of testosterone trials have found a significant increase in cardiovascular event rates in older men receiving testosterone therapy. Inferences about adverse events from previous trials included in these meta-analyses are limited by poor ascertainment, small numbers of events, heterogeneity of study populations, and small numbers of participants. Two retrospective analyses also found a higher frequency of cardiovascular events in association with testosterone therapy in older men with preexisting heart disease. Retrospective database analyses are limited by their inherent inability to verify the indication for treatment, diagnoses, or other relevant quantitative information and are susceptible to confounding by many other factors. Adequately powered prospective studies are needed to determine the effect on testosterone replacement on cardiovascular risk.

Androgen Abuse by Athletes and Recreational Bodybuilders The illicit use of androgenic-anabolic steroids (AAS) to enhance athletic performance first surfaced in the 1950s among power lifters and spread rapidly to other sports, professional as well as high school athletes, and recreational bodybuilders. In the early 1980s, the use of AAS spread beyond the athletic community into the general population, and now as many as 3 million Americans, most of them men, have likely used these compounds. Most AAS users are not athletes, but rather recreational weightlifters, who use these drugs to look lean and more muscular. The most commonly used AAS include testosterone esters, nandrolone, stanozolol, methandienone, and methenolol. AAS users generally use increasing doses of multiple steroids in a practice known as stacking.

The adverse effects of long-term AAS abuse remain poorly understood. Most of the information about the adverse effects of AAS has emerged from case reports, uncontrolled studies, or clinical trials that used replacement doses of testosterone. The adverse event data from clinical trials using physiologic replacement doses of testosterone have been extrapolated unjustifiably to AAS users who may administer 10–100 times the replacement doses of testosterone over many years and to support the claim that AAS use is safe. A substantial fraction of androgenic steroid users also use other drugs that are perceived to be muscle building or performance enhancing, such as GH; erythropoiesis-stimulating agents; insulin; and stimulants such as amphetamine, clenbuterol, cocaine, ephedrine, and thyroxine; and drugs perceived to reduce adverse effects such as hCG, aromatase inhibitors, or estrogen antagonists. The men who abuse androgenic steroids are more likely to engage in other high-risk behaviors than nonusers. The adverse events associated with AAS use may be due to AAS themselves, concomitant use of other drugs, high-risk behaviors, and host characteristics that may render these individuals more susceptible to AAS use or to other high-risk behaviors.

The high rates of mortality and morbidities observed in AAS users are alarming. One Finnish study reported 4.6 times the risk of death among elite power lifters than in age-matched men from the general population. The causes of death among power lifters included suicides, myocardial infarction, hepatic coma, and non-Hodgkin's lymphoma. A retrospective review of patient records in Sweden also reported higher standardized mortality ratios for AAS users than for nonusers. Thiblin and colleagues found that 32% of deaths among AAS users were suicidal, 26% homicidal, and 35% accidental. The median age of death among AAS users (24 years) is even lower than that for heroin or amphetamine users.

Numerous reports of cardiac death among young AAS users raise concerns about the adverse cardiovascular effects of AAS. High doses of AAS may induce proatherogenic dyslipidemia, increase thrombosis risk via effects on clotting factors and platelets, and induce vasospasm through their effects on vascular nitric oxide.

Replacement doses of testosterone, when administered parenterally, are associated with only a small decrease in HDL cholesterol and little or no effect on total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels. In contrast, supraphysiologic doses of testosterone and orally administered, 17α-alkylated, nonaromatizable AAS are associated with marked reductions in HDL cholesterol and increases in LDL cholesterol.

Recent studies of AAS users using tissue Doppler and strain imaging and MRI have reported diastolic and systolic dysfunction, including significantly lower early and late diastolic tissue velocities, reduced E/A ratio, and reduced peak systolic strain in AAS users than in nonusers. Power athletes using AAS often have short QT intervals but increased QT dispersion, which may predispose them to ventricular arrhythmias. Long-term AAS use may be associated with myocardial hypertrophy and fibrosis. Myocardial tissue of power lifters using AAS has been shown to be infiltrated with fibrous tissue and fat droplets. The finding of ARs on myocardial cells suggests that AAS might be directly toxic to myocardial cells.

Long-term AAS use suppresses LH and FSH secretion and inhibits endogenous testosterone production and spermatogenesis. Men who have used AAS for more than a few months experience marked suppression of the hypothalamic-pituitary-testicular (HPT) axis after stopping AAS that may be associated with sexual dysfunction, fatigue, infertility, and depression; in some AAS users, HPT suppression may last more than a year, and in a few individuals, complete recovery may never occur. The symptoms of androgen deficiency caused by androgen withdrawal may cause some men to revert back to using AAS, leading to continued use and AAS dependence. As many as 30% of AAS users develop a syndrome of AAS dependence, characterized by long-term AAS use despite adverse medical and psychiatric effects.

Supraphysiologic doses of testosterone may also impair insulin sensitivity. Orally administered androgens also have been associated with insulin resistance and diabetes.

Unsafe injection practices, high-risk behaviors, and increased rates of incarceration render AAS users at increased risk of HIV and hepatitis B and C. In one survey, nearly 1 in 10 gay men had injected AAS or other substances, and AAS users were more likely to report high-risk unprotected anal sex than other men.

Some AAS users develop hypomanic or manic symptoms during AAS exposure (irritability, aggressiveness, reckless behavior, and occasional psychotic symptoms, sometimes associated with violence) and major depression (sometimes associated with suicidality) during AAS withdrawal. Users may also develop other forms of illicit drug use, which may be potentiated or exacerbated by AAS.

Elevated liver enzymes, cholestatic jaundice, hepatic neoplasms, and peliosis hepatis have been reported with oral, 17α-alkylated AAS. AAS use may cause muscle hypertrophy without compensatory adaptations in tendons, ligaments, and joints, thus increasing the risk of tendon and joint injuries. AAS use is associated with acne, baldness, and increased body hair.

The suspicion of AAS use may be raised by the increased hemoglobin and hematocrit, suppressed LH and FSH and testosterone levels, low high-density lipoproteins cholesterol, and low testicular volume and sperm density in a person who looks highly muscular. Accredited laboratories use gas chromatography–mass spectrometry or liquid chromatography–mass spectrometry to detect anabolic steroid abuse. In recent years, the availability of high-resolution mass spectrometry and tandem mass spectrometry has further improved the sensitivity of detecting androgen abuse. Illicit testosterone use is detected generally by the application of the measurement of the urinary testosterone-to-epitestosterone ratio and further confirmed by the use of the ^{13}C:^{12}C ratio in testosterone by the use of isotope ratio combustion mass spectrometry. Exogenous testosterone administration increases urinary testosterone glucuronide excretion and consequently the testosterone-to-epitestosterone ratio. Ratios >4 suggest exogenous testosterone use but can also reflect genetic variation. Genetic variations in the uridine diphosphoglucuronyl transferase 2B17 (*UGT2B17*), the major enzyme for testosterone glucuronidation, affect the testosterone-to-epitestosterone ratio. Synthetic testosterone has a lower ^{13}C:^{12}C ratio than endogenously produced testosterone, and these differences in ^{13}C:^{12}C ratio can be detected by isotope ratio combustion mass spectrometry, which is used to confirm exogenous testosterone use in individuals with a high testosterone-to-epitestosterone ratio.