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## Platinum Priority – Editorial and Reply from Authors

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# Adverse Effects of Androgen Deprivation and the Limits of National Tumor Registries

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For nearly a half-century, androgen-deprivation therapy (ADT) has been a mainstay of the treatment of prostate cancer (PCa). ADT is virtually always the first-line approach for patients with metastatic disease, and multiple randomized trials have shown that combining external-beam radiation therapy with ADT improves mortality rates for men with intermediate- to high-risk disease [1–4]. Primary ADT as monotherapy for men with clinically localized disease is not known to improve survival compared with conservative management except for men with high-risk disease [5], and among this high-risk subset, ADT monotherapy is inferior to treatment regimens which include local therapy [6,7]. Although ADT monotherapy for localized disease is therefore not endorsed by practice guidelines on either side of the Atlantic [8,9], it is commonly used, particularly among older men [10]. Overall, up to 46% of men with PCa receive ADT at some point during treatment [11]. Use of ADT is also widely variable across clinical practice sites and providers [12,13]. It should be noted that this discussion to a large extent reflects a Western perspective; in Asia, primary ADT has a greater role, and apparently better efficacy and less toxicity [14,15].

Recent studies have raised concerns regarding the long-term effects of ADT on musculoskeletal, endocrine, cardiovascular, hematologic, and cognitive functions, though the strength of evidence for each of these areas varies substantially. There is little argument that ADT can reduce muscle and bone mass and increase skeletal fracture risk—risk that can be partially reduced with zoledronic acid or denosumab [16,17]. ADT likewise increases fat mass, low-density lipoprotein and triglyceride levels, and insulin resistance [18,19]. Whether these changes translate to actual increased cardiovascular mortality is a more controversial question. Analyses of large registries have suggested that a link between ADT use and major cardiovascular morbidity does in fact exist [18,20,21]. Secondary analysis of trials

randomizing men to radiation therapy with and without hormonal therapy, however, has consistently found no increase in cardiovascular mortality, even with long-term treatment [4,22,23].

The article by Van Hemelrijck et al. in this issue of *European Urology* explores the impact of ADT in a population-based Swedish cancer registry, focusing in particular on the incidence of multiple adverse events over time among men receiving ADT [24]. On its face, this concept may be intuitive; it is known, for example, that men who experience one skeletal event are at higher risk for subsequent events [25], and of course men with established cardiovascular disease are at greater risk for additional cardiovascular events. An effort to quantify this cumulative risk in the setting of ADT is certainly laudable. The authors identified adverse events in 26% of the cohort with a median 4-yr follow-up, and in fact, patients experiencing at least one event—particularly a cardiovascular complication—were more likely to experience additional events.

The study has substantial strengths, most notably its thorough capture of nearly all PCa in the country, as well as reasonably robust follow-up [24]. However, the study also has major limitations. First, the analysis considered all forms of hormonal therapy together. In particular, 11% of the cohort received antiandrogens only; these medications do not have the same metabolic consequences as castrating therapies, and they should not have been included. Likewise, orchiectomy has been shown in at least some studies to have different effects from medical castration [18]. Considering all these treatments together markedly limits the clinical interpretation of the results. Furthermore, no information was available on duration of therapy. The translation of World Health Organization grade to Gleason score in the analysis was performed incorrectly and may have introduced significant error into the multivariable analysis.

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These flaws reflect not carelessness on the part of the authors but rather fundamental limitations of claims-based data analyses that are widely population-based but ultimately limited in their clinical detail. A recent competing risks analysis suggested that caution must be exerted in analyzing cardiovascular end points in data sets that might contain, for example, codes for diabetes and hypertension but minimal detail on the severity of those problems. In these situations, confounding by indication and other sources of unmeasured confounding are substantial concerns [26].

PCa research is challenging: the prolonged natural history of the disease and the proliferation of alternative treatment combinations mandate careful, ideally prospective collection of highly detailed data. Collecting such data, whether in the setting of a randomized trial or a clinically rich disease-specific registry [27], takes years and is very expensive. National tumor registries, whether or not supplemented with claims data, are excellent, readily available sources of data for descriptions of epidemiologic trends and treatment patterns, but they should not be used as shortcuts to detailed outcomes analyses. Most such population-based sources do not include sufficient clinical data for adequate risk adjustment, and without this information, outcomes analyses should be interpreted with caution. Analyses of cancer outcomes may be valid in some cases; analyses of noncancer outcomes in particular are more challenging. These data sources are prone to biases attributed to missing data and unmeasured confounding, and these problems cannot be simply adjusted away statistically or glossed over in discussion.

ADT is well established to improve survival when used appropriately, that is, for men with nonlocalized disease and men receiving external-beam radiation therapy for intermediate- to high-risk disease. Multiple papers have likewise established that ADT adversely affects multiple physiologic pathways. Ultimately, then, whether or not the specific rates and outcomes determined in this analysis are reliable, the paper should serve as an important reminder in the clinical setting to consider these multiple effects of ADT, many of which can be ameliorated with focused diet and exercise programs, medical therapy, or both.

As the landscape of treatment options for advanced PCa becomes ever more complex, careful and prospective assessment of both cancer and noncancer outcomes, with detailed control for the subtleties of comorbid illness, will become increasingly important. Such analyses will require more details than are provided by any existing population-based data registries, and consideration should be given now as to how such data can be collected reliably and consistently across large populations of patients.

**Conflicts of interest:** The author has a consulting agreement with Amgen and Dendreon and honoraria from Takeda and Astellas.

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## Platinum Priority

### Reply from Authors re: Matthew R. Cooperberg. Adverse Effects of Androgen Deprivation and the Limits of National Tumor Registries. *Eur Urol* 2012;61:701–3

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We would like to thank Cooperberg [1] for his interest in our recent study [2], which focused on exploring the frequency of multiple events (fractures, stroke, heart disease, and thromboembolic disease) following prostate cancer (PCa) diagnosis. However, our question of whether a specific group of men is at increased risk of developing multiple adverse events, such as heart disease, stroke, thromboembolic disease, and fractures, may have been misinterpreted. We did not claim to quantify the association between specific types of endocrine treatment and the risk of multiple adverse events in this study.

In fact, in previous studies we have assessed the association between endocrine treatment and risk of heart disease and thromboembolism [3,4] as well as fractures (unpubl. data) in more detail. We found a lower risk of heart disease and thromboembolism for men on peroral monotherapy with antiandrogen than for men on gonadotropin-releasing hormone (GnRH) agonists. Our results are based on almost all cases of PCa diagnosed in Sweden during 1997–2007 and thus are probably a better representation of the “real world” than randomised trials.

Cooperberg [1] refers to studies with and without androgen deprivation therapy in combination with radia-

tion not showing any cardiac morbidity, but these are randomised trials on smaller, limited populations and thus might not present the entire picture. Cooperberg is right in pointing out that it is a limitation that treatment delivered more than 6 mo after date of diagnosis was not registered. For instance, an unknown proportion of men who primarily received curative therapy, surveillance, or antiandrogens would subsequently have received other treatments such as GnRH agonists. However, more data are currently captured in the National Prostate Cancer Register (NPCR) of Sweden. As of 2003, a chart review is performed 5 yr after date of diagnosis for men <70 yr of age with localised PCa to capture progression, secondary treatment, and adverse effects of primary treatment. Furthermore, information from the Prescribed Drug Register is available from 2005 on and can be used to assess medical treatment for PCa at all time points after date of diagnosis.

Another concern of Cooperberg [1] is our translation of World Health Organisation (WHO) grade to Gleason score. To the best of our knowledge, there is no universally accepted way of converting between the poorly defined WHO grading system and the currently used Gleason classification [5]. In brief, the WHO system is based on an evaluation of nuclear atypia as well as glandular architecture, and the Gleason classification is based on a number of well-defined categories of glandular architecture. The WHO classification includes three grades: I, well differentiated; II, intermediately differentiated; and III, poorly differentiated. The Gleason score is often collapsed into three categories: GS 2–6, well differentiated; GS 7, some parts poorly differentiated; and GS 8–10, poorly differentiated. In a study of men with advanced PCa, the risk of PCa death according to tumour differentiation was the same in an analysis of tumours graded according to Gleason and WHO (same conversion as in this paper) compared with a separate analysis of Gleason-graded tumours only [6]. Therefore, we believe that our conversion from the WHO system to the Gleason classification is justified and reasonable.

The concluding statement of our paper is supported by the quality of data in Swedish nationwide population-based registers. It is certainly true that such registers, whether

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