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REVIEW

Testosterone and cardiovascular disease – the controversy and the facts

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Abstract

Since November 2013, there has been a flurry of articles written in the media touting the risk of cardiovascular (CV) disease in men treated with testosterone, based on two recent reports. Since first synthesized in 1935, testosterone therapy has demonstrated substantial benefits for men with testosterone deficiency (also called hypogonadism). Testosterone has an acceptable safety profile and literature spanning more than 30 years, suggesting a decreased CV risk with low levels of testosterone and benefits associated with testosterone therapy. However, nonmedical media outlets have seized on reports of increased CV risk, and published scathing editorials impugning testosterone therapy as a dangerous and overprescribed treatment. Here, we review these recent studies, and find no scientific basis for assertions of increased CV risk. This article is intended to provide the clinician with the facts needed for an informed discussion with men who suffer from testosterone deficiency and who desire treatment for their symptoms.

Keywords

Cardiovascular disease, hypogonadism, myocardial infarction, testosterone, testosterone deficiency, testosterone replacement therapy

History

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Introduction

Testosterone (T) therapy has been a standard and effective treatment for men with T deficiency (also called hypogonadism) since it was first synthesized in 1935. There was an early 'honeymoon period' for T therapy after it first became available, with a 1940 article in the *New England Journal of Medicine* [1] noting improvements in sexual desire and performance, increased strength, and sense of well-being in treated men with hypogonadism, a description that matches many current reports. This honeymoon ended in the early 1940s with publication of reports that castration, or estrogen treatment designed to lower T to castrate levels, caused regression of metastatic prostate cancer (PCa), and T administration-'activated' PCa [2]. T use became rare for the next several decades, restricted only to the most severe cases of T deficiency, such as young men with pituitary tumors or anorchia due to cancer or trauma. However, over the past 15–20 years, there has been steady growth in the use of T therapy [3], as a result of increased physician awareness of T deficiency and the benefits of treatment, increased convenience of T formulations, and reduced fear of PCa [4].

Now suddenly two recent studies are reporting increased cardiovascular (CV) risks in men who received T prescriptions. Although the literature over the past 30 years suggested that *low* T concentrations were associated with CV risk and T therapy has been shown in multiple studies to offer benefits, the media and some public health experts have seized on these two recent reports as evidence that T therapy is dangerous. Combined with the upsurge in prescriptions and aggressive direct-to-consumer marketing, pressure from the pharmaceutical industry has resulted in the claim that T therapy is overprescribed. The best example of these beliefs is an editorial in the *New York Times* published 4 February 2014 titled, 'Overselling Testosterone, Dangerously' [5].

Absent from these reports is an objective assessment of these two new studies, neither of which provide solid evidence of T therapy increasing CV risk. This article serves as a review of the literature on T therapy and CV risk, with an emphasis on those two recent studies.

Materials and methods

This article is a review of studies investigating CV risks associated with T therapy, with particular emphasis on two recent studies (Vigen et al.; Finkle et al.) that have prompted broader medical concerns on this issue. A systematic review of the literature was performed using MEDLINE with key words 'testosterone', 'androgen', 'CV disease', 'myocardial infarction' (MI), 'stroke', 'mortality', and 'death'. In addition, key references were identified based on other reviews and frequent citations.

Studies reporting increased CV risks

The first of the recent studies that reported increased CV risks with T therapy, published in November 2013 in the *Journal of the American Medical Association* by Vigen et al., was a retrospective analysis of a dataset (n = 8709) of men in the VA health system who had undergone coronary angiography [6]. Among men with T concentrations <300 ng/dl, the

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authors reported an increased rate of heart attack, stroke, and death in men who received a T prescription compared with men who did not. No significant differences in event rates were noted for any year of follow up; however, the authors concluded that there exists a 29% increase in events for T-treated.

Strangely, the percentage of men who suffered an event was actually lower by one-half for the men receiving T compared with the no T group (10.1% vs 21.2%). The authors concluded that the T-treated group had a higher rate of events than the untreated group based on complex statistical modeling utilizing >50 variables. This modeling failed to include substantially lower baseline T levels in the T group, despite evidence that lower T values are associated with increased CV risk and mortality. In addition, the authors improperly excluded 1132 men who suffered a stroke or heart attack prior to receiving a T prescription. Without that exclusion, the rate of events in the no T group would have been increased by 71%, reversing the author's conclusion.

The authors have subsequently published corrections to their original article, detailing a series of data errors, in which the group of 1132 excluded individuals was changed to 128 men, an error involving >1000 men, a second group had its numbers increased by >900 men. Additionally, 9% of the group was discovered to comprise women. Based on these errors, 29 medical societies have called for retraction of this study, citing 'gross data mismanagement and contamination', rendering the study 'no longer credible' [7]. It is impossible to conclude from this study that T prescriptions increase rates of CV events.

The second study published in *PLoS One* by Finkle et al. was a retrospective analysis of insurance claims data in 55,593 men, in which the only information available were diagnosis codes, procedure codes, and prescription data [8]. The primary reported result was an increased rate of nonfatal MI up to 90 days after filling a T prescription compared with the 12 months prior to receiving the T prescription. The authors also compared these pre- and post-prescription rates for phosphodiasterase-5 inhibitors (PDE5is), reporting no increase in MI following PDE5i prescription. Subgroups by age revealed increased risk of MI with men aged >65 years without a prior history of heart disease, and for men aged <65 years with a prior history of heart disease. The authors concluded that the risk of MI is substantially increased in older men and in younger men with preexisting known heart disease [9].

This study received enormous media attention, despite a number of critical methodological shortcomings. First, since this was a retrospective study of actual practice rather than an experimental study, all men in the study were selected because they had received a T prescription [8]. The 12-month period prior to the prescription reflects physician practices, specifically, how often physicians felt comfortable providing a T prescription to men with a prior history of MI within the prior year. In contrast, the post-T-prescription period of up to 90 days reflects actual rates of MI in that population. These two periods are unrelated and, therefore, conclusions drawn from their direct comparison are invalid. Since the primary result of the study was the ratio of post-T-prescription MI rates to pre-T-prescription rates, any reluctance of physicians to offer a T prescription to men with a history of MI would result in a reduced MI rate pre-prescription, and an increased apparent post- or pre-rate.

Second, although the authors had data over several years, they chose to report results only for the very short period after men filled a first T prescription. This period was based on first refill [7], which in theory could be up to 90 days; however, for many men, this period would be as short as 30 days. This means the time period the authors chose to investigate occurred when the patient had minimal drug exposure. Note that the primary results merely compare MI rates in this short period after receiving a prescription within the 12 prior months. As a retrospective dataset analysis, there was no control group, and it is thus impossible to determine whether the observed increase in CV events was due to the underlying condition (T deficiency) or its treatment [9]. Given the known association between low T concentrations and CV risk and the minimal exposure time to treatment, the most plausible interpretation of the data is that men newly diagnosed with T deficiency are at increased risk of nonfatal MI. If T therapy truly increased a man's risk of CV events, one would logically expect that risk to increase over time. It is notable and questionable that the authors had access to much longer periods of patient observation but did not report on this time period, raising concerns over the reliability of the study.

Third, although the relative risk in the study by Finkle et al. [8] was significantly increased by 36% in the post- to-pre-T-prescription ratio (rate ratio 1.36; 95% confidence interval: 1.03–1.81), the excess risk of MI with T prescriptions was remarkably low. The pre-prescription MI rate in the T-treated group was 3.48/1000 person-years, and the post-prescription rate was 4.75/1000 person-years. The excess nonfatal MI risk was, therefore, 1.27 events for every 1000 person-years. Such a small difference is clinically insignificant. More importantly, the actual observed post-T-prescription rate of 4.75 MI/1000 person-years is substantially lower than the risk of 13 MI/1000 person-years, based on the NIH Heart Attack Calculator using reasonably favorable criteria (non-smoker, high-density lipoprotein (HDL) 40, systolic blood pressure 140 mmHg) for a man of similar age (54 years old) to the mean age in the study (54.4 years old) [10].

Finally, the comparison of MI rates with PDE5i prescriptions is misleading and provides no useful information. The authors suggest that the lack of increased MI rate with PDE5is means that the increase in MIs noted with T prescriptions implicates T treatment as a risk. However, this is a classic case of 'apples and oranges'. These were two dissimilar groups (men with T deficiency and men with erectile dysfunction) that were each subjected to dissimilar treatments and were thus inappropriate to compare. Finally, the very low numbers of CV events in each of the subgroups (8 cases in men ≥65 years with heart history; 12 cases in men ≥65 years without heart history; 15 cases in men <65 years with heart history; and 30 cases in men <65 years without heart history) based on age and presence or absence of heart disease, combined with the extremely low overall

CV risk renders any conclusion regarding risk of T therapy for subgroups highly questionable.

One additional study bears mention in regard to CV risk with T therapy. In 2010, Basaria et al. reported a significantly greater rate of CV events in men who received T therapy compared with men who received placebo [11]. This study intended to investigate the effect of T therapy on muscular and functional responses in men ≥65 years with limited mobility and a total serum T level of 100 to 350 ng/dl (3.5–12.1 nmol/l) or a free serum T levels of <50 pg/ml (173 pmol/l). Individuals were randomly assigned to receive placebo gel or T gel, applied daily for 6 months. In this population of older men with limitations in mobility and a high prevalence of chronic diseases including hypertension, diabetes, hyperlipidemia, and obesity, there were 23 adverse CV events in the T gel group compared with only 5 events in the placebo group. This study is frequently cited as evidence for increased CV risk with T therapy because it was a randomized, placebo-controlled trial. However, this study was not designed to investigate CV events, and most events were anecdotal and of uncertain clinical significance, including pedal edema, palpitations, and premature ventricular contractions noted on electrocardiogram. As the authors themselves noted, 'the lack of a consistent pattern in these events and the small number of overall events suggest the possibility that the differences detected between the two trial groups may have been due to chance alone'.

Evidence for epidemiological studies and decreased T levels

There is, at present, indirect evidence that there is a positive relationship between T levels and vascular health [12,13]. There is also evidence of decreased T levels associated with hypertension, increased inflammation, increased prevalence of type 2 diabetes mellitus, and atherosclerosis progression [14]. These studies also point out that men with type 2 diabetes mellitus, obesity, or coronary heart disease all have reduced T levels [15]. The final epidemiologic study of the all-cause mortality in 16,184 community-based subjects with a mean follow up of 9.7 years concluded that low T levels are associated with an increased risk of CV-related mortality [16].

Decreased T levels and mortality

Longitudinal, epidemiological studies, as well as other clinical studies showed increased CV-related mortality in men with T deficiency [17,18]. In the EPIC-Norfork study, a population-based study with monitoring up to 10 years, the quartile of men with the lowest T levels demonstrated the greatest mortality, whereas the quartile with the highest T levels displayed the least mortality [19]. In a group of men with angiographically confirmed CV disease, those with normal levels of T had a significantly longer survival than those with lower levels of T. Also, men with type 2 diabetes mellitus who had low T had a shorter survival than men with normal T but with type 2 diabetes mellitus. It is also of interest that a subgroup of men who had received treatment to normalize the decrease in their T levels had the same survival as those men who had a normal T level [20]. This study concluded that men with endogenous high T concentrations are inversely related to mortality due to CV disease and all causes. In fact, low T may be a predictive marker for those at high risk of CV disease.

Relationship between CVD risk biomarkers: C-reactive protein, TNF-alpha

Researchers have identified biochemical and clinical markers that are documented to be increased risk factors of CV disease. These include high blood pressure, insulin resistance, increased body fat, altered lipids, altered coagulation profiles, and increased inflammation, which contribute to the development and progression of atherosclerosis and ultimately CV disease [21]. For example increased C-reactive protein (CRP), an inflammatory marker, has been documented to be increased in men with low serum T levels. A significant number of men with coronary artery disease exhibit T deficiency, with ~23% of these men with T levels <7.5 nmol\l (215 ng\dl) and 53% with T levels <12 nmol\l (344 ng\dl) [22]. Another study looking at the relationship between T concentrations and high-sensitivity CRP, another CV risk marker, noted that lower levels of serum T were associated with the highest levels of high-sensitivity CRP [23]. Elevated levels of inflammatory markers, particularly CRP, indicate an increased risk of coronary heart disease. Although plasma lipid levels were more strongly associated with an increased risk than were inflammatory markers, the level of CRP remained a significant contributor to the prediction of coronary heart disease [24].

An animal model in male rats helped in identifying that low T levels increased TNF-α compared to those animals that a normal T level. After T treatment, the T therapy group showed a remarkable improvement of cardiac performance and a significant decrease in the level of serum TNF-α as compared with the controls with right heart failure and low T levels [25]. At least in the animal model, T replacement suggested an improvement in cardiac function.

T therapy has been documented to decrease blood pressure and thus concomitant risk of CV disease as the blood pressure declines. In a long-term observation of men with hypertension and low T who received T therapy, a reduction in systolic blood pressure by 22 mmHg and in diastolic blood pressure by 19 mmHg was observed. Although this can be attributed to weight loss, another mechanism of T-replacement therapy includes improvements of endothelial function, leading to a vasodilatory effect [26]. A study by Sader et al. demonstrated that hypogonadal men had improvement in flow-mediated dilatation, which is an endothelium-dependent response, after receiving T therapy [27].

Another discriminating marker for arteriosclerotic heart disease is the computed tomography calcium score. Using multiple linear regression, a study evaluated associations between log sex hormone levels and log coronary calcium score after adjusting for confounding variables in 105 men with some degree of coronary calcification defined as coronary calcium score ≥1. In multiple linear regression analysis, bioavailable T was inversely associated with coronary calcium score (p = 0.046), after

adjusting for age, body mass index (BMI), smoking status, alcohol consumption, regular exercise, mean blood pressure, resting heart rate, CRP, fasting plasma glucose, total cholesterol, triglyceride, HDL cholesterol, hypertension medication, and hyperlipidemia medication. This study indicates that bioavailable T is inversely associated with the degree of subclinical coronary artery calcification in non-obese men [28].

Evidence of CVD in men receiving androgen deprivation therapy

For nearly two decades androgen deprivation therapy (ADT) has been the gold standard for the treatment of advanced PCa. Luteinizing hormone-releasing hormone agonists and antagonists have been used to produce castrate levels of serum T in men with advanced PCa. Many of these men experience changes in body composition such as a decrease in lean muscle mass and an increase in fat mass [29]. Within a 12-week time period post-ADT, a marked increase in insulin levels (63%) has been noted, suggesting increased insulin resistance [30]. Results from other studies have demonstrated that men receiving ADT have an earlier onset of MI [31].

In men with diabetes who received ADT, there was an increase in fibrinogen and plasminogen activator inhibitor 1 levels, which suggests the induction of procoagulation factors in these patients with both diabetes and PCa. These observations strongly suggest that ADT induces metabolic alterations that contribute to the pathophysiology of CV disease [32].

T levels and BMI, metabolic syndrome, and lipids

Metabolic syndrome encompasses a combination of medical disorders, which increase the risk of developing CV disease and diabetes. A meta-analysis of 20 studies reported that even after adjusting for age and BMI, metabolic syndrome is independently associated with hypogonadism [33].

Visceral obesity is associated with increased atherogenic dyslipidemia, hypertension, insulin resistance, hyperglycemia, as well as prothrombotic and proinflammatory states. Studies have demonstrated that reduced sex hormone levels, that is, T levels, are associated with increased inflammatory markers, with an inverse relationship between serum T levels and inflammatory markers noted in elderly men. Treatment with T therapy for 1 year in patients with newly diagnosed type 2 diabetes mellitus was associated with an improvement in body composition [34].

Another study demonstrated that men with T deficiency who received hormone replacement therapy showed significant, progressive reduction in BMI, weight loss, and a decrease in waist circumference, which was maintained for at least 30 weeks [35].

An important question to consider is whether such reduction in weight loss and waist circumference is sustainable over time. The longest placebo-controlled study using T therapy followed a cohort of men for >3 years. This study, from the University of Muenster, showed a progressive decline of waist circumference over the first 3 years reaching 173 cm in the group which received T-replacement therapy. In the same T-treatment group, there was an average weight reduction of 18.9 kg. This and other studies have shown reproducible results with substantial and clinically meaningful reductions in waist circumference and BMI [36].

Decreased T levels and atherosclerosis

Decreased T is related to an increase in atherosclerosis, especially of the carotid arteries. Carotid intima-media thickness (IMT) is one of the most commonly used surrogate end points of atherosclerosis. It is used as a subclinical marker of atherosclerosis, and it is a common outcome measure in most studies on disease progression and effects of treatment, including T supplementation. Low T levels were related to carotid IMT independent of other CV risk factors [37], and T replacement therapy reduced carotid IMT independently from BMI [38]. A reduction of carotid intimal thickness has been demonstrated in response to T treatment [39]. The reduction of IMT of the carotid artery appeared to be dose-dependent in that men who achieved higher levels of T after treatment with hormone replacement therapy showed a more pronounce reduction of intimal thickness.

Decreased T levels and diabetes mellitus: insulin resistance

Low T is associated with metabolic syndrome, insulin resistance, and type 2 diabetes mellitus [40]. A direct effect of T on insulin sensitivity has been demonstrated experimentally. The direct effect may be mediated via mitochondria function [41].

A study that considered the issue of insulin resistance looked at the effect of a diet and exercise program with T-replacement therapy in men with type 2 diabetes mellitus who had both metabolic syndrome and a T deficiency. The results revealed that the diet and exercise only cohort achieved a reduction in HbA1c of 0.5% at the end of 1 year, but the group that followed diet, exercise, and used T replacement had a 1.2% reduction in their HbA1c [42].

Low T levels are commonly found in men with type 2 diabetes mellitus and are associated with aging and obesity. Whether T treatment in men with type 2 diabetes myelitis decreases insulin resistance above that attributable to its fat-reducing effect is currently unknown. Perhaps future studies should compare T treatment with lifestyle changes (exercise and weight loss measures), and other insulin-sensitizing agents [43].

Previous studies have suggested that T replacement may be cardioprotective – stress test and ST segment depression is attenuated in men treated with T. T replacement may promote vasodilatation [44]. Numerous studies have documented that normalization of serum T levels in hypogonadal men improves all CV risk factors including a reduction in body fat, reduction in insulin resistance, a decrease in low-density cholesterol levels, decrease in inflammatory markers, and a reduction in blood pressure.

A further study (randomized, single, blind, placebo-controlled crossover study) of overtly hypogonadal men with angina, using intramuscular injections of T, demonstrated a beneficial effect on the men's ischemic threshold [45].

Based on the currently available data, there is no convincing evidence of an adverse effect of T-replacement therapy on coronary heart disease or chronic heart failure, and some authors have suggested there may even be a role for T in the prevention or treatment of CV diseases in men [46,47]. Research from Boston University School of Medicine suggests that T treatment in hypogonadal men restores normal lipid profiles and may reduce the risk of CV disease [48]. Another report has demonstrated that low endogenous T may have an adverse impact on the known risk factors of coronary artery disease, and that T treatment in men has potentially beneficial effects on virtually all of the coronary risk factors, as well as an independent anti-atherogenic action. In addition, T therapy has been shown to improve the ischemic threshold, quality of life, and depression scores in patients with symptomatic coronary disease [49].

Practical, safe approach to older men with T deficiency

Clinicians should consider a number of issues when presented with an older male patient suspected of T deficiency, including goals of treatment and safety. T therapy is indicated in men with sexual symptoms, such as reduced sexual desire, erectile dysfunction, loss of spontaneous erections, and difficulty in achieving orgasm [50]. These signs combined with documented biochemical evidence are consistent with T deficiency. At present, there is inadequate evidence to recommend T therapy for the purpose of cardioprotection or to promote general health. The symptoms of T deficiency can be divided into sexual and nonsexual groups. Sexual symptoms include reduced sexual desire, erectile dysfunction, and difficulty in achieving orgasm [51]. Nonsexual symptoms include fatigue, reduced energy, weakness, reduced muscle mass or strength, depressed mood, and irritability. Signs of T deficiency include anemia and reduced bone mineral density.

The diagnosis requires documentation of low serum T levels. The Endocrine Society has recommended a total T threshold of 300 ng/dl; however, a number of international groups allow for a less stringent threshold of ≥350 ng/dl, depending on clinical presentation [52]. A synthesis of international expert opinions includes thresholds up to 400 ng/dl in symptomatic individuals [53]. An important confounder in the older individual is that concentrations of sex hormone-binding globulin increase with age, resulting in a more normal-appearing concentration of total T, even in the presence of low values of free T, which represents the bioactive fraction. Men with characteristic symptoms and low values of free T are candidates for treatment, regardless of total T concentrations. Calculated free T concentrations <80 pg/ml are consistent with the diagnosis of T deficiency [54].

The routine measurement of prolactin levels is less well defined because isolated hyperprolactinemia is rare and most patients with hyperprolactinemia have abnormally low T levels. Patients who present with symptoms of hyperprolactinemia, such as decreased libido and headache with depressed T levels are suggestive of prolactin abnormality and prolactin levels should be obtained [55,56].

As with the use of PDE5is, clinicians must consider whether the patient can tolerate the stress of sexual activity prior to prescribing T. Standard cautions are to avoid use of T in men with elevated hematocrit or prostate specific antigen, moderate-to-severe lower urinary tract symptoms, or obstructive sleep apnea. Contraindications to T therapy are a history of male breast cancer or history of PCa. This last concern is currently being reevaluated at specialized centers [57].

It is uncertain whether elderly men are at an increased risk of adverse effects with T therapy than younger men. The study by Finkle et al. suggested that this may be the case, with a greater post-treatment to pretreatment risk ratio in men ≥65 years than in younger men. However, as previously noted, this ratio was strongly influenced by prescribing patterns during the pretreatment phase of the study, in which relatively few men in the older age group with an MI in the prior 12 months received a T prescription. In addition, the study by Basaria et al. reported increased CV risks in their study population of men ≥65 years, but as noted above, most of those adverse events were of questionable clinical significance. A similar UK trial of T therapy versus placebo in older, frail men revealed no greater CV or other risks in men who received T compared to men who received placebo [58]. One item that may well be of particular relevance in older men is the likelihood of pedal edema due to the fluid retentive properties of T. There are no solid data to indicate that estradiol levels should be obtained routinely in older men on T therapy.

Indications for cardiology referral prior to initiation of T therapy include patients with CV symptoms of shortness of breath, angina on exertion, peripheral edema or congestive heart failure, or abnormal lipid testing.

Follow-up management of patients on T-replacement therapy after the first month of treatment includes complete blood count, prostate specific antigen, serum T, and a digital rectal examination. It may be useful in some men to obtain lipid levels and luteinizing hormone levels. The latter is usually suppressed if adequate serum T concentrations have been achieved via T therapy. Although liver function testing has been occasionally suggested, standard forms of T therapy – topicals, injections, and pellets – do not alter liver function and have not been associated with liver toxicity. Their use is, therefore, not mandatory for monitoring. If monitoring studies are all within normal limits, then repeating the same testing every 6–12 months is appropriate [59].

Treatment for documented androgen deficiency with T-replacement therapy includes intramuscular injections, topical gels or liquids, patches (Androderm^{TM}), and pellets. Oral preparations currently available in the USA should be avoided because of associated hepatotoxicity. However, an oral preparation of T undecanoate does not appear to have this problem and is available in many countries outside the USA. Oral T undecanoate products are currently under development for possible use in the USA. T injections performed q1–3 weeks are the least-expensive treatment currently available for patients. A new formulation of injectable T undecanoate which lasts for 10 weeks (five injections per year) is also now available [60]. It is important to note that T undecanoate has been associated with pulmonary oil microembolism (POME) reaction. It is believed that POME is caused by tiny droplets of oil

that are absorbed systemically and travel to the lungs. Symptoms of POME include cough or urge to cough, difficulty breathing, sweating, chest pain, dizziness, and fainting [61].

T pellets are inserted subcutaneously in the physician's office, providing normal physiologic serum T levels for 3–5 months [62,63].

Summary

Low T produces significant symptoms in men and can be easily correct with T-replacement therapy. Certainly there is controversy in the relationship between T and CV disease, but there exists good evidence that T is associated with a decrease in atherosclerosis, hypertension, IMT of the carotid arteries, insulin resistance, and mortality in men of all causes. Although there are as yet no large, prospective, randomized controlled trials to provide a definitive conclusion regarding the CV risks of T therapy compared with placebo, current evidence appears to support the position that T is generally safe and beneficial when used in treating truly symptomatic hypogonadal men.

Declaration of interest

N Baum has been a speaker for Watson. A Morgentaler has received research funding from Auxilium, Warner Chilcott, Antares, and Lilly, been a consultant and advisor for Bayer, and a speaker for Merck. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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