0.17).

In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of atorvastatin on cardiovascular disease (CVD) endpoints was assessed in 2838 subjects (94% white, 68% male), ages 40–75 with type 2 diabetes based on WHO criteria, without prior history of cardiovascular disease and with LDL ≤ 160 mg/dL and TG ≤ 600 mg/dL. In addition to diabetes, subjects had 1 or more of the following risk factors: current smoking (23%), hypertension (80%), retinopathy (30%), or microalbuminuria (9%) or macroalbuminuria (3%). No subjects on hemodialysis were enrolled in the study. In this multicenter, placebo-controlled, double-blind clinical trial, subjects were randomly allocated to either atorvastatin calcium tablets 10 mg daily (1429) or placebo (1411) in a 1:1 ratio and were followed for a median duration of 3.9 years. The primary endpoint was the occurrence of any of the major cardiovascular events: myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke. The primary analysis was the time to first occurrence of the primary endpoint.

Baseline characteristics of subjects were: mean age of 62 years, mean HbA_{1c} 7.7%; median LDL-C 120 mg/dL; median TC 207 mg/dL; median TG 151 mg/dL; median HDL-C 52 mg/dL.

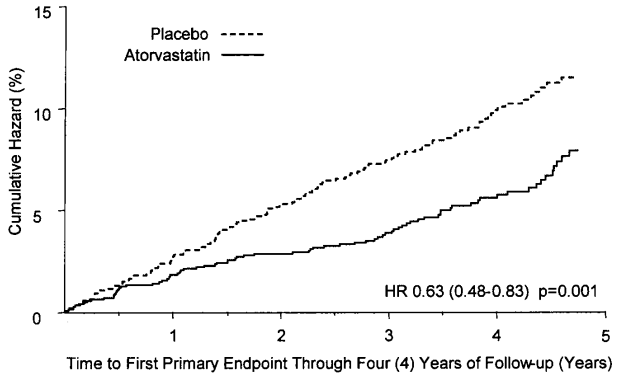
The effect of atorvastatin 10 mg/day on lipid levels was similar to that seen in previous clinical trials.

Atorvastatin significantly reduced the rate of major cardiovascular events (primary endpoint events) (83 events in the atorvastatin calcium tablets group vs. 127 events in the placebo group) with a relative risk reduction of 37%, HR 0.63, 95% CI (0.48, 0.83) (p=0.001) (see Figure 2). An effect of atorvastatin calcium tablets was seen regardless of age, sex, or baseline lipid levels.

Atorvastatin significantly reduced the risk of stroke by 48% (21 events in the atorvastatin calcium tablets group vs. 39 events in the placebo group), HR 0.52, 95% CI (0.31, 0.89) (p=0.016) and reduced the risk of MI by 42% (38 events in the atorvastatin calcium tablets group vs. 64 events in the placebo group), HR 0.58, 95.1% CI (0.39, 0.86) (p=0.007). There was no significant difference between the treatment groups for angina, revascularization procedures, and acute CHD death.

There were 61 deaths in the atorvastatin calcium tablets group vs. 82 deaths in the placebo group (HR 0.73, p=0.059).

Figure 2: Effect of Atorvastatin 10 mg/day on Time to Occurrence of Major Cardiovascular Event (myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke) in CARDS



In the Treating to New Targets Study (TNT), the effect of atorvastatin calcium tablets 80 mg/day vs. atorvastatin calcium tablets 10 mg/day on the reduction in cardiovascular events was assessed in 10,001 subjects (94% white, 81% male, 38% ≥65 years) with clinically evident coronary heart disease who had achieved a target LDL-C level <130 mg/dL after completing an 8-week, open-label, run-in period with atorvastatin calcium tablets 10 mg/day. Subjects were randomly assigned to either 10 mg/day or 80 mg/day of atorvastatin calcium tablets and followed for a median duration of 4.9 years. The primary endpoint was the time-to-first occurrence of any of the following major cardiovascular events (MCVE): death due to CHD, non-fatal myocardial infarction, resuscitated cardiac arrest, and fatal and non-fatal stroke. The mean LDL-C, TC, TG, non-HDL, and HDL cholesterol levels at 12 weeks were 73, 145, 128, 98, and 47 mg/dL during treatment with 80 mg of atorvastatin calcium tablets and 99, 177, 152, 129, and 48 mg/dL during treatment with 10 mg of atorvastatin calcium tablets.

Treatment with atorvastatin calcium tablets 80 mg/day significantly reduced the rate of MCVE (434 events in the 80 mg/day group vs. 548 events in the 10 mg/day group) with a relative risk reduction of 22%, HR 0.78, 95% CI (0.69, 0.89), p=0.0002 (see Figure 3 and Table 5). The overall risk reduction was consistent regardless of age (<65, ≥65) or gender.

Figure 3: Effect of Atorvastatin 80 mg/day vs. 10 mg/day on Time to Occurrence of Major Cardiovascular Events (TNT)

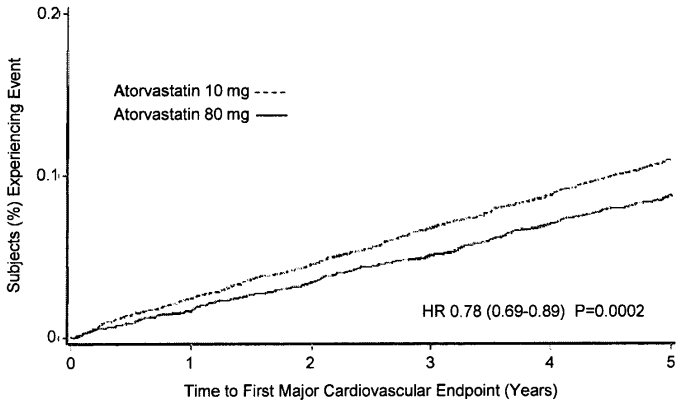


TABLE 5. Overview of Efficacy Results in TNT

Endpoint	Atorvastatin 10 mg (N=5006)		Atorvastatin 80 mg (N=4995)		HR[a] (95%CI)
PRIMARY ENDPOINT	n	(%)	n	(%)	
First major cardiovascular endpoint	548	(10.9)	434	(8.7)	0.78 (0.69, 0.89)
Components of the Primary Endpoint					
CHD death	127	(2.5)	101	(2.0)	0.80 (0.61, 1.03)
Non-fatal, non-procedure related MI	308	(6.2)	243	(4.9)	0.78 (0.66, 0.93)
Resuscitated cardiac arrest	26	(0.5)	25	(0.5)	0.96 (0.56, 1.67)
Stroke (fatal and non-fatal)	155	(3.1)	117	(2.3)	0.75 (0.59, 0.96)
SECONDARY ENDPOINTS*					
First CHF with hospitalization	164	(3.3)	122	(2.4)	0.74 (0.59, 0.94)
First PVD endpoint	282	(5.6)	275	(5.5)	0.97 (0.83, 1.15)
First CABG or other coronary revascularization procedure[b]	904	(18.1)	667	(13.4)	0.72 (0.65, 0.80)
First documented angina endpoint[b]	615	(12.3)	545	(10.9)	0.88 (0.79, 0.99)
All-cause mortality	282	(5.6)	284	(5.7)	1.01 (0.85, 1.19)
Components of All-Cause Mortality					
Cardiovascular death	155	(3.1)	126	(2.5)	0.81 (0.64, 1.03)
Noncardiovascular death	127	(2.5)	158	(3.2)	1.25 (0.99, 1.57)
Cancer death	75	(1.5)	85	(1.7)	1.13 (0.83, 1.55)
Other non-CV death	43	(0.9)	58	(1.2)	1.35 (0.91, 2.00)
Suicide, homicide, and other traumatic non-CV death	9	(0.2)	15	(0.3)	1.67 (0.73, 3.82)

a Atorvastatin 80 mg: atorvastatin 10 mg
b Component of other secondary endpoints
* Secondary endpoints not included in primary endpoint
HR=hazard ratio; CHD=coronary heart disease; CI=confidence interval; MI=myocardial infarction; CHF=congestive heart failure; CV=cardiovascular; PVD=peripheral vascular disease; CABG=coronary artery bypass graft
Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons

Of the events that comprised the primary efficacy endpoint, treatment with atorvastatin calcium tablets 80 mg/day significantly reduced the rate of non-fatal, non-procedure related MI and fatal and non-fatal stroke, but not CHD death or resuscitated cardiac arrest (Table 5). Of the predefined secondary endpoints, treatment with atorvastatin calcium tablets 80 mg/day significantly reduced the rate of coronary revascularization, angina, and hospitalization for heart failure, but not peripheral vascular disease. The reduction in the rate of CHF with hospitalization was only observed in the 8% of patients with a prior history of CHF.

There was no significant difference between the treatment groups for all-cause mortality (Table 5). The proportions of subjects who experienced cardiovascular death, including the components of CHD death and fatal stroke, were numerically smaller in the atorvastatin calcium tablets 80 mg group than in the atorvastatin calcium tablets 10 mg treatment group. The proportions of subjects who experienced noncardiovascular death were numerically larger in the atorvastatin calcium tablets 80 mg group than in the atorvastatin calcium tablets 10 mg treatment group.

In the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL), treatment with atorvastatin calcium tablets 80 mg/day was compared to treatment with simvastatin 20–40 mg/day in 8,888 subjects up to 80 years of age with a history of CHD to assess whether reduction in CV risk could be achieved. Patients were mainly male (81%), white (99%) with an average age of 61.7 years, and an average LDL-C of 121.5 mg/dL at randomization; 76% were on statin therapy. In this prospective, randomized, open-label, blinded endpoint (PROBE) trial with no run-in period, subjects were followed for a median duration of 4.8 years. The mean LDL-C, TC, TG, HDL, and non-HDL cholesterol levels at Week 12 were 78, 145, 115, 45, and 100 mg/dL during treatment with 80 mg of atorvastatin calcium tablets and 105, 179, 142, 47, and 132 mg/dL during treatment with 20–40 mg of simvastatin.

There was no significant difference between the treatment groups for the primary endpoint, the rate of first major coronary event (fatal CHD, non-fatal MI, and resuscitated cardiac arrest): 411 (9.3%) in the atorvastatin calcium tablets 80 mg/day group vs. 463 (10.4%) in the simvastatin 20–40 mg/day group, HR 0.89, 95% CI (0.78, 1.01), p=0.07.

There were no significant differences between the treatment groups for all-cause mortality: 366 (8.2%) in the atorvastatin calcium tablets 80 mg/day group vs. 374 (8.4%) in the simvastatin 20–40 mg/day group. The proportions of subjects who experienced CV or non-CV death were similar for the atorvastatin calcium tablets 80 mg group and the simvastatin 20–40 mg group.

14.2 Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia *(Fredrickson* Types IIa and IIb)

Atorvastatin reduces total-C, LDL-C, VLDL-C, apo B, and TG, and increases HDL-C in patients with hyperlipidemia and mixed dyslipidemia. Therapeutic response is seen within 2 weeks, and maximum response is usually achieved within 4 weeks and maintained during chronic therapy.

Atorvastatin calcium tablets are effective in a wide variety of patient populations with hyperlipidemia, with and without hypertriglyceridemia, in men and women, and in the elderly.

In two multicenter, placebo-controlled, dose-response studies in patients with hyperlipidemia, atorvastatin calcium tablets given as a single dose over 6 weeks, significantly reduced total-C, LDL-C, apo B, and TG. (Pooled results are provided in Table 6.)

TABLE 6. Dose Response in Patients With Primary Hyperlipidemia (Adjusted Mean % Change From Baseline)[a]

Dose	N	TC	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Placebo	21	4	4	3	10	-3	7
10	22	-29	-39	-32	-19	6	-34
20	20	-33	-43	-35	-26	9	-41
40	21	-37	-50	-42	-29	6	-45
80	23	-45	-60	-50	-37	5	-53

[a] Results are pooled from 2 dose-response studies.

In patients with *Fredrickson* Types IIa and IIb hyperlipoproteinemia pooled from 24 controlled trials, the median (25th and 75th percentile) percent changes from baseline in HDL-C for atorvastatin calcium tablets 10, 20, 40, and 80 mg were 6.4 (-1.4, 14), 8.7 (0, 17), 7.8 (0, 16), and 5.1 (-2.7, 15), respectively. Additionally, analysis of the pooled data demonstrated consistent and significant decreases in total-C, LDL-C, TG, total-C/HDL-C, and LDL-C/HDL-C.

In three multicenter, double-blind studies in patients with hyperlipidemia, atorvastatin was compared to other statins. After randomization, patients were treated for 16 weeks with either atorvastatin calcium tablets 10 mg per day or a fixed dose of the comparative agent (Table 7).

TABLE 7. Mean Percentage Change From Baseline at Endpoint (Double-Blind, Randomized, Active-Controlled Trials)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Study 1							
Atorvastatin 10 mg	707	-27[a]	-36[a]	-28[a]	-17[a]	+7	-37[a]
Lovastatin 20 mg	191	-19	-27	-20	-6	+7	-28
95% CI for Diff[l]		-9.2, -6.5	-10.7, -7.1	-10.0, -6.5	-15.2, -7.1	-1.7, 2.0	-11.1, -7.1
Study 2							
Atorvastatin 10 mg	222	-25[b]	-35[b]	-27[b]	-17[b]	+6	-36[b]
Pravastatin 20 mg	77	-17	-23	-17	-9	+8	-28
95% CI for Diff[l]		-10.8, -6.1	-14.5, -8.2	-13.4, -7.4	-14.1, -0.7	-4.9, 1.6	-11.5, -4.1
Study 3							
Atorvastatin 10 mg	132	-29[c]	-37[c]	-34[c]	-23[c]	+7	-39[c]
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff[l]		-8.7, -2.7	-10.1, -2.6	-8.0, -1.1	-15.1, -0.7	-4.3, 3.9	-9.6, -1.9

[l] A negative value for the 95% CI for the difference between treatments favors atorvastatin for all except HDL-C, for which a positive value favors atorvastatin. If the range does not include 0, this indicates a statistically significant difference.
[a] Significantly different from lovastatin, ANCOVA, p ≤0.05
[b] Significantly different from pravastatin, ANCOVA, p ≤0.05
[c] Significantly different from simvastatin, ANCOVA, p ≤0.05

The impact on clinical outcomes of the differences in lipid-altering effects between treatments shown in Table 7 is not known. Table 7 does not contain data comparing the effects of atorvastatin 10 mg and higher doses of lovastatin, pravastatin, and simvastatin. The drugs compared in the studies summarized in the table are not necessarily interchangeable.

14.3 Hypertriglyceridemia *(Fredrickson* Type IV)

The response to atorvastatin in 64 patients with isolated hypertriglyceridemia treated across several clinical trials is shown in the table below (Table 8). For the atorvastatin calcium tablets-treated patients, median (min, max) baseline TG level was 565 (267–1502).

TABLE 8. Combined Patients With Isolated Elevated TG: Median (min, max) Percentage Change From Baseline

	Placebo (N=12)	atorvastatin 10 mg (N=37)	atorvastatin 20 mg (N=13)	atorvastatin 80 mg (N=14)
Triglycerides	-12.4 (-36.6, 82.7)	-41.0 (-76.2, 49.4)	-38.7 (-62.7, 29.5)	-51.8 (-82.8, 41.3)
Total-C	-2.3 (-15.5, 24.4)	-28.2 (-44.9, -6.8)	-34.9 (-49.6, -15.2)	-44.4 (-63.5, -3.8)
LDL-C	3.6 (-31.3, 31.6)	-26.5 (-57.7, 9.8)	-30.4 (-53.9, 0.3)	-40.5 (-60.6, -13.8)
HDL-C	3.8 (-18.6, 13.4)	13.8 (-9.7, 61.5)	11.0 (-3.2, 25.2)	7.5 (-10.8, 37.2)
VLDL-C	-1.0 (-31.9, 53.2)	-48.8 (-85.8, 57.3)	-44.6 (-62.2, -10.8)	-62.0 (-88.2, 37.6)
non-HDL-C	-2.8 (-17.6, 30.0)	-33.0 (-52.1, -13.3)	-42.7 (-53.7, -17.4)	-51.5 (-72.9, -4.3)

14.4 Dysbetalipoproteinemia *(Fredrickson* Type III)

The results of an open-label crossover study of 16 patients (genotypes: 14 apo E2/E2 and 2 apo E3/E2) with dysbetalipoproteinemia *(Fredrickson* Type III) are shown in the table below (Table 9).

TABLE 9. Open-Label Crossover Study of 16 Patients With Dysbetalipoproteinemia (*Fredrickson* Type III)

		Median % Change (min, max)	
	Median (min, max) at Baseline (mg/dL)	atorvastatin 10 mg	atorvastatin 80 mg
Total-C	442 (225, 1320)	-37 (-85, 17)	-58 (-90, -31)
Triglycerides	678 (273, 5990)	-39 (-92, -8)	-53 (-95, -30)
IDL-C + VLDL-C	215 (111, 613)	-32 (-76, 9)	-63 (-90, -8)
non-HDL-C	411 (218, 1272)	-43 (-87, -19)	-64 (-92, -36)

14.5 Homozygous Familial Hypercholesterolemia

In a study without a concurrent control group, 29 patients ages 6 to 37 years with homozygous FH received maximum daily doses of 20 to 80 mg of atorvastatin calcium tablets. The mean LDL-C reduction in this study was 18%. Twenty-five patients with a reduction in LDL-C had a mean response of 20% (range of 7% to 53%, median of 24%); the remaining 4 patients had 7% to 24% increases in LDL-C. Five of the 29 patients had absent LDL-receptor function. Of these, 2 patients also had a portacaval shunt and had no significant reduction in LDL-C. The remaining 3 receptor-negative patients had a mean LDL-C reduction of 22%.

14.6 Heterozygous Familial Hypercholesterolemia in Pediatric Patients

In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (FH) or severe hypercholesterolemia, were randomized to atorvastatin calcium tablets (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin calcium tablets for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level ≥ 190 mg/dL or 2) a baseline LDL-C level ≥ 160 mg/dL and positive family history of FH or documented premature cardiovascular disease in a first or second-degree relative. The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5–385.0 mg/dL) in the atorvastatin calcium tablets group compared to 230.0 mg/dL (range: 160.0–324.5 mg/dL) in the placebo group. The dosage of atorvastatin calcium tablets (once daily) was 10 mg for the first 4 weeks and uptitrated to 20 mg if the LDL-C level was > 130 mg/dL. The number of atorvastatin calcium tablets-treated patients who required uptitration to 20 mg after Week 4 during the double-blind phase was 80 (57.1%).

Atorvastatin significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26-week double-blind phase (see Table 10).

TABLE 10. Lipid-altering Effects of Atorvastatin in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia (Mean Percentage Change From Baseline at Endpoint in Intention-to-Treat Population)

DOSAGE	N	Total-C	LDL-C	HDL-C	TG	Apolipoprotein B
Placebo	47	-1.5	-0.4	-1.9	1.0	0.7
Atorvastatin	140	-31.4	-39.6	2.8	-12.0	-34.0

The mean achieved LDL-C value was 130.7 mg/dL (range: 70.0–242.0 mg/dL) in the atorvastatin group compared to 228.5 mg/dL (range: 152.0–385.0 mg/dL) in the placebo group during the 26-week double-blind phase.

The safety and efficacy of doses above 20 mg have not been studied in controlled trials in children. The long-term efficacy of atorvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

15 REFERENCES

[1] National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents, *Pediatrics.* 89(3):495-501. 1992.

16 HOW SUPPLIED/STORAGE AND HANDLING

10 mg tablets: coded "PD 155" on one side and "10" on the other.
NDC 59762-0155-1 bottles of 90
NDC 59762-0155-2 bottles of 1000

20 mg tablets: coded "PD 156" on one side and "20" on the other.
NDC 59762-0156-1 bottles of 90
NDC 59762-0156-2 bottles of 1000

40 mg tablets: coded "PD 157" on one side and "40" on the other.
NDC 59762-0157-1 bottles of 90
NDC 59762-0157-2 bottles of 500

80 mg tablets: coded "PD 158" on one side and "80" on the other.
NDC 59762-0158-1 bottles of 90
NDC 59762-0158-2 bottles of 500

Storage
Store at controlled room temperature 20 - 25°C (68 - 77°F) [see USP].

17 PATIENT COUNSELING INFORMATION

Patients taking atorvastatin calcium tablets should be advised that cholesterol is a chronic condition and they should adhere to their medication along with their National Cholesterol Education Program (NCEP)-recommended diet, a regular exercise program as appropriate, and periodic testing of a fasting lipid panel to determine goal attainment.

Patients should be advised about substances they should not take concomitantly with atorvastatin *[see Warnings and Precautions (5.1)]*. Patients should also be advised to inform other healthcare professionals prescribing a new medication that they are taking atorvastatin calcium tablets.

17.1 Muscle Pain
All patients starting therapy with atorvastatin calcium tablets should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness, or weakness particularly if accompanied by malaise or fever or if these muscle signs or symptoms persist after discontinuing atorvastatin calcium tablets. The risk of this occurring is increased when taking certain types of medication or consuming larger quantities (>1 liter) of grapefruit juice. They should discuss all medication, both prescription and over the counter, with their healthcare professional.

17.2 Liver Enzymes
It is recommended that liver enzyme tests be performed before the initiation of atorvastatin calcium tablets and if signs or symptoms of liver injury occur. All patients treated with atorvastatin calcium tablets should be advised to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. .

17.3 Pregnancy
Women of childbearing age should be advised to use an effective method of birth control to prevent pregnancy while using atorvastatin calcium tablets. Discuss future pregnancy plans with your patients, and discuss when to stop atorvastatin calcium tablets if they are trying to conceive. Patients should be advised that if they become pregnant, they should stop taking atorvastatin calcium tablets and call their healthcare professional.

17.4 Breastfeeding
Women who are breastfeeding should be advised to not use atorvastatin calcium tablets. Patients who have a lipid disorder and are breastfeeding, should be advised to discuss the options with their healthcare professional.

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APPENDIX E: ASPIRIN PACKAGE INSERT

Aspirin
Comprehensive Prescribing Information

DESCRIPTION

BAYER® SAFETY COATED ASPIRIN
Delayed Release Enteric Aspirin for Oral Administration
Regular Strength 325 mg Caplets and Low Strength 81 mg Tablets

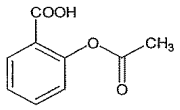
Inactive Ingredients

Regular Strength 325 mg - Carnauba Wax, Cellulose, D&C Yellow #10 Aluminum Lake, FD&C Yellow #6 Aluminum Lake, Hypromellose, Iron Oxides, Methacrylic Acid Copolymer, Polysorbate 80, Propylene Glycol, Shellac, Sodium Lauryl Sulfate, Starch, Titanium Dioxide, Triacetin.

Low Strength 81 mg – Black Iron Oxide, Brown Iron Oxide, Carnauba Wax, Corn Starch, Croscarmellose Sodium, D&C Yellow #10 Aluminum Lake, FD&C Yellow #6 Aluminum Lake, Hypromellose, Lactose Monohydrate, Methacrylic Acid Copolymer, Microcrystalline Cellulose, Polysorbate 80, Powdered Cellulose, Pregelatinized Starch, Propylene Glycol, Shellac, Sodium Lauryl Sulfate, Titanium Dioxide, Triacetin.

Antiplatelet, Antiarthritic

Aspirin



$C_9H_8O_4$
Mol. Wt.: 180.16
C 60.00 %; H 4.48 %; O 35.52%

Aspirin is an odorless white, needle-like crystalline or powdery substance. When exposed to moisture, aspirin hydrolyzes into salicylic and acetic acids, and gives off a vinegary-odor. It is highly lipid soluble and slightly soluble in water.

CLINICAL PHARMACOLOGY

Mechanism of Action

Aspirin is a more potent inhibitor of both prostaglandin synthesis and platelet aggregation than other salicylic acid derivatives. The differences in activity between aspirin and salicylic acid are thought to be due to the acetyl group on the aspirin molecule. This acetyl group is responsible for the inactivation of cyclo-oxygenase via acetylation.

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Pharmacokinetics

Absorption: In general, immediate release aspirin is well and completely absorbed from the gastrointestinal (GI) tract. Following absorption, aspirin is hydrolyzed to salicylic acid with peak plasma levels of salicylic acid occurring within 1-2 hours of dosing (see **Pharmacokinetics-** *Metabolism*). The rate of absorption from the GI tract is dependent upon the dosage form, the presence or absence of food, gastric pH (the presence or absence of GI antacids or buffering agents), and other physiologic factors. Enteric coated aspirin products are erratically absorbed from the GI tract.

Distribution: Salicylic acid is widely distributed to all tissues and fluids in the body including the central nervous system (CNS), breast milk and fetal tissues. The highest concentrations are found in the plasma, liver, renal cortex, heart and lungs. The protein binding of salicylate is concentration-dependent, i.e., non-linear. At low concentrations (< 100 micrograms/milliliter (mcg/mL)), approximately 90 percent of plasma salicylate is bound to albumin while at higher concentrations (> 400 mcg/mL), only about 75 percent is bound. The early signs of salicylic overdose (salicylism), including tinnitus (ringing in the ears), occur at plasma concentrations approximating 200 mcg/mL. Severe toxic effects are associated with levels > 400 mcg/mL. (See **Adverse Reactions and Overdosage**.)

Metabolism: Aspirin is rapidly hydrolyzed in the plasma to salicylic acid such that plasma levels of aspirin are essentially undetectable 1-2 hours after dosing. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites. Salicylic acid has a plasma half-life of approximately 6 hours. Salicylate metabolism is saturable and total body clearance decreases at higher serum concentrations due to the limited ability of the liver to form both salicyluric acid and phenolic glucuronide. Following toxic doses (10-20 grams (g)), the plasma half-life may be increased to over 20 hours.

Elimination: The elimination of salicylic acid follows zero order pharmacokinetics; (i.e., the rate of drug elimination is constant in relation to plasma concentration). Renal excretion of unchanged drug depends upon urine pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from < 5 percent to > 80 percent. Alkalinization of the urine is a key concept in the management of salicylate overdose. (See **Overdosage**.) Following therapeutic doses, approximately 10 percent is found excreted in the urine as salicylic acid, 75 percent as salicyluric acid, 10 percent and 5 percent as the phenolic and acyl glucuronides, respectively.

Pharmacodynamics

Aspirin affects platelet aggregation by irreversibly inhibiting prostaglandin cyclo-oxygenase. This effect lasts for the life of the platelet and prevents the formation of the platelet aggregating factor thromboxane A_2. Non-acetylated salicylates do not inhibit this enzyme and have no effect on platelet aggregation. At somewhat higher doses, aspirin reversibly inhibits the formation of prostaglandin I_2 (prostacyclin), which is an arterial vasodilator and inhibits platelet aggregation.

At higher doses aspirin is an effective anti-inflammatory agent, partially due to inhibition of inflammatory mediators via cyclo-oxygenase inhibition in peripheral tissues. In vitro studies suggest that other mediators of inflammation may also be suppressed by aspirin administration, although the precise mechanism of action has not been elucidated. It is this nonspecific suppression of cyclo-oxygenase activity in peripheral tissues following large doses that leads to its primary side effect of gastric irritation. (See **Adverse Reactions**.)

CLINICAL STUDIES

Ischemic Stroke and Transient Ischemic Attack (TIA): In clinical trials of subjects with TIAs due to fibrin platelet emboli or ischemic stroke, aspirin has been shown to significantly reduce the risk of the combined endpoint of stroke or death and the combined endpoint of TIA, stroke, or death by about 13-18 percent.

Suspected Acute Myocardial Infarction (MI): In a large, multi-center study of aspirin, streptokinase, and the combination of aspirin and streptokinase in 17,187 patients with suspected acute MI, aspirin treatment produced a 23 percent reduction in the risk of vascular mortality. Aspirin was also shown to have an additional benefit in patients given a thrombolytic agent.

Prevention of Recurrent MI and Unstable Angina Pectoris: These indications are supported by the results of six large, randomized, multi-center, placebo-controlled trials of predominantly male post-MI subjects and one randomized placebo-controlled study of men with unstable angina pectoris. Aspirin therapy in MI subjects was associated with a significant reduction (about 20 percent) in the risk of the combined endpoint of subsequent death and/or nonfatal reinfarction in these patients. In aspirin-treated unstable angina patients the event rate was reduced to 5 percent from the 10 percent rate in the placebo group.

Chronic Stable Angina Pectoris: In a randomized, multi-center, double-blind trial designed to assess the role of aspirin for prevention of MI in patients with chronic stable angina pectoris, aspirin significantly reduced the primary combined endpoint of nonfatal MI, fatal MI, and sudden death by 34 percent. The secondary endpoint for vascular events (the first occurrence of MI, stroke, or vascular death) was also significantly reduced (32 percent).

Revascularization Procedures: Most patients who undergo coronary artery revascularization procedures have already had symptomatic coronary artery disease for which aspirin is indicated. Similarly, patients with lesions of the carotid bifurcation sufficient to require carotid endarterectomy are likely to have had a precedent event. Aspirin is recommended for patients who undergo revascularization procedures if there is a preexisting condition for which aspirin is already indicated.

Rheumatologic Diseases: In clinical studies in patients with rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis and osteoarthritis, aspirin has been shown to be effective in controlling various indices of clinical disease activity.

ANIMAL TOXICOLOGY

The acute oral 50 percent lethal dose in rats is about 1.5 g/kilogram (kg) and in mice 1.1 g/kg. Renal papillary necrosis and decreased urinary concentrating ability occur in rodents chronically administered high doses. Dose-dependent gastric mucosal injury occurs in rats and humans. Mammals may develop aspirin toxicosis associated with GI symptoms, circulatory effects, and central nervous system depression. (See **Overdosage**.)

INDICATIONS AND USAGE

Vascular Indications (Ischemic Stoke, TIA, Acute MI, Prevention of Recurrent MI, Unstable Angina Pectoris, and Chronic Stable Angina Pectoris): Aspirin is indicated to: (1) Reduce the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli, (2) reduce the risk of vascular mortality in patients with a suspected acute MI, (3) reduce the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris, and (4) reduce the combined risk of MI and sudden death in patients with chronic stable angina pectoris.

Revascularization Procedures (Coronary Artery Bypass Graft (CABG), Percutaneous Transluminal Coronary Angioplasty (PTCA), and Carotid Endarterectomy): Aspirin is indicated in patients who have undergone revascularization procedures (i.e., CABG, PTCA, or carotid endarterectomy) when there is a preexisting condition for which aspirin is already indicated.

Rheumatologic Disease Indications (Rheumatoid Arthritis, Juvenile Rheumatoid Arthritis, Spondyloarthropathies, Osteoarthritis, and the Arthritis and Pleurisy of Systemic Lupus Erythematosus (SLE)): Aspirin is indicated for the relief of the signs and symptoms of rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, spondyloarthropathies, and arthritis and pleurisy associated with SLE.

CONTRAINDICATIONS

Allergy: Aspirin is contraindicated in patients with known allergy to nonsteroidal anti-inflammatory drug products and in patients with the syndrome of asthma, rhinitis, and nasal polyps. Aspirin may cause severe urticaria, angioedema, or bronchospasm (asthma).

Reye's Syndrome: Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of aspirin in certain viral illnesses.

WARNINGS

Alcohol Warning: Patients who consume three or more alcoholic drinks every day should be counseled about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin.

Coagulation Abnormalities: Even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. This can adversely affect patients with inherited (hemophilia) or acquired (liver disease or vitamin K deficiency) bleeding disorders.

GI Side Effects: GI side effects include stomach pain, heartburn, nausea, vomiting, and gross GI bleeding. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Physicians should inform patients about the signs and symptoms of GI side effects and what steps to take if they occur.

Peptic Ulcer Disease: Patients with a history of active peptic ulcer disease should avoid using aspirin, which can cause gastric mucosal irritation and bleeding.

PRECAUTIONS

General

Renal Failure: Avoid aspirin in patients with severe renal failure (glomerular filtration rate less than 10 mL/minute).

Hepatic Insufficiency: Avoid aspirin in patients with severe hepatic insufficiency.

Sodium Restricted Diets: Patients with sodium-retaining states, such as congestive heart failure or renal failure, should avoid sodium-containing buffered aspirin preparations because of their high sodium content.

Laboratory Tests

Aspirin has been associated with elevated hepatic enzymes, blood urea nitrogen and serum creatinine, hyperkalemia, proteinuria, and prolonged bleeding time.

Drug Interactions

Angiotensin Converting Enzyme (ACE) Inhibitors: The hyponatremic and hypotensive effects of ACE inhibitors may be diminished by the concomitant administration of aspirin due to its indirect effect on the renin-angiotensin conversion pathway.

Acetazolamide: Concurrent use of aspirin and acetazolamide can lead to high serum concentrations of acetazolamide (and toxicity) due to competition at the renal tubule for secretion.

Anticoagulant Therapy (Heparin and Warfarin): Patients on anticoagulation therapy are at increased risk for bleeding because of drug-drug interactions and the effect on platelets. Aspirin can displace warfarin from protein binding sites, leading to prolongation of both the prothrombin time and the bleeding time. Aspirin can increase the anticoagulant activity of heparin, increasing bleeding risk.

Anticonvulsants: Salicylate can displace protein-bound phenytoin and valproic acid, leading to decrease in the total concentration of phenytoin and an increase in serum valproic acid levels.

Beta Blockers: The hypotensive effects of beta blockers may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow, and salt and fluid retention.

Diuretics: The effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow, and salt and fluid retention.

Methotrexate: Salicylate can inhibit renal clearance of methotrexate, leading to bone marrow toxicity, especially in the elderly or renal impaired.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs): The concurrent use of aspirin with other NSAIDs should be avoided because this may increase bleeding or lead to decreased renal function.

Oral Hypoglycemics: Moderate doses of aspirin may increase the effectiveness of oral hypoglycemic drugs, leading to hypoglycemia.

Uricosuric Agents (Probenecid and Sulfinpyrazone): Salicylates antagonize the uricosuric action of uricosuric agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Administration of aspirin for 68 weeks at 0.5 percent in the feed of rats was not carcinogenic. In the Ames Salmonella assay, aspirin was not mutagenic; however, aspirin did induce chromosome aberrations in cultured human fibroblasts. Aspirin inhibits ovulation in rats. (See **Pregnancy**).

Pregnancy

Pregnant women should only take aspirin if clearly needed. Because of the known effects of NSAIDs on the fetal cardiovascular system (closure of the ductus arteriosus), use during the third trimester of pregnancy should be avoided. Salicylate products have also been associated with alterations in maternal and neonatal hemostasis mechanisms, decreased birth weight, and with perinatal mortality.

Labor and Delivery

Aspirin should be avoided 1 week prior to and during labor and delivery because it can result in excessive blood loss at delivery. Prolonged gestation and prolonged labor due to prostaglandin inhibition have been reported.

Nursing Mothers

Nursing mothers should avoid using aspirin because salicylate is excreted in breast milk. Use of high doses may lead to rashes, platelet abnormalities, and bleeding in nursing infants.

Pediatric Use

Pediatric dosing recommendations for juvenile rheumatoid arthritis are based on well-controlled clinical studies. An initial dose of 90-130 mg/kg/day in divided doses, with an increase as needed for anti-inflammatory efficacy (target plasma salicylate levels of 150-300 mcg/mL) are effective. At high doses (i.e., plasma levels of greater than 200 mcg/mL), the incidence of toxicity increases.

ADVERSE REACTIONS

Many adverse reactions due to aspirin ingestion are dose-related. The following is a list of adverse reactions that have been reported in the literature. (See **Warnings.**)

Body as a Whole: Fever, hypothermia, thirst.

Cardiovascular: Dysrhythmias, hypotension, tachycardia.

Central Nervous System: Agitation, cerebral edema, coma, confusion, dizziness, headache, subdural or intracranial hemorrhage, lethargy, seizures.

Fluid and Electrolyte: Dehydration, hyperkalemia, metabolic acidosis, respiratory alkalosis.

Gastrointestinal: Dyspepsia, GI bleeding, ulceration and perforation, nausea, vomiting, transient elevations of hepatic enzymes, hepatitis, Reye's syndrome, pancreatitis.

Hematologic: Prolongation of the prothrombin time, disseminated intravascular coagulation, coagulopathy, thrombocytopenia.

Hypersensitivity: Acute anaphylaxis, angioedema, asthma, bronchospasm, laryngeal edema, urticaria.

Musculoskeletal: Rhabdomyolysis.

Metabolism: Hypoglycemia (in children), hyperglycemia.

Reproductive: Prolonged pregnancy and labor, stillbirths, lower birth weight infants, antepartum and postpartum bleeding.

Respiratory: Hyperpnea, pulmonary edema, tachypnea.

Special Senses: Hearing loss, tinnitus. Patients with higher frequency hearing loss may have difficulty perceiving tinnitus. In these patients, tinnitus cannot be used as a clinical indicator of salicylism.

Urogenital: Interstitial nephritis, papillary necrosis, proteinuria, renal insufficiency and failure.

DRUG ABUSE AND DEPENDENCE

Aspirin is non-narcotic. There is no known potential for addiction associated with the use of aspirin.

OVERDOSAGE

Salicylate toxicity may result from acute ingestion (overdose) or chronic intoxication. The early signs of salicylic overdose (salicylism), including tinnitus (ringing in the ears), occur at plasma concentrations approaching 200 mcg/mL. Plasma concentrations of aspirin above 300 mcg/mL are clearly toxic. Severe toxic effects are associated with levels above 400 mcg/mL. (See **Clinical Pharmacology**). A single lethal dose of aspirin in adults in not known with certainty but death may be expected at 30 g. For real or suspected overdose, a Poison Control Center should be contacted immediately. Careful medical management is essential.

Signs and Symptoms: In acute overdose, severe acid-base and electrolyte disturbances may occur and are complicated by hyperthermia and dehydration. Respiratory alkalosis occurs early while hyperventilation is present, but is quickly followed by metabolic acidosis.

Treatment: Treatment consists primarily of supporting vital functions, increasing salicylate elimination, and correcting the acid-base disturbance. Gastric emptying and/or lavage is recommended as soon as possible after ingestion, even if the patient has vomited spontaneously. After lavage and/or emesis, administration of activated charcoal, as a slurry, is beneficial, if less than 3 hours have passed since ingestion. Charcoal adsorption should not be employed prior to emesis and lavage.

Severity of aspirin intoxication is determined by measuring the blood salicylate level. Acid-base status should be closely followed with serial blood gas and serum pH measurements. Fluid and electrolyte balance should also be maintained. In severe cases, hyperthermia and hypovolemia are the major immediate threats to life. Children should be sponged with tepid water. Replacement fluid should be administered intravenously and augmented with correction of acidosis. Plasma electrolytes and pH should be monitored to promote alkaline diuresis of salicylate if renal function is normal. Infusion of glucose may be required to control hypoglycemia.

Hemodialysis and peritoneal dialysis can be performed to reduce the body drug content. In patients with renal insufficiency or in cases of life-threatening intoxication, dialysis is usually required. Exchange transfusion may be indicated in infants and young children.

DOSAGE AND ADMINISTRATION

Each dose of aspirin should be taken with a full glass of water unless patient is fluid restricted. Anti-inflammatory and analgesic dosages should be individualized. When aspirin is used in high doses, the development of tinnitus may be used as a clinical sign of elevated plasma salicylate levels except in patients with high frequency hearing loss.

Ischemic Stroke and TIA:

50-325 mg once a day. Continue therapy indefinitely.

Suspected Acute MI:

The initial dose of 160-162.5 mg is administered as soon as an MI is suspected. The maintenance dose of 160-162.5 mg a day is continued for 30 days post-infarction. After 30 days, consider further therapy based on dosage and administration for prevention of recurrent MI.

Prevention of Recurrent MI:

75-325 mg once a day. Continue therapy indefinitely.

Unstable Angina Pectoris:

75-325 mg once a day. Continue therapy indefinitely.

Chronic Stable Angina Pectoris:

75-325 mg once a day. Continue therapy indefinitely.

CABG:

325 mg daily starting 6 hours post-procedure. Continue therapy for one year post-procedure.

PTCA:

The initial dose of 325 mg should be given 2 hours pre-surgery. Maintenance dose is 160-325 mg daily. Continue therapy indefinitely.

Carotid Endarterectomy:

Doses of 80 mg once daily to 650 mg twice daily, started pre-surgery, are recommended. Continue therapy indefinitely.

Rheumatoid Arthritis:

The initial dose is 3 g a day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 mcg/mL. At high doses (i.e., plasma levels of greater than 200 mcg/mL), the incidence of toxicity increases.

Juvenile Rheumatoid Arthritis:

Initial dose is 90-130 mg/kg/day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 mcg/mL. At high doses (i.e., plasma levels of greater than 200 mcg/mL), the incidence of toxicity increases.

Spondyloarthropathies:

Up to 4 g per day in divided doses.

Osteoarthritis:

Up to 3 g per day in divided doses.

Arthritis and Pleurisy of SLE:

The initial dose is 3 g a day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 mcg/mL. At high doses (i.e., plasma levels of greater than 200 mcg/mL), the incidence of toxicity increases.

HOW SUPPLIED

BAYER® SAFETY COATED ASPIRIN is available in 81 mg tablets and 325 mg caplets. The 81 mg tablets are available in bottles of 32, 120, 180 and 240. The 325 mg caplets are available in bottles of 100.

Tablet Identification

81 mg tablet: round, yellow, "81" printed on one side
325 mg caplet: capsule shaped tablets, yellow, "Bayer 325" printed on one side

Storage Conditions

Store at room temperature.

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