

# Androgen-deprivation Therapy— A Help or a Hindrance for Survival in High-risk Prostate Cancer?

a report by

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There is mounting evidence that androgen-deprivation therapy (ADT) for prostate cancer carries significant health risks. General awareness of the unpleasant but typically tolerable side effects of androgen suppression is not lacking. Recent studies have reported clinically significant cardiovascular morbidity and increased mortality, calling into question the safety of androgen suppression. In the mid-1990s, there was a precipitous rise in the use of ADT in the face of emerging data of improved disease control and preliminary results of a randomized trial that demonstrated an overall survival (OS) benefit with ADT.<sup>1</sup> What followed was a dramatic expansion in the role of hormone therapy from primarily palliation of symptomatic metastases to a component of definitive treatment. It is estimated that over 600,000 men in the US currently receive ADT.<sup>2</sup> A recent report on practice patterns suggested that almost 70% of hormone therapy is prescribed to patients for whom benefit has not been proved.<sup>3</sup>

The role of androgen suppression in the primary treatment of prostate cancer is most clear for locally advanced disease. Patients with high-risk features (prostate specific antigen [PSA] >20ng/ml, Gleason score  $\geq$ 8, T3–4) are typically treated with external-beam radiotherapy (EBRT) with ADT, radical prostatectomy, or prostate seed implant plus supplemental EBRT with or without ADT (see *Figure 1*). It has been over 20 years since the standard use of ADT for locally advanced disease was first established. Given the recent interest regarding hormone therapy, this article will re-examine its impact, particularly on survival, as well as the available evidence in the context of concerns that have emerged in the last two decades.

## Modalities and Mechanism of Action

The Nobel Prize in medicine was awarded to Dr Charles Huggins in 1966 for his discoveries regarding androgen dependence in prostate cancer. His work demonstrated that orchiectomy led to clinical improvement in patients with metastatic disease and, conversely, androgen injections caused worsening of symptoms.<sup>4</sup> Androgens promote the growth of both benign glandular epithelial cells and malignant cells in the prostate. Depriving cancer cells of their stimulant causes regression that can be translated into symptomatic control in metastatic disease and possible improvement in cure rates in the definitive setting. After prolonged hormone therapy, prostate cancer develops independence of androgens and becomes refractory to ADT for metastatic disease.

Orchiectomy as the primary means of ADT has largely been replaced by pharmacological agents for their reversibility; such agents are supported by 10 randomized trials and meta-analyses showing equivalence to surgical castration.<sup>5</sup> The gonadotropin-releasing hormone (GnRH) agonists

leuprolide and goserelin are the two most commonly used drugs. Under normal conditions, GnRH is released by the hypothalamus in a pulsatile fashion, stimulating the pituitary gland to secrete luteinizing hormone, which in turn promotes testosterone production in the testes. Over time, GnRH agonists induce downregulation of its receptors in the pituitary, thus leading to castrate levels of testosterone. Combined androgen blockade can be achieved by adding the anti-androgens bicalutamide or flutamide, which act directly on the prostate gland and decrease the adrenal contribution of androgens. In conjunction with radiotherapy, ADT is thought to reduce disease burden and therefore augment cell kill and improve tumor control. Androgen suppression has also been shown to promote apoptosis<sup>6,7</sup> and decrease hypoxia,<sup>8</sup> thereby producing a synergistic effect with concurrent ionizing radiation. *In vivo* experiments have also shown induction of an immune response.<sup>9</sup> Systemically, ADT may serve to eliminate micrometastases. The biological mechanism of androgen deprivation in combination with radiotherapy and their interactions has not been fully elucidated; however, further clarity is expected with ongoing investigations.

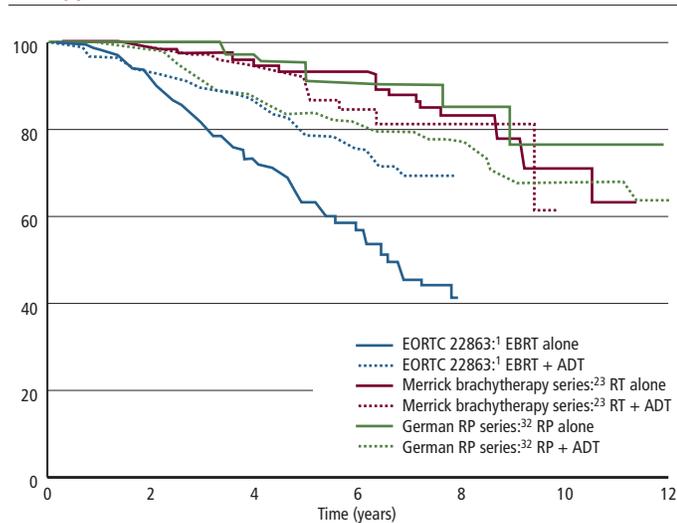
Although there are clear advantages to the reversibility of drugs and dampened psychophysical insult compared with orchiectomy, the development of pharmacological therapies, with their financial incentives and ease of use, has led to cavalier and inappropriate application, as evidenced by the millions of men who have received androgen suppression for indications that were not proved.<sup>10,11</sup> In Medicare patients alone, over \$1 billion was spent on GnRH agonists in 2001, leading to a federal act instituted in 2004 that cut reimbursement; consequently, 2005 reimbursement for GnRH agonists decreased by 40–50% compared with 2003.<sup>12</sup> Interestingly, from 2004 to 2005, coinciding with the year following the mandate to reduce reimbursement, there was a decline in the use of GnRH agonists and a corresponding increase in surgical castration, although not of equal magnitude.<sup>12</sup> One can only hope that this imbalance is a result of more judicious ADT use, and not a consequence of withholding proper treatment in the face of diminishing financial returns.



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**Figure 1: Overall Survival for Radical Prostatectomy, External-beam Radiation, and Brachytherapy, Stratified by Androgen-deprivation Therapy Status**



EORTC = European Organization for Research and Treatment of Cancer; EBRT = external-beam radiotherapy; ADT = androgen deprivation therapy; RT = radiation therapy; RP = radical prostatectomy.

## Androgen-deprivation Therapy and External-beam Radiotherapy

Numerous phase III randomized trials have been completed investigating the role of ADT with EBRT in high-risk patients (see *Table 1*). Three trials demonstrated an OS benefit and all studies found an improvement in prostate cancer mortality; these trials form the basis for the current standard use of ADT in the high-risk setting. One of the landmark studies was a European collaborative trial that randomized 415 patients with high-grade and/or T3–4 prostate cancer to EBRT alone or EBRT plus concurrent and adjuvant ADT for three years.<sup>1</sup> At five years, there was a 26% statistically significant OS benefit in patients who received hormone therapy. Recent important updates of two Radiation Therapy Oncology Group (RTOG) studies provided 10-year outcomes that remarkably also showed improvement in OS of 26%.<sup>13,14</sup> Given that it has been 10–20 years since the inception of these trials, it is important to note the changes in practice over this period in order to appropriately apply these data to current times. First, with the exception of one,<sup>15</sup> these studies primarily used clinical staging as eligibility criteria and represent a more locally advanced group than what is diagnosed today as high-risk. For example, in the European Organization for Research and Treatment of Cancer (EORTC) trial, 91% of patients had T3–T4 tumors and 33% had PSA >40ng/ml;<sup>1</sup> however, this is not a common presentation today. A more typical high-risk patient of the current era with a moderately elevated PSA, normal digital rectal exam, and a Gleason score of 8 formed the minority of the historic trials. In the setting of gross tumor and higher disease burden seen in earlier studies, ADT likely played a more critical role, as EBRT alone compared with conventional doses without image guidance was likely to be insufficient.

The second major change in the landscape of prostate cancer is that in recent years a number of dose escalation trials have shown improvement in biochemical control rates with doses greater than 70Gy<sup>16–19</sup> and, as a result, the radiation doses of 65–70Gy utilized in all of the ADT trials are

considered inadequate by today's standards. As such, debate surrounds the role of androgen suppression with higher doses of radiation and a suggestion that ADT was simply compensating for inadequate doses. There are retrospective data suggesting that the benefit of escalated doses is greater than the addition of ADT to conventional doses and, as such, ADT cannot replace radiation dose.<sup>20</sup> However, to date there has been no survival benefit shown with dose escalation; therefore, one could argue that even with increasing radiation doses ADT may still confer an additional benefit in highly selected patients. This remains to be answered in a randomized trial.

## Androgen-deprivation Therapy and Brachytherapy

The use of prostate seed brachytherapy has historically been reserved for low- to intermediate-risk prostate cancer, as early outcomes of high-risk disease treated with brachytherapy were poor.<sup>21</sup> However, this was prior to the era of rigorous dosimetric cut-points and coverage of peri-prostatic tissue. Numerous modern series from high-volume institutions have now demonstrated superior control rates with the use of brachytherapy.<sup>22–24</sup> The more favorable disease profile of high-risk brachytherapy series compared with EBRT studies must be borne in mind: in the largest series average Gleason scores were 7–8 and PSA was 12–15ng/ml.<sup>23,25</sup> ADT is commonly used prior to brachytherapy for the purpose of reducing prostate size to improve the technical feasibility and side effect profile; however, it is not routinely used for the purpose of achieving better tumor control. There has been no randomized trial investigating the impact of ADT on outcomes in conjunction with brachytherapy; therefore, we currently rely on retrospective series to guide management.

Merrick et al. reported 204 high-risk patients treated with pelvic EBRT followed by brachytherapy and found that men treated with ADT had a significant improvement in biochemical control, with 10-year biochemical progression-free survival (PFS) of 80% in hormone-naïve patients compared with 90–95% in patients who received ADT.<sup>23</sup> This provides some evidence that even with ablative radiation dose to the prostate, it may still be beneficial to use ADT in high-risk disease. There was no difference in cause-specific survival (CSS) or OS, although with long-term CSS rates greater than 90% it would likely require a large sample size to detect a difference. A published series of intermediate- to high-risk patients treated at Mount Sinai also showed an improvement in biochemical control with the addition of neoadjuvant and adjuvant ADT. Five-year freedom from biochemical failure (FBF) for high-risk patients was 74% with ADT versus a dismal 46% without.<sup>25</sup> However, there was no difference among all patients who received a good-quality implant with a five-year FBF of 80% with or without ADT, whereas in patients who received a low-dose implant the five-year FBF was 79 versus 38% (p=0.0037). Based on disease risk to assess the impact of both dose and androgen suppression specifically in high-risk patients, the patients were not subdivided further; however, in high-risk patients who received both ADT and a high-dose implant the reported four-year FBF was 77%. In a multivariate analysis, ADT use was the most significant predictor of biochemical control in both the high-risk patients and the low-dose group. A recent multicenter analysis investigating the impact of radiation doses noted a significant improvement in five-year biochemical control with ADT from 77.5 to 96% (p=0.001) in patients who received high-dose implants.<sup>26</sup> Longer follow-up is necessary to confirm these results and allow for the restoration of testosterone levels.

**Table 1: Phase III Randomized Trials Investigating the Role of Androgen-deprivation Therapy with External-beam Radiotherapy in High-risk Patients**

	Inclusion	Treatment Arms	Overall Survival	Cause-specific Survival
RTOG 85-31 <sup>13</sup> (n=977)	cT3 or N1	Indefinite adjuvant EBRT alone	49% 39% (10 years)	84% 78% p=0.0052
RTOG 86-10 <sup>14</sup> (n=456)	Bulky cT2–4	Neoadjuvant + concurrent 4 months EBRT alone	43% 34% (10 years)	77% 64% p=0.01
EORTC 22863 <sup>1</sup> (n=412)	cT1–2 gr 3 cT3–4	Concurrent + adjuvant 3 years EBRT alone	78% 62% (5 years)	– – p=0.0002
TROG 9601 <sup>30</sup> (n=818)	cT2b–4N0	Neoadjuvant + concurrent 3 months Neoadjuvant + concurrent 6 months EBRT alone	– – –	92% 94% 91% (5 years) p=0.04
MGH <sup>15</sup> (n=206)	cT1b–2b + ≥1 risk factor	Neoadjuvant + concurrent 6 months EBRT alone	74% 61% (8 years)	– – p=0.01
RTOG 92-02 (n=1,554)	cT2c–4	Neoadjuvant + concurrent 4 months Neoadjuvant + concurrent + adjuvant 28 months	79% 80% (5 years)	91% 95% (5 years) p=0.003
EORTC 22961 (n=970)	cT1c–T2b N1 T2c–T4 N0–1	Concurrent + adjuvant 6 months Concurrent + adjuvant 3 years	81% 85% (5 years)	– – p=0.019

EORTC = European Organization for Research and Treatment of Cancer; EBRT = external beam radiotherapy; TROG = Tasman Radiation Oncology Group; MGT = Massachusetts General Hospital; RTOG = Radiation Therapy Oncology Group.

There are conflicting data regarding the use of ADT with brachytherapy, with some evidence of biochemical improvement in high-risk patients; however, the lack of survival benefit further supports the theory that with an adequate radiation dose the benefit of ADT may be lost, although longer follow-up is needed. To help answer this question, there is an ongoing multi-institutional randomized trial investigating the use of ADT with brachytherapy in high-risk patients; however, the trial may close early without results as accrual is poor.

**Androgen-deprivation Therapy and Radical Prostatectomy**

Historically, radical prostatectomy (RP) has not been the treatment of choice for high-risk prostate cancer, primarily due to concerns regarding the ability to obtain clear margins in locally advanced disease. With the use of PSA and earlier detection, the contemporary cohort of high-risk patients consists less of bulky disease and more of higher-grade tumors, making some patients appropriate candidates for surgery. At least 10 randomized trials have been performed investigating the role of ADT in conjunction with RP; however, most of these studies largely concerned early-stage disease. Some studies showed improvement in pathological findings with less positive margins, histological downgrading, and decreased rates of lymph-node involvement.<sup>27–30</sup> Despite improved pathological outcomes, this did not consistently translate into any difference in disease control. No trials showed an improvement in OS, with the exception of a study published by Messing et al.<sup>31</sup> that randomized 98 pathologically node-positive patients to immediate versus deferred ADT after RP. Ten-year OS was 75 versus 50% (p=0.04) and CSS 85 versus 53% (p=0.0004), favoring immediate ADT. It is noteworthy that patients in the delayed arm were not treated until there were clinically evident metastases. A German retrospective series assessed

the outcomes of 275 patients with PSA ≥20ng/ml treated with radical prostatectomy with or without ADT<sup>32</sup> and did not find a statistically significant improvement in overall survival.

ADT has been incorporated as part of the regimen in numerous trials assessing the utility of chemotherapy as part of multimodality therapy for high-risk disease. The Southwest Oncology Group (SWOG) performed a phase III study (S9921) comparing adjuvant ADT after RP with ADT plus six cycles of mitoxantrone and prednisone. TAX-3501 was a three-arm randomized trial comparing surveillance, adjuvant ADT, and adjuvant ADT plus docetaxel in high-risk patients. Both studies closed early due to poor accrual. The Cancer and Leukemia Group B (CALGB) 90203, an ongoing trial, is investigating neoadjuvant ADT with docetaxel versus RP alone. In summary, outside of node-positive disease, there are no data supporting the use of ADT in conjunction with RP.

**Timing and Duration**

Both the European<sup>1,33</sup> and the US<sup>13,34</sup> groups conducted trials comparing long- and short-term ADT with EBRT after earlier studies showed benefit with long-term ADT. In RTOG 92-02, men with clinical T2c–T4 disease were randomized to four months of neoadjuvant and concurrent ADT or a total of two years of ADT.<sup>34</sup> More than 50% of men had T3–4 disease and 33% had PSA >30ng/ml. There was a significant improvement in five-year CSS and biochemical failure, but no difference in OS. An OS benefit was detected in an unplanned subset analysis of patients with Gleason scores of 8–10: five-year OS was 81% for long-term ADT versus 71% for short-term ADT (p=0.044). The EORTC 22961 study compared six months versus three years of concurrent and adjuvant treatment with the goal of showing non-inferiority of shorter-course ADT.<sup>33</sup> Seventy-five percent of patients had

T3–4 disease and median PSA was 19ng/ml. Results presented at a national meeting after a median follow-up of five years showed that patients who remained on ADT for three years had significantly better OS, CSS, and biochemical control. Thus, the existing data suggest that in the group of high-risk, locally advanced patients seen more commonly in an earlier era, long-term ADT of two to three years with EBRT to 65–70Gy leads to improved OS.

In the aforementioned retrospective analyses of patients treated with brachytherapy and supplemental EBRT,<sup>23</sup> there was no difference seen between more than six months compared with less than six months of ADT. This may be a reflection of response in patients with a more favorable risk profile, i.e. longer-term ADT does not confer additional benefit in this group. Based on these data, a shorter course may be adequate with brachytherapy.

The optimal timing of androgen suppression is not entirely clear as the main EBRT trials used adjuvant, neoadjuvant and concurrent, and concurrent and adjuvant, as well as neoadjuvant, concurrent, and adjuvant regimens. The interaction of androgen suppression with radiation is complex, as evidenced by recent results of RTOG 94-1335, which showed improvement in survival with neoadjuvant and concurrent ADT with pelvic radiation, but a survival detriment with short-term adjuvant ADT. Given the observed *in vitro* synergistic effects, most would advocate for concurrent ADT with EBRT if it is to be given.

### Adverse Effects and Their Impact on Survival

ADT influences quality of life significantly enough for some men to discontinue therapy before the recommended length of treatment. There are numerous adverse effects resulting from induced hypogonadism: sexual dysfunction, hot flashes, weight gain, mood lability, sleep disturbance, gynecomastia, shrinkage of genitalia, decrease in bone density, depression, and cognitive decline. More recently, there has been heightened concern regarding adverse physiological alterations that can influence OS. Androgen suppression alters body composition by both decreasing lean body mass and increasing fat mass, even in the setting of short-term androgen suppression.<sup>36–39</sup> Also, it has become evident that there is a direct relationship between a low testosterone level and decreased insulin sensitivity, which is supported by improvement with testosterone replacement in hypogonadal men.<sup>40</sup> ADT initially induces hyperinsulinemia, which maintains euglycemia; however, with longer androgen suppression, hyperglycemia and frank diabetes develop.<sup>41</sup> In one study, 44% of men who received ADT for at least 12 months developed diabetes compared with 12% of hormone-naïve men.<sup>42</sup>

There are conflicting data on the impact of ADT on lipid profile—some studies have shown elevated low-density lipoprotein (LDL) and triglycerides,<sup>41</sup> while others found no difference—but there is consistency in increased total cholesterol and high-density lipoprotein (HDL) across studies.<sup>43</sup> Due to the observed increases in HDL,<sup>44,45</sup> it is not entirely clear how the overall change in lipid profile alone affects cardiovascular disease. Nonetheless, the constellation of these physiological changes comprises the metabolic syndrome, which is associated with increased risk for cardiovascular disease and diabetes.<sup>46</sup> In a cross-sectional study, 55% men who had received more than 12 months of ADT met the criteria for metabolic syndrome compared with 20–22% in the non-ADT and control groups.<sup>41</sup>

Due to these adverse physiological changes, a number of recent studies have been performed to evaluate the incidence of cardiovascular disease in androgen-suppressed patients and its influence on survival. A population-based study of over 70,000 men with non-metastatic prostate cancer found that rates of incident diabetes, incident coronary artery disease, myocardial infarction (MI), and sudden cardiac death were all incrementally higher in men treated with GnRH agonists.<sup>47</sup> D’Amico et al. performed a pooled analysis of the three above-mentioned trials to evaluate the incidence of fatal MI, and found that in men 65 years of age or older three to eight months of ADT was associated with increased fatal MIs compared with men treated with radiotherapy alone.<sup>48</sup> There was an insufficient number of events in patients under 65 years of age to draw any conclusions in this age group. Similar results were reported from an analysis of a prostate cancer registry: patients 65 years of age or older treated with definitive radiation had a higher five-year estimate of cardiovascular death of 8.4% with ADT versus 5.7% without, although this was not statistically significant ( $p=0.20$ ).<sup>49</sup> However, there was a statistically increased risk for cardiovascular death in patients of all ages treated with radical prostatectomy and ADT. Careful examination of the data reveals that many of the cardiovascular events occur years after discontinuation of ADT, which is either a reflection of unbalanced baseline cardiovascular risk factors or the latency and irreversibility of the early effects of ADT. Testosterone recovery can take eight to 18 months, during which time patients are still at risk for toxicities.<sup>50</sup>

Given the recent heightened awareness of the influence of the cardiovascular system, these particular data have been reviewed for landmark randomized trials. In an update of RTOG 86-10, there was no statistically significant difference in 10-year rates of cardiovascular deaths: 12.5% versus 9% without ADT ( $p=0.32$ ).<sup>14</sup> An updated analysis of RTOG 92-02 was performed: the five-year rate of cardiovascular mortality was approximately 5% with both long- and short-term ADT and 10% in the subset of patients with a history of cardiovascular disease.<sup>51</sup> Data from EORTC 22961 showed no difference in cardiovascular disease between six months and three years of ADT.<sup>33</sup> These were *post hoc* analyses and, as such, have their limitations. In future trials, it would be worth noting the proportion of patients in each arm treated with ADT at the time of recurrence, as this would also contribute to the incidence of associated morbidity through the follow-up period.

Increased risk for fracture secondary to ADT may also contribute to the survival equation when balancing the risks and benefits of treatment. Androgen suppression has been shown in numerous studies to decrease bone mineral density.<sup>52–54</sup> ADT for prostate cancer is now one of the leading causes of osteoporosis in the US.<sup>2</sup> Large population-based retrospective series have demonstrated an increased risk for fracture in men who received ADT.<sup>55,56</sup> Although the cause of increased fracture risk is due also to greater fall risk secondary to metastatic disease and treatment-related frailty, decreased bone density from prolonged androgen suppression is certainly a major contributor. It is well accepted that hip fractures in the elderly affect survival; similarly, aside from the obvious associated morbidity, skeletal fractures in men with prostate cancer have also been shown to increase mortality.<sup>57</sup>

There is some evidence that the use of ADT may be detrimental to survival (see *Figure 1*). A *post hoc* subset analysis of the D’Amico trial suggested that in patients with moderate to severe comorbidity the addition of ADT decreased OS, with eight-year estimates of 54 versus 25%, although this

was not statistically significant ( $p=0.08$ ). In addition, this subset consisted of only 25 patients in each arm, hardly sufficient to draw firm conclusions. Furthermore, 71% of study participants had intermediate-risk disease, where the benefit of ADT is likely smaller. An OS detriment with the addition of ADT was found in a retrospective study performed over 2,000 consecutive patients of all risk groups treated with brachytherapy. A subset analysis of high-risk patients was not performed.<sup>58</sup> Although patients in the study were notably older, with a median age of 73 years compared with 65–68 years in other series, the results of this study and the D’Amico trial may be indicative that in patients without clear benefit, e.g. intermediate risk or treatment with ablative doses, ADT is not beneficial and may be harmful.

**Summary**

At the start of the Nobel Prize address given by Dr Huggins a little over 40 years ago, he stated: “Mostly man with cancer lives one year or a little longer after the neoplasm becomes manifest, and it would appear that some inhibition of growth of the tumor takes place to produce this protracted course.” It is of great comfort and encouragement that our field has made immense strides in the last decades, and “this protracted course” is now longer than a single year. However, the responsibility that comes with improving survival is mitigating long-term adverse effects of treatment and maintaining an acceptable quality of life.

The use of ADT in conjunction with EBRT at historical doses of 65–70Gy in high-risk patients portends an OS benefit, as demonstrated in several large randomized controlled trials, with some evidence that long-term ADT

provides superior OS in high-risk, locally advanced disease. It remains to be seen whether ADT will provide additional benefit in the modern era of escalated radiation doses; meanwhile, it is imperative that we bear in mind the role of dose escalation when making management decisions based on historical trials. No survival advantage has been shown when androgen suppression is added to radical prostatectomy, with the exception of node-positive disease. There are no randomized studies evaluating its role with prostate brachytherapy: retrospective analyses have demonstrated significant improvement in biochemical control, but no difference in survival.

It is concerning that practice patterns have been shown to be driven by inappropriate extrapolation of existing data and financial gain.<sup>3,12</sup> This is particularly worrisome in light of growing evidence that ADT may be detrimental to the survival of our patients. Recently available data suggest increased cardiovascular morbidity and mortality associated with androgen suppression, which must not be taken lightly. Given the large number of men receiving ADT, this is a serious health concern. ADT should be used discriminately and strictly in settings where a clear benefit has been shown. The role of ADT in potentially curable patients has been demonstrated in high-risk patients receiving conventional doses of EBRT and node-positive disease following radical prostatectomy. In all other scenarios, ADT in conjunction with local therapy should be considered unproved. Only in the rigorously selected patient will the benefit of ADT outweigh its risks. Modifiable cardiac risk factors ought to be addressed when initiating ADT and special attention paid to the health status of patients worldwide to ensure that we are not harming patients in the pursuit of improving cure rates and other less noble causes. ■

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