Platinum Priority – Editorial

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Androgen-deprivation Therapy and Cardiovascular Harm: Let’s Not Throw Out the Baby with the Bathwater

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The controversy about the possible role of androgen-deprivation therapy (ADT) in cardiovascular harm was ignited in 2006 with the publication of a large observational US Surveillance Epidemiology and End Results (SEER)–Medicare analysis by Keating et al. suggesting that ADT use in the form of a gonadotropin-releasing hormone (GnRH) agonist was associated with a 44% increased risk of diabetes, a 16% increased risk of coronary heart disease, an 11% increased risk of myocardial infarction (MI), and a 16% increased risk of sudden cardiac death in men with prostate cancer (PCa) [1]. It is interesting to note that apart from the diabetes risk, this excess cardiovascular event risk was not seen with orchiectomy, suggesting that this effect may have been specific to GnRH agonists rather than simply a low testosterone level. This study and others, including a pooled reanalysis of two randomized trials that suggested that ADT was associated with a shorter time to MI in men >65 yr [2], led to a 2010 joint statement by US medical societies representing cardiology, oncology, urology, and radiation oncology asserting that “it is reasonable, on the basis of the above data, to state that there may be a relation between ADT and cardiovascular events and death” [3]. Later in 2010, the US Food and Drug Administration issued a safety warning requiring GnRH agonist labeling to disclose an “increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke) in men receiving these medications for the treatment of prostate cancer” [4].

In this issue of European Urology, Jespersen and colleagues present evidence from a large Danish observational study with results that strongly support what was seen in the US SEER–Medicare series [5]. Specifically, among 31 571 patients with PCa, GnRH agonist use was associated with a 31% increased risk of MI and a 16% increased risk of stroke, but once again this effect was not seen among men who received orchiectomy.

This is an excellent, well-designed study with large numbers and very complete follow-up. The study raises serious warnings about the potential for GnRH agonists to cause adverse cardiac events and represents an important contribution to this literature. However, as with all observational studies, it remains impossible to know for sure whether ADT actually caused the excess MIs and strokes observed or whether patients selected for ADT were simply more predisposed to developing them in the first place. Advanced statistical techniques, including propensity analysis and instrumental variable analysis, can be used to try to correct for the bias inherent in the nonrandom assignment of treatment, but ultimately no technique can give an observational study the level of proof that is found in randomized trials.

This is where the link between ADT and cardiovascular death starts to become more tenuous: While the evidence that ADT causes cardiovascular events or death comes largely from observational studies, individual randomized trials of ADT compared with no ADT have failed to detect an increased risk of cardiovascular events or death from ADT. A recent meta-analysis of 4141 patients in eight randomized trials of ADT compared with no ADT for unfavorable-risk nonmetastatic PCs found nearly identical rates of cardiovascular mortality with ADT (11.0%) compared with no ADT (11.2%), with a hazard ratio of 0.93 (p = 0.41) [6].

What can explain the discrepancy between the observational and randomized data? One possibility is simply that the association seen in observational data is spurious.
However, another credible hypothesis is that only a subset of vulnerable men with preexisting comorbidity actually experience excess cardiovascular mortality from ADT, and because randomized trials tend to enroll mainly healthy men, too few of those vulnerable patients were included in the trials to detect an increase in cardiovascular events with ADT. While none of the published ADT randomized trials prestratified by comorbidity, a post hoc analysis of one of the trials found that patients with moderate to severe comorbidity had a near–significant \((p = 0.08)\) decrease in overall survival with ADT, implying that cardiovascular death due to ADT negated any benefit in PCA-specific mortality in this vulnerable subgroup \[7\]. In addition, some retrospective analyses have suggested that men with a prior history of congestive heart failure or MI experience poorer all-cause mortality when treated with ADT \[8\]. To truly validate this concept, future randomized trials testing the value of ADT should stratify by comorbidity. One example of such a trial is the Radiation Therapy Oncology Group 08–15, which randomizes men with intermediate-risk and moderately high-risk localized disease to dose-escalated irradiation with or without 6 months of ADT. This trial is stratified by Adult Comorbidity Evaluation–27 comorbidity level and will be able to determine whether the harms of ADT truly outweigh the benefits for men with moderate to severe comorbidity.

Given the current controversy about whether ADT causes cardiovascular events and death, what should we be doing in the clinic? While I believe that there is probably a vulnerable subgroup of men with severe comorbidities who receive net harm from ADT, this group likely represents a small minority of the population. We need to maintain a healthy respect for the fact that ADT has been proven time and time again in large phase 3 trials to be the most effective adjuvant therapy to improve overall survival in men with unfavorable-risk disease. As more observational studies on the potential link between ADT and cardiovascular death gain notoriety, the pendulum may swing too far away from ADT, to the point at which people for whom it is clearly indicated no longer receive it because of theoretical concerns about cardiovascular risk. This situation would be the unfortunate oncologic equivalent of throwing out the baby with the bathwater.

To help balance the emerging observational links between ADT and cardiovascular mortality with known benefits of ADT from randomized trials, I would suggest the following four simple rules for using adjuvant ADT today.

First, make sure all patients starting ADT are “medically optimized.” Regardless of whether or not ADT truly causes cardiovascular death, we know from prospective studies that ADT increases insulin resistance, total cholesterol, and triglycerides and decreases lean body mass while increasing body fat \[9\]. All these adverse effects are worth managing, and patients should be followed closely by their primary physicians when starting ADT.

Second, do not give ADT to patients for whom there is no oncologic benefit. The best way to avoid potential cardiovascular harm of ADT, if there is any, is to not give ADT to patients who do not need it. This recommendation includes the previously common practice of giving patients with localized disease an automatic dose of ADT to put the cancer “on hold” while they decide what type of definitive treatment to pursue. This rule also includes men with low-risk disease who may be receiving ADT to help shrink their prostate to make them marginally better candidates for brachytherapy.

Third, do not withhold ADT in men with high-risk and locally advanced disease. Despite its warts, ADT has resoundingly proved itself as a highly effective, relatively nontoxic (compared with chemotherapy) way to improve overall survival in men with high-risk and locally advanced disease. The meta-analysis previously mentioned found a 31\% \((p < 0.001)\) reduction in PCA-specific mortality and a 14\% \((p < 0.001)\) reduction in overall mortality with the use of adjuvant ADT in high-risk and locally advanced disease \[6\]. While it is possible that small subgroups of men with high-risk disease and significant comorbidity will be harmed by ADT \[10\], we do not yet know with certainty from phase 3 trials exactly who these patients are and exactly which comorbidities should rule patients out for ADT.

Fourth, in borderline cases, try to weigh the known cancer benefits against the potential for cardiac harm. Intermediate-risk PCs is a heterogeneous disease in which some patients are more likely to benefit from ADT than others. For patients with low-volume Gleason 3 + 4 = 7 with PSA < 10, the risk of harboring micrometastases is low; for such patients it may be fine to avoid ADT, particularly if they have severe cardiac comorbidities.

Jespersen and colleagues should be congratulated for their excellent work providing further evidence of the potential link between ADT and cardiovascular mortality. Clinicians today will need to incorporate this information into their daily practice. More research from stratified analyses of phase 3 trials is needed to determine precisely which patients, if any, are at greatest risk for cardiovascular mortality from ADT. Additional work is also needed to understand the precise mechanism by which ADT may be inducing cardiovascular events so that they can be prevented. Both Jespersen et al. \[5\] and the original SEER–Medicare study by Keating et al. \[1\] found a link with GnRH agonists but not orchiectomy, which provides a rationale for investigating the specific action of GnRH agonists rather than simply the effects of having a low testosterone level. Also, given that the majority of the excess events appear to occur early (eg, within the first 2 yr of ADT \[2,8\]), the events are unlikely to be caused by the slow process of ADT increasing cardiovascular risk factors (obesity, high levels of low-density lipoproteins, insulin resistance) that leads to an increased risk of cardiovascular events several years later; these events are more likely to be some type of acute direct effect of ADT on cardiovascular function and outcomes.
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References