rather to a shift towards nephron-sparing and minimally invasive strategies, as suggested by previous studies [1,2] and in line with contemporary American Urological Association (AUA) guideline recommendations [3]. In other words, adoption of robotic surgery permitted nephron preservation rather than unnecessary sacrifice in a group of patients for whom surgical extirpation was already decided on. Thus, we should be careful not to overdraw conclusions from a narrow temporal point at which practice standards were being shifted to accommodate a different paradigm. Further investigation is necessary to assess whether the more recently promulgated AUA guidelines, which emphasize AS as an option for tumors of <2 cm in size, regardless of age, will shift more patients towards AS [4]. Moreover, as we enter the "omics" era [5], the focus of the discussion should be how we can better characterize SRMs not only by their size but also by histology and other biological features.

Conflicts of interest: The authors have nothing to disclose.

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Re: Health Consequences of Androgenic Anabolic Steroid Use

Hortitz H, Andersen JT, Dalhoff KP

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Experts' summary:
Horwitz and colleagues provide data on the health consequences of androgenic anabolic steroid (AAS) abuse [1]. The authors performed a retrospective review of Danish men who had tested positive (urine) for AAS as part of the Anti Doping Denmark program and identified age-matched controls from the general population.

A total of 545 men who had tested positive for AAS between January 2006 and March 2018 were compared to 5540 population controls matched for age, gender, and date. Men who had tested positive for AAS had a threefold higher risk of death during the follow-up period (95% confidence interval [CI] 1.3–7.0; $p = 0.007$) and twofold higher hospital contacts ($p < 0.001$) as compared to nonabusers of AAS. In addition, AAS abusers had a 13-fold higher risk of gynecomastia, twofold higher risk of infertility, and threefold higher risk of requiring medicine for erectile dysfunction ($p < 0.001$) as compared to nonabusers. Importantly, no associations were found between ischemic heart disease and AAS abuse (95% CI 0.6–4.8), but AAS was associated with nonischemic heart disease, including a threefold higher risk of cardiomyopathy and atrial fibrillation and fivefold higher risk of thromboembolic disorders ($p < 0.01$). These data were replicated in a similar cohort of men who were suspected of AAS abuse (men who refused testing).

Experts' comments:
This manuscript adds to the continued controversy surrounding the safety of exogenous testosterone use [2–4]. However, there are key differences between therapeutic testosterone replacement therapy (TRT) and AAS abuse. It is important not to extrapolate the potential dangers of AAS abuse highlighted here to all testosterone therapies. The study has many strengths, including the wealth of data provided by the Danish registry system. However, there are several limitations to consider. It is not clear what type, dosage, and duration of anabolic steroids were used by these men. Owing to privacy concerns, the cause of mortality was not published, which would be valuable for an understanding of the driving factors. Regrettably, the authors did not include bodybuilders who did not test positive for AAS as an additional control group. Is the current bodybuilding lifestyle (training regimen, supplements, risky behavior, etc.) or AAS abuse the driver of health consequences observed here? Regardless of these limitations, the data support the notion that AAS abuse is associated with greater all-cause mortality and additional negative health outcomes. We expect that the phase 4 TRAVERSE study (NCT03518034) mandated by the US Food and Drug Administration will provide more definitive data on the safety of TRT for patients with symptomatic hypogonadism.

Another concern highlighted by this manuscript is the risk of non-mortality-related problems, including a 2.4-fold increase in infertility. The majority of this cohort were young men early in their reproductive years (mean age 26.2 yr). In a recent review in *European Urology Focus* we discussed treatment options for men with low testosterone

for whom maintaining fertility potential is a critical factor in determining an appropriate treatment plan [5].

Taken together, these data highlight that AAS abuse is risky behavior. The manuscript by Horwitz and colleagues provides a critical resource in counseling men who are considering or currently using AAS to improve their muscular potential. However, TRT in an appropriate clinical setting remains an important therapeutic option for men with symptomatic hypogonadism. While AAS abuse probably has significant health consequences, results from the TRAVERSE study will be critical to determine how this translates to therapeutic TRT use.

Conflicts of interest: The authors have nothing to disclose.

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Re: Radiofrequency-induced Thermo-chemotherapy Effect Versus a Second Course of Bacillus Calmette-Guérin or Institutional Standard in Patients with Recurrence of Non-muscle-invasive Bladder Cancer Following Induction or Maintenance Bacillus Calmette-Guérin Therapy (HYMN): A Phase III, Open-label, Randomised Controlled Trial

Tan WS, Panchal A, Buckley L, et al

Eur Urol 2019;75:63–71

Experts' summary:
This multicentre prospective study recruited patients with recurrent non-muscle-invasive bladder cancer (NMIBC) previously treated with bacillus Calmette-Guérin (BCG) to receive second-line treatment in the form of radiofrequency-induced thermochemotherapy (RITE) with mitomycin (MMC) or the institutional standard of care (BCG rechallenge in most cases). The trial closed prematurely after 104 patients were randomised because of the shorter disease-free survival noted among patients with carcinoma in situ (Cis) in the experimental arm (24-mo disease-free survival [DFS] 24% vs 47%). Apart from this finding, the study showed no DFS differences between the study arms in general or among non-Cis patients, and there was no difference in the rate of complete responses at 3 mo among Cis patients. Moreover, a safety analysis did not indicate any difference in the risk of treatment-related toxicity between the study arms. The authors concluded that RITE with MMC can be considered as a second-line treatment for BCG-treated patients with recurrent papillary NMIBC with no concomitant Cis foci [1].

Experts' comments:
Patients who do not tolerate or respond to BCG therapy and for whom radical cystectomy is not an option are always problematic. In this scenario, there is no standard treatment and no standard follow-up schemes, and the risk of disease progression is high, especially in cases defined as BCG failure. The HYMN trail raised hopes for identification of an effective treatment modality, but failed to meet these expectations. The patient heterogeneity at baseline (intermediate- and high-risk cases, BCG failure and no failure, papillary and flat lesions), treatment diversity in the control group (BCG rechallenge, conventional intravesical MMC, intravesical MMC with an electromotive drug administration [EMDA] system), a low number of randomised patients, and underpowered results (especially in subgroup analyses) make unambiguous conclusions on the value of RITE in this clinical situation difficult. Nevertheless, after the study by Arends et al. [2], the HYMN trial is the second published randomised controlled trial comparing RITE with BCG showing no progression-free survival benefit with RITE. In our opinion, this is the most important clinical endpoint with a probable effect on overall survival. As long as BCG therapy—a gold standard—is available, except for BCG failure cases, it offers at least comparable efficacy and safety, and is much less expensive and time-consuming for high-risk NMIBC patients. Another option for high-risk NMINBC patients is a combined treatment. The combination of BCG therapy and intravesical chemotherapy is associated with an unacceptable rate of adverse events [3]. However, the different toxicity profile of immune checkpoint inhibitors potentially offers an alternative regimen for combination with BCG, which is currently under investigation (NCT03519256, NCT02792192, NCT03711032, NCT03528694).

The HYMN trail results also prompt reflection on achievements for high-risk NMIBC in the last few decades.