The Double-Edged Sword of ADT: Emerging Evidence of Cardiovascular, Pulmonary, and Renal Risks


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Source:

In their review article, Drs. Crawford and Moul seek to describe the cardiovascular (CV), renal, and pulmonary complications associated with the use of long-term androgen deprivation therapy (ADT) in men with prostate cancer.[1] Furthermore, they attempt to determine whether there is a difference in CV and renal complications between different types of ADT, including luteinizing hormone–releasing hormone (LHRH) agonists, gonadotropin-releasing hormone (GnRH) antagonists, and bilateral orchiectomy.

Why study these side effects? ADT has a profound anticancer effect and is the standard of care for men with metastatic disease, both improving symptoms and prolonging survival. Despite this benefit, ADT is associated with multiple known side effects, including bone loss, reduced libido, and vasomotor instability. As a variety of new hormonal agents are increasing survival times for men with metastatic disease,[2,3] it is becoming increasingly important to consider CV, renal, and other potentially more serious risks associated with long-term ADT, especially in an aging population.

As the authors note, there has been increasing evidence in recent years linking ADT with increased CV and renal health risks, especially in men with underlying CV disease. Perhaps the most widely accepted rationale for the increased risk is the cardioprotective effects of testosterone. Decreasing testosterone levels are associated with obesity, hyperlipidemia, hyperglycemia, and insulin-resistance, all of which increase the risk of subsequent CV events. While the epidemiologic data are still somewhat controversial, a number of studies have demonstrated an increase in CV risks with ADT, raising the possibility of a causal relationship. Surveillance, Epidemiology and End Results (SEER) data showed a significantly increased risk of CV events in a cohort of more than 70,000 men receiving ADT,[4] and other retrospective analyses have found a similar risk in large cohorts.[5-7] Unfortunately, the majority of studies exploring this association are observational, cohort, or case-control studies; randomized controlled trials in this area are mostly underpowered and suffer from limited follow-up time for CV and renal endpoints. For example, a meta-analysis[8] included data from trials in which the control group was confounded by crossover bias, and the majority of men in the intervention arm chose to discontinue therapy early, making time of exposure to ADT unclear.

Similarly, it is unclear whether LHRH agonists (ie, leuprolide) confer more CV risk than GnRH antagonists (ie, degarelix); while the data evaluating cardiac events with LHRH agonists vs GnRH antagonists suggest fewer cardiac complications from GnRH antagonists, the best study exploring this difference is limited by short follow-up (12 months) and was conducted as a post-hoc analysis.[9] Biologically, it has been proposed that stimulation of GnRH receptors present on atherosclerotic plaques increase the inflammatory response. Therefore, GnRH antagonism may decrease plaque inflammation and rupture. This mechanism remains speculative at this time and requires further evaluation and evidence. Similarly, further prospective trials need to be performed to better evaluate whether there is any true difference in CV risks between LHRH agonists and GnRH antagonists.

Similar limitations are present in the data evaluating renal injury from ADT. A study of more than 10,000 men in the United Kingdom[10] suggested a small but statistically significant difference in the incidence of kidney injury in men receiving ADT compared with controls, and a similar retrospective analysis has suggested a higher rate of acute kidney injury in men receiving ADT.[11] While ADT-induced hyperlipidemia or hyperglycemia may contribute to increased risks, it remains puzzling that the risk of acute kidney injury was higher in men receiving LHRH agonists than in those undergoing bilateral orchiectomy, and a better biologic explanation is currently lacking. The
long-term clinical consequences of temporary acute kidney injury in this population are similarly unknown. Drs. Crawford and Moul correctly note that there are no data yet to suggest a difference in the incidence of acute kidney injury in patients treated with LHRH agonists vs GnRH antagonists. The authors of this review also cite recent evidence from Taiwan that treatment with an LHRH agonist is associated with an increased risk of serious pneumonia.[12] This is an interesting observation, but further epidemiologic confirmation is needed. Similarly, while multiple biologic rationales are proposed, including morphologic and biochemical changes in the lungs, alterations in antibiotic susceptibility, outgrowth of pathogens in the gut flora, and decreased neutrophil production, all remain clinically unproven to date.

While the epidemiologic data are still evolving, National Comprehensive Cancer Network guidelines for prostate cancer management currently recommend both routine screening for CV disorders and early intervention in this population. This seems to be a reasonable recommendation given the increasing evidence of the CV risks associated with ADT. In our opinion, while data demonstrating an increase in pneumonia and acute kidney injury are less robust, and data concerning long-term consequences of these events are still lacking, attention should be paid to these potential risks as well. Lastly, while the authors sought to define a difference in incidence of complications between LHRH agonists and GnRH antagonists, we find the data to be quite limited, and suggest that more prospective research is needed before one can definitively recommend use of a GnRH antagonist over an LHRH agonist solely for protection against CV or renal disease.

This article discusses mounting evidence of “unseen” but serious side effects of ADT. As men with prostate cancer are living longer, increasing recognition of CV and renal risks is important to help minimize morbidity and mortality in this population. We suggest a careful discussion with patients about the expected risks and benefits of ADT. This is especially true in men for whom the benefit of ADT is uncertain, such as those with low-risk localized disease undergoing definitive radiation therapy, or those with a biochemical recurrence without objective metastases. For all patients, we recommend counseling about the potential CV risks when initiating therapy, the benefits of exercise and attention to diet, and close monitoring over time, especially in men with pre-existing CV or renal disease. Lastly, we suggest that future research is needed not only to better characterize the incidence of these effects from ADT, but to explore possible physiologic mechanisms in order to better mitigate these risks and help patients live longer, healthier lives.

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References:


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