resectable primary tumor [1,2]. However, the question remains whether this approach currently applies to patient care in the era of targeted therapies.

In the CARMENA trial, Méjean et al. [3] concluded that sunitinib alone was noninferior to CN followed by sunitinib for patients with low- or intermediate-risk metastatic RCC. Patients with metastatic clear-cell RCC were randomized to sunitinib alone ($n = 224$) or CN followed by sunitinib ($n = 226$). The primary endpoint of overall survival (OS) was assessed using intention to treat (ITT) analysis.

Experts' comments:
The conclusions of this study have been widely questioned given what appear to be major deviations from the assigned treatment plan, potential issues of bias in patient selection, the trial design, and other issues.

For example, 17% of patients in the sunitinib-only arm received delayed nephrectomy, while 7% of patients in the CN + sunitinib arm did not receive CN and 17% never received sunitinib. Why? It might be that the patients studied had higher risk than anticipated. This contention is supported by the fact that the study outcomes were significantly inferior than planned (OS of 18 mo for sunitinib and 14 mo for CN + sunitinib, versus the planed 26 mo). The authors also admit that some potential patients were excluded from participation "at the investigator's discretion" if they had low-risk metastatic disease. In addition, it is widely accepted that deviations from protocol following randomization in ITT/noninferiority trials may cause groups to appear more similar when true treatment differences exist [4].

Much of my academic work has involved clinical trials. I applaud the authors of the CARMENA report for their efforts to answer an important clinical question. However, I believe that their trial is flawed and does not support their contention that CN is of no benefit for patients with metastatic renal cancer. I believe that CN still has a significant role today for patients who are well selected by a team composed of a urologist and a medical oncologist before treatment.

In sum, while the role of CN may continue to evolve as newer and more effective therapies continue to discovered, I believe that the CARMENA trial should not dissuade physicians from currently offering CN to appropriately selected patients.

Conflicts of interest: The author has nothing to disclose.

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Re: The Temporal Association of Robotic Surgical Diffusion with Overtreatment of the Small Renal Mass

Shah PH, Alom MA, Leibovich BC, et al

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Experts' summary:
The authors utilized the National Cancer Data Base to evaluate contemporary practice patterns in the management of small renal masses (SRMs; <4 cm). Some 52 804 patients managed between 2010 and 2014 were analyzed, and trends in the use of active surveillance (AS), ablation, and surgery (robotic, laparoscopic or, open) were assessed overall and for subsets of elderly (>75 yr) and unhealthy (Charlson comorbidity index ≥2) patients. The authors found that surgery remained the primary treatment option (in >70% of patients), despite a small increase in patients managed with AS (from 4.8% to 6%). Moreover, they noted an exponential increase in robotic partial nephrectomy (RPN) and radical nephrectomy (RRN) procedures. This trend was observed in all groups included in the evaluation. On multivariable analysis, year of diagnosis (2014 vs 2010) was associated with higher use of robotic renal surgery versus AS (odds ratio 1.44; $p < 0.001$). The authors conclude that surgical overtreatment of SRM can be attributed to robotic dissemination.

Experts' comments:
While we commend the authors for their work, a closer look at the data might allow a different, and more balanced, interpretation, ultimately avoiding what we believe is a misleading message about the role and impact of robotic surgery in SRM management. The percentage of SRMs managed with "surgery" remained stable over the study period (75% in 2010 vs 74.2% in 2014), with significant increases in RPN (from 19% to 35%) and RRN (from 2.7% to 4.4%) being offset by declines in other "surgical" options (open PN 24% to 15%; laparoscopic PN 8% to 6%; open RN 10% to 5%; and laparoscopic RN 10% to 8%). Thus, from looking at the larger picture we can conclude that implementation of robotic surgery did not translate to overtreatment, but

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