However, total and free testosterone levels are even lower in men with prostate cancer, who have undergone prostatectomy, when compared with age-matched controls without cancer. Androgen deficiency in men with prostate cancer is associated with distressing symptoms such as fatigue, sexual dysfunction, hot flushes, mobility limitation, and decreased physical function. Even with a bilateral nerve-sparing procedure, more than 50% of men develop sexual dysfunction after surgery. Although there is some recovery of sexual function with passage of time, 40–50% of men undergoing radical prostatectomy find their sexual performance to be problematic 18 months after surgery. Sexual performance problems are a source of psychosocial distress in men with localized prostate cancer. In addition to its causal contribution to distressing symptoms, androgen deficiency in men with prostate cancer increases the risk of bone fractures, diabetes, coronary heart disease, and frailty.

Testosterone Therapy in Men with History of Prostate Cancer A history of prostate cancer has historically been considered a contraindication for testosterone therapy. This guidance is based on observations that testosterone promotes the growth of metastatic prostate cancer. Metastatic prostate cancer generally regresses after orchidectomy and androgen deprivation therapy. Androgen receptor signaling plays a central role in maintaining growth of normal prostate and prostate cancer. PSA levels are lower in hypogonadal men and increase after testosterone therapy. Prostate volume is lower in hypogonadal men and increases after testosterone therapy to levels seen in age-matched controls.

However, the role of testosterone in prostate cancer is complex. Epidemiologic studies have not revealed a consistent relationship between serum testosterone and prostate cancer. In a landmark randomized trial, testosterone therapy of older men with low testosterone did not affect intraprostatic androgen levels or the expression of androgen-dependent prostatic genes. The suppression of circulating testosterone levels by a gonadotropin-releasing hormone (GnRH) antagonist also does not affect intraprostatic androgen concentrations. Open-label trials and retrospective analyses of testosterone therapy in men with prostate cancer, who have undergone radical prostatectomy and have undetectable PSA levels after radical prostatectomy, have found very low rates of PSA recurrence. Even in men with high-grade prostatic intraepithelial neoplasia (HGPIN)—a group at high risk of developing prostate cancer—testosterone therapy for 1 year did not increase PSA or rates of prostate cancer.

After radical prostatectomy, in the absence of residual cancer, PSA becomes undetectable within a month. An undetectable PSA after radical prostatectomy is a good indicator of biochemical recurrence-free survival at 5 years. Therefore, men with organ-confined prostate cancer (pT2), Gleason score ≤6, and a preoperative PSA of <10 ng/mL, who have had undetectable PSA levels (<0.1 ng/mL) for >2 years after radical prostatectomy, have very low risk of disease recurrence (<0.5% at 10 years) and may be considered for testosterone therapy on an individualized basis. If testosterone therapy is instituted, it should be associated with careful monitoring of PSA levels and done in consultation with a urologist.

MEDICAL COMPLICATIONS OF ANDROGEN DEPRIVATION THERAPY

In patients with prostate cancer and distant metastases, androgen deprivation therapy (ADT) improves survival. In patients with locally advanced disease, ADT in combination with external-beam radiation or as an adjuvant therapy (after prostatectomy and pelvic lymphadenectomy) also has been shown to improve survival. However, ADT is being increasingly used as primary therapy in men with localized disease and in men encountering biochemical recurrence without clear evidence of survival advantage. Because most men with prostate cancer die of conditions other than their primary malignancy, recognition and management of these adverse effects is paramount.

Profound hypogonadism resulting from ADT is associated with sexual dysfunction, vasomotor symptoms, gynecomastia, decreased muscle mass and strength, frailty, increased fat mass, anemia, fatigue, bone loss, loss of body hair, depressive symptoms, and reduced quality of life. Diabetes and cardiovascular disease have recently been added to the list of these complications (Fig. 7e-3). Treatment with GnRH

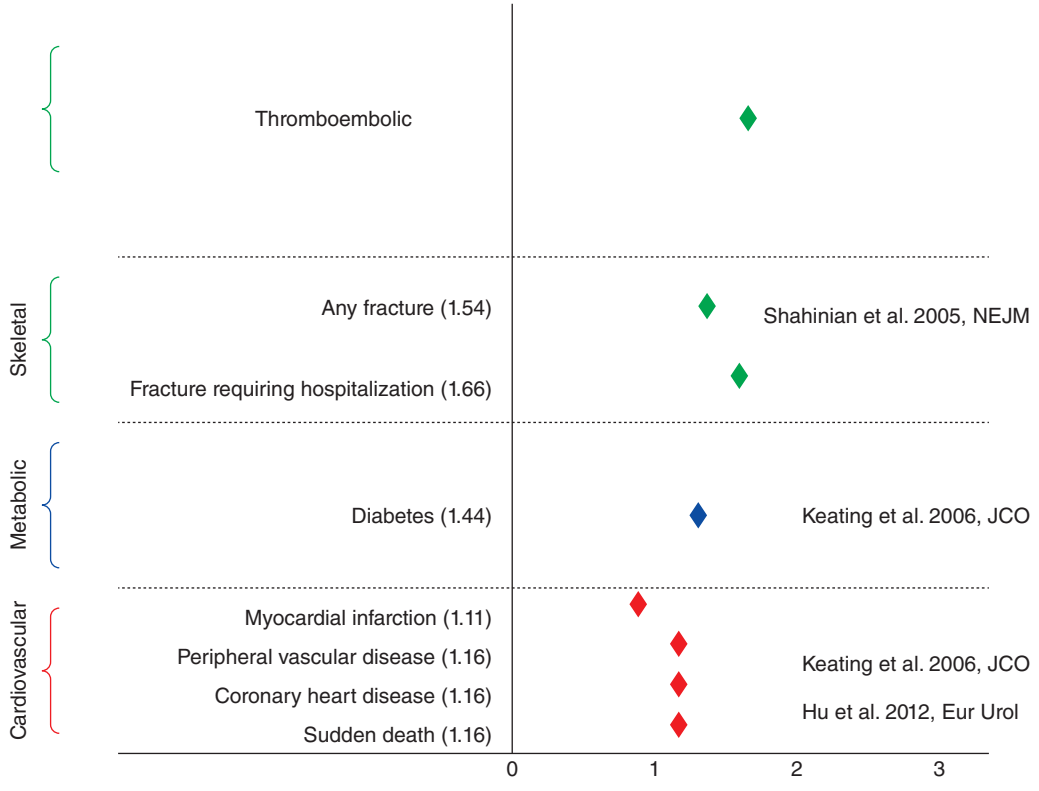

FIGURE 7e-3 Adverse cardiometabolic and skeletal effects of androgen deprivation therapy (ADT) in men receiving ADT for prostate cancer. Administration of ADT has been associated with increased risk of thromboembolic events, fractures, and diabetes. Some, but not all, studies have reported increased risk of cardiovascular events in men receiving ADT. *(Data on relative risk were derived from VB Shahinian et al: N Engl J Med 352:154, 2005; NL Keating et al: J Clin Oncol 24:4448, 2006; and JC Hu et al: Eur Urol 61:1119, 2012.)*