Cardiovascular Morbidity in a Randomized Trial Comparing GnRH Agonist and GnRH Antagonist among Patients with Advanced Prostate Cancer and Preexisting Cardiovascular Disease

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Purpose: Androgen deprivation therapy may increase the risk of cardiovascular disease. Limited data suggest that GnRH (gonadotropin-releasing hormone) antagonist may be associated with a lower risk of cardiovascular disease than GnRH agonist.

Materials and Methods: We performed a phase II, randomized, open label study in men with prostate cancer and preexisting cardiovascular disease who were randomized to receive GnRH agonists or antagonists for 1 year. The primary outcome was endothelial function measured by the EndoPAT 2000 device (Itamar Medical, Caesarea, Israel). The predefined secondary outcome was a new cardiovascular event. Patients were followed for the development of cardiovascular disease, defined as death, myocardial infarction, a cerebrovascular event, percutaneous angioplasty with coronary stent insertion or hospitalizations due to cardiac events.

Results: A total of 80 patients were enrolled in study, including 41 and 39 who received GnRH antagonist and agonist, respectively. Patients in each arm had similar baseline characteristics. We did not detect a difference in the primary end point (endothelial function) between the groups (mean ± SD reactive hyperemia index 2.07 ± 0.15 vs 1.92 ± 0.11, p=0.42). However, during the trial period a new cardiovascular event (the secondary end point) developed in 15 patients. Of cases new major cardiovascular and cerebrovascular events developed in 9, including death in 2, myocardial infarction in 1, a cerebrovascular event in 2 and percutaneous angioplasty with coronary stent insertion in 4. Of

Abbreviations and Acronyms

ADT = androgen deprivation therapy
CRP = C-reactive protein
CVA = cerebrovascular event
CVD = cardiovascular disease
CVE = cardiovascular event
GnRH = gonadotrophin-releasing hormone
hsTn = high sensitivity troponin
LH = luteinizing hormone
MACCE = major cardiovascular and cerebrovascular event
MI = myocardial infarction
NTproBNP = N-terminal pro-B-type natriuretic peptide
RHI = reactive hyperemia index

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the patients 20% randomized to GnRH agonist experienced a major cardiovascular and cerebrovascular event compared to 3% of those on GnRH antagonist ($p=0.013$). The absolute risk reduction in major cardiovascular and cerebrovascular events at 12 months using GnRH antagonist was 18.1% (95% CI 4.6–31.2, $p=0.032$).

Conclusions: To our knowledge this is the first prospective study to test cardiovascular outcomes among patients with prostate cancer who received androgen deprivation therapy. No differences in the primary end point were noted between the study arms. However, the secondary end point revealed that patients treated with GnRH agonist experienced significantly more major cardiovascular and cerebrovascular events than those treated with GnRH antagonist. These phase II results suggest that in patients with prostate cancer who have preexisting cardiovascular disease selecting the androgen deprivation therapy modality may differentially affect cardiac outcomes.

Key Words: prostatic neoplasms, cardiovascular diseases, gonadotrophin-releasing hormone, androgen antagonists, treatment outcome

ANDROGEN deprivation therapy is used to inhibit the progression of advanced prostate cancer.[1] Retrospective studies have shown an association between ADT use and an increased risk of CVD, including peripheral arterial disease,[2] and MI, stroke and cardiovascular related morbidity.[3] In fact, since 2010, the United States FDA (Food and Drug Administration) has mandated that ADT manufacturers must include the CVD risk as part of the safety information.[4] While observational studies have presented strong evidence supporting the risk of CVD associated with ADT, randomized studies have not demonstrated increased risk.[5]

Androgen deprivation is conventionally accomplished by GnRH agonists. The GnRH antagonist degarelix is a relatively new drug which works by competitively inhibiting GnRH receptors.[6] Through different mechanisms of pituitary GnRH receptor blockade GnRH agonists and antagonists inhibit LH secretion, which consequently inhibits testosterone production.[6] Post hoc analysis of 6 trials in which patients with prostate cancer were randomized to GnRH agonist or GnRH antagonist showed that degarelix was associated with half the number of cardiac events compared with GnRH agonists specifically in men with preexisting CVD.[7] However, another group found conflicting results.[8]

In patients with CVD endothelial dysfunction represents a systemic pathological state of the endothelium.[9] The EndoPAT 2000 (Itamar Medical, Caesarea, Israel) is a noninvasive device which enables rapid assessment of endothelial function by recording endothelium mediated changes in response to reactive hyperemia.[10] It calculates a normalized value termed the RHI. Studies using the device demonstrated that a low RHI score correlated with impaired endothelial function.[11] Most importantly, the RHI appears to predict cardiovascular outcomes.[12]

To our knowledge there have been no published randomized studies on cardiovascular morbidity among patients with prostate cancer who receive ADT. We compared endothelial function and CVEs among patients with advanced prostate cancer and preexisting CVD who were randomized to receive GnRH agonist or GnRH antagonist.

PATIENTS AND METHODS

Trial Design

At 2 centers we performed a phase II, randomized, open label superiority study of the use of GnRH antagonist compared to GnRH agonist in men with advanced prostate cancer and preexisting cardiovascular disease. All patients provided written informed consent. The study was approved by the internal review board at each center (IRB No. 0102-15-RMC) and it is registered in ClinicalTrials.gov (NCT02475057).

Participants

We included in study men with high risk or metastatic prostate cancer who were scheduled to receive ADT for at least 1 year. All subjects had a documented history of CVD, including MI, CVA, ischemic heart disease or peripheral vascular disease. We excluded patients who received ADT 6 months prior to study enrollment. The supplementary material (https://www.jurology.com) provides additional eligibility criteria.

Interventions

Participants were randomized to receive an initial loading dose of 240 mg of the GnRH antagonist degarelix followed by 11 monthly injections of 80 mg or 4 injections of 3-month depot of GnRH agonist at treating physician discretion. Adherence to drug administration was monitored by trial administration. Additional prostate cancer treatments were allowed and left to the discretion of the treating physician. All additional treatments were recorded by trial administration.

Outcomes

The study primary end point was to compare endothelial function between the 2 arms. Endothelial function was measured at baseline, and 6 and 12 months after ADT initiation by peripheral arterial plethysmography using the EndoPAT 2000 device.[10]

CVEs were a predefined secondary outcome. Patients were followed every 3 months for the development of any

new CVE, including death, MI, CVA, a transient ischemic attack, heart catheterization with or without intervention and cardiac related hospitalization. MACCEs were defined as death, MI, CVA and heart catheterization with stent insertion.[13] A cardiologist blinded to treatment assignment reviewed all medical records and categorized all cardiac events.

To complement the secondary analysis of cardiac events we used 4 well-known cardiac biomarkers, which were measured at the Rabin Medical Center central laboratory, at baseline and at 3, 6 and 12 months of treatment. The biomarkers included hsTn, CRP, D-dimer and NTproBNP.[14] The supplementary material (https://www.jurology.com) provides further details.

Sample Size

The primary outcome measure was the RHI measured by the EndoPAT 2000 device. In previous studies the RHI had a SD of 0.42 and a clinically meaningful difference in endothelial function in a high risk group of men with preexisting CVD was an RHI of 0.26.[10] Therefore, we needed to randomize 80 subjects to reject the null hypothesis that the population means of the 2 treatment groups were equal with a probability (power) of 0.8. The type I error probability associated with the test of this null hypothesis was 0.05.

Randomization

Subjects were randomized between the 2 intervention arms in a 1:1 ratio. Randomization was stratified by metastatic vs nonmetastatic cancer status and baseline endothelial function. For stratification we used the average RHI of 1.765 in males 60 to 80 years old with a history of CVD.[15] Randomization was done by minimization using MINIM software.[16] The allocation sequence was created and coordinated at the study central office.

Blinding

This was an open label study. Treatment allocation was known to patients, physicians and research team. Emergency room physicians and other treating physicians were blinded to measured outcomes. Statistical analysis and categorization of all CVEs were performed by a cardiologist blinded to treatment allocation.

Statistical Analysis

The primary outcome was an analysis of endothelial function using the Student t-test to compare the RHI at 12 months. We also performed ANCOVA accounting for baseline levels. As the secondary outcome all randomized subjects were included in an intent to treat analysis of CVEs and MACCEs. Time to the first CVE and MACCE was estimated by the Kaplan-Meier method and treatment groups were compared by the log rank test. Between group differences in the frequency of 1-year CVEs and MACCEs were evaluated by the chi-square test and absolute risk reduction.

For confirmatory biomarker analysis we performed repeat measures ANOVA to determine differences in serum biomarker levels (hsTn, D-dimer, CRP and NTproBNP) in subjects with CVE or MACCE vs subjects with no event and with time at baseline, and 3, 6 and 12 months using a conservative F-test for interaction between time and CVE. The F-test Greenhouse-Geisser correction was used to adjust the degrees of freedom for deviation from sphericity (1 of the assumptions of repeat measures ANOVA). Also, we used ROC analysis to determine the ability of baseline cardiac biomarkers to predict CVE and MACCE. All statistical analyses were done with SPSS® Statistics, version 21.00 with $p < 0.05$ considered statistically significant.

RESULTS

Patient Characteristics

We enrolled 80 subjects between August 2015 and June 2017 at a total of 2 centers, including Rabin Medical Center and Rambam Medical Center. Of the men 39 and 41 were randomized to GnRH agonist and antagonist, respectively (fig. 1).

Median patient age was 72 years (IQR 67.9–77.7). At presentation 59 patients (74%) had localized prostate cancer and 21 (26%) had metastatic disease. Cancer characteristics and additional treatments were similar in the 2 treatment groups (table 1). Of the patients 25 (31%) had diabetes and 58 (73%) had hypertension while 69% received at least 4 different medications. A total of 74 patients (92.5%) were treated medically for secondary cardiovascular prevention, including statins in 65%, antiplatelet aggregation in 71% and blood pressure lowering agents in 61%. A total of 53 patients (66%) had a history of ischemic heart disease, 30 (37%) experienced a MI within a year before randomization and 14 (18%) had had a previous CVA. Baseline characteristics were balanced with no statistically significant difference between the 2 arms (table 1).

Prostate Specific Antigen and Testosterone Response

Median prostate specific antigen declined to 0.8 ng/ml after 3 months of ADT and further declined to 0.07 ng/ml at 12 months. Castration (testosterone levels less than 20 ng/dl) was achieved within 3 months in 92.5% of patients and 96% by 12 months. The prostate specific antigen response and the testosterone decrease was equal in the 2 arms (supplementary material, https://www.jurology.com).

Endothelial Function

As measured by the EndoPAT 2000, endothelial function did not differ between the treatment arms at 12 months of ADT (mean $\pm$ SD RHI 2.07 $\pm$ 0.15 vs 1.92 $\pm$ 0.11, $p=0.42$). The RHI did not differ between the 2 arms at baseline or at 6 or 12 months of ADT treatment (ANCOVA $p = 0.45$, table 2).

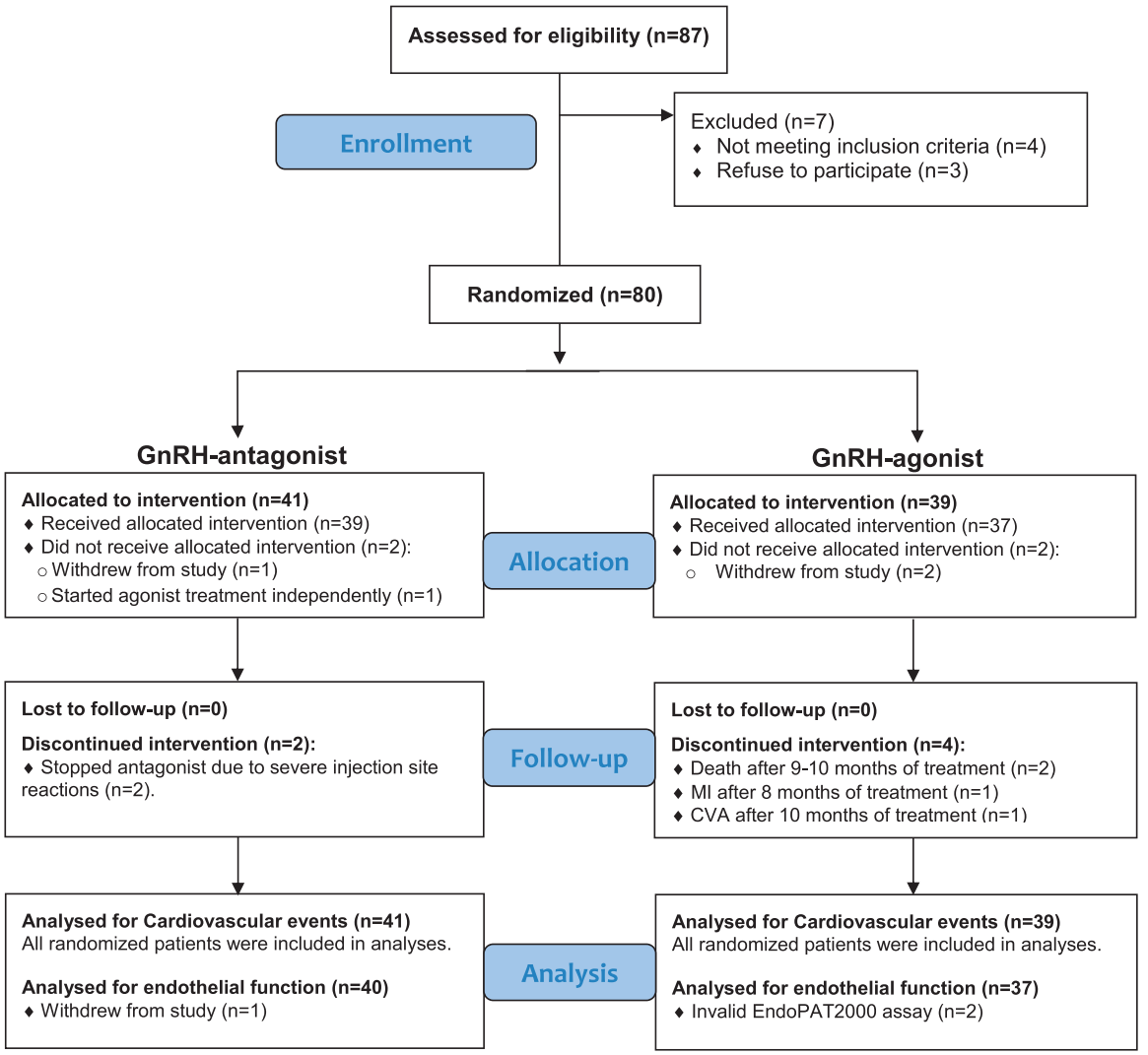

Figure 1. Enrollment, randomization and followup. Subjects were stratified by RHI greater than 1.765 vs 1.765 or less and cancer metastasis status at trial entry and randomly assigned in 1:1 ratio to receive GnRH antagonist or agonist for 12 months.

Events

Cardiovascular. A new CVE developed in 15 patients (19%) (table 3). Of the patients randomized to GnRH agonist 13 (33%) experienced a CVE compared to 2 (5%) of those randomized to GnRH antagonists ($p=0.001$, table 3). Table 4 shows a detailed list of events.

Major Cardiovascular and Cerebrovascular. Nine CVEs were considered MACCEs, including death in 2 patients, MI in 1, CVA in 2 and percutaneous angioplasty with coronary stent insertion in 4 (table 3). As reported in the death certificate the cause of death was CVA in 1 patient, and prostate cancer and ischemic heart disease in 1. Eight patients (20%) randomized to GnRH agonist experienced a MACCE compared to 1 (3%) randomized to GnRH antagonists ($p=0.013$, table 3). At 12 months the absolute risk reduction of MACCE associated with GnRH antagonist was 18.1% (95% CI 4.6–31.2).

Time

Median time to any CVE was 8.8 months (IQR 3.4–10.8). Median time to MACCE was 9.7 months (IQR 6.7–10.8). In subjects randomized to GnRH antagonist time to the first MACCE and time to any CVE were significantly delayed ($p=0.013$ and 0.001, respectively, fig. 2).

Cardiac Biomarkers

A priori we decided to complement the analysis of cardiac outcomes by measuring serum levels of 4 well-known cardiac biomarkers, including hsTn, CRP, D-dimer and NTproBNP. Baseline levels of biomarkers were similar in the 2 arms (supplementary material, https://www.jurology.com).

Baseline serum NTproBNP showed good discrimination for all CVEs and for MACCEs (AUC 0.77, 95% CI 0.64–0.91, $p=0.001$ and AUC 0.73, 95% CI 0.54–0.91, $p=0.03$, respectively, fig. 3,

Table 1. *Baseline participant characteristics*

	GnRH Agonist	GnRH Antagonist
No. pts	39	41
Median age (IQR)	71 (69–78)	72 (66–77)
Median kg/m^2 body mass index (IQR)	27.4 (25.1–29.1)	28 (25–29.9)
Median PSA (IQR)	9.5 (6.3–28)	11.42 (7–20.9)
No. International Society of Urological Pathology prostate biopsy grade group (%):		
3	14 (36)	19 (46)
4	10 (26)	11 (27)
5	15 (38)	11 (27)
No. prostate Ca status (%):		
Localized	29 (74)	30 (73)
Metastatic	10 (26)	11 (27)
No. baseline Ca treatment (%):		
ADT + radiation	31 (79)	33 (80)
ADT + chemotherapy	5 (13)	3 (7)
ADT alone	3 (8)	5 (12)
No. cardiovascular disease history (%):		
Myocardial infarction within 1 yr before randomization	15 (38)	15 (37)
Cerebrovascular condition	8 (21)	6 (15)
Ischemic heart disease	26 (67)	27 (66)
Peripheral vascular disease	2 (5)	4 (10)
No. comorbidity (%):		
Hypertension	29 (74)	29 (71)
Diabetes	15 (38)	10 (24)
Renal failure	1 (3)	3 (7)
No. smoking (%):		
Never	17 (44)	17 (41)
Past	16 (41)	18 (44)
Current	5 (13)	4 (10)
Unknown	1 (3)	2 (5)
Median No. total medications (IQR)	5 (4–8)	4 (3–7)
Median No. indications (IQR)	5 (3–5)	3 (3–5)
No. cardiovascular disease prevention drug (%):		
Statin	29 (74)	29 (71)
Antiplatelet	31 (79)	26 (63)
β-blocker	18 (46)	15 (37)
Angiotensin converting enzyme inhibitor	15 (38)	21 (51)

A and *B*). Baseline D-dimer, hsTn and CRP did not predict CVEs or MACCEs (supplementary material, https://www.jurology.com).

On repeated measures analysis we found that NTproBNP levels differed with time in patients with vs without a CVE. NTproBNP levels remained stable during the study period among patients without a CVE or MACCE but they increased among patients with an event (MACCE and all CVEs p =0.03 and 0.014, respectively, fig. 3, *C* and *D*). As most CVEs and MACCEs occurred between 6 and 12 months, the NTproBNP levels peaked at that time and declined thereafter. Changes in D-dimer, hsTn and CRP levels were not associated with CVEs or MACCEs (supplementary material, https://www.jurology.com).

DISCUSSION

To our knowledge our study is the first to provide prospectively collected cardiovascular outcomes in patients with prostate cancer who had preexisting CVD and were started on ADT. While we did not observe a change in endothelial function, we clearly detected a high incidence of CVEs within year 1 of ADT initiation. The prespecified analysis revealed that during year 1 of ADT a new CVE developed in 22.5% of patients. Most importantly, the incidence of these CVEs differed significantly between the study arms. The incidence rate of all CVEs and of MACCEs was significantly higher among patients randomized to GnRH agonists compared to GnRH antagonists. The absolute increased risk of MACCE was 18.1%.

Our secondary outcome analysis met the criteria to assess the credibility of a secondary outcome effect.[17] The hypothesis and the direction of the effect

Table 2. *Endothelial function measured by EndoPAT 2000 RHI*

	GnRH Agonist	GnRH Antagonist	p Value (2-sided Student t-test)
No. pts	37	40	—
Mean ± SE baseline	1.92 (0.09)	1.9 (0.08)	0.81
Mean ± SE 6 Mos	2.08 (0.09)	2.0 (0.09)	0.54
Mean ± SE 12 Mos*	2.07 (0.15)	1.92 (0.11)	0.42

* ANCOVA = 0.45 adjusted for baseline.

Table 3. *CVEs and MACCEs by study arm*

	GnRH Agonist	GnRH Antagonist	p Value (log-rank test)
No. CVEs and MACCEs:*			—
Pts	39	41	
Death	2	—	
Myocardial infarction	1	—	
Cerebrovascular accident	2	—	
Heart catheterization with stent	3	1	
Cardiac related emergency room visits	5	1	
Total No. (%):			
CVEs	13 (33.3)	2 (4.8)	0.001
MACCEs	8 (20.5)	1 (2.4)	0.013

* Cardiovascular related events included death, myocardial infarction, cerebrovascular accident, transient ischemic attack, heart catheterization with or without intervention and cardiac related hospitalization, and MACCEs included death, myocardial infarction, cerebrovascular accident and heart catheterization with stent.

were specified a priori, only a few hypotheses were tested and the effect was independent of other assessed variables. The combined analyses of all CVE, MACCE and biomarker analyses consistently demonstrated that ADT with GnRH antagonist resulted in significantly fewer CVEs and associated changes in serum NTproBNP levels compared to ADT with GnRH agonists.

Retrospective analyses also support a better cardiovascular safety profile for GnRH antagonist.[18] Albertsen et al performed a post hoc analysis of randomized trials comparing GnRH agonist and GnRH antagonist.[7] They reported that degarelix was associated with half the number of cardiac events compared with GnRH agonists. Notably Albertsen et al also reported CVEs in 14.7% of subjects in year 1 of GnRH agonist use, an event rate comparable to our results.

Other retrospective studies did not reveal a significant difference in the CVD outcome between GnRH antagonists and agonists.[8] This discrepancy could be attributable to the population included in study. In the series by Albertsen et al men who were most prone to CVEs and in whom the cardiovascular safety profile of GnRH antagonists and agonists varied significantly were those with preexisting CVD but not those without CVD.[7] We now provide prospective evidence from a randomized study supporting a reduced risk for a MACCE within 1 year of ADT using GnRH antagonist in patients with prostate cancer who have preexisting CVD.

The potential mechanistic role of ADT in promoting CVEs is unclear.[19] We designed our study to test the effect of ADT on endothelial function. The endothelium is the largest organ system in the body

Table 4. *Cardiovascular related events*

Event (description)	Days to Event
GnRH agonist	
Death:	
Cardiovascular accident	303
Prostate Ca + ischemic heart disease	293
Myocardial infarction (hospital admission due to chest pain, electrocardiogram changes, elevated troponin, refused percutaneous transluminal coronary angioplasty)	260
Cardiovascular accident:	
Hospital admission due to lt hemiparesis, cardiovascular accident confirmed by computerized tomography, magnetic resonance imaging + neurologist	340
Hospital admission due to rt hemiparesis, cardiovascular accident confirmed by computerized tomography and neurologist	312
Heart catheterization with stent:	
Admitted to hospital due to unstable angina, referred to emergent percutaneous transluminal coronary angioplasty, which revealed occlusion of 2 coronary vessels, underwent drug eluting stent insertion to distal lt anterior descending coronary artery, mid to distal lt anterior descending coronary artery, ostial intermediate	248
Underwent elective percutaneous transluminal coronary angioplasty due to stable angina, diagnosed with obtuse marginal artery occlusion, underwent percutaneous transluminal coronary angioplasty with drug eluting stent	148
Underwent elective percutaneous transluminal coronary angioplasty due to stable angina, diagnosed with occlusion in diagonal + mid lt anterior descending coronary artery, underwent percutaneous transluminal coronary angioplasty with drug eluting stent	294
Cardiac related emergency room visits:	
Admitted to hospital due to 2 consecutive syncope episodes	1
Admitted to hospital due to bradycardia	82
Admitted to emergency room due to chest pain, not hospitalized, cardiac dipyridamole spectroscopy demonstrated lt distal coronary artery ischemia, refused heart percutaneous transluminal coronary angioplasty	322
Admitted to hospital due to dyspnea + severe heart failure, diagnostic heart catheterization revealed 50% occlusion proximal-mid lt anterior descending coronary artery, 70% distal lt anterior descending coronary artery, 70% proximal circumflex artery	156
Admitted to hospital due to dyspnea + chest pain, no change from baseline on echocardiography but carotid Doppler showed 90% lt carotid artery occlusion	307
GnRH antagonist	
Heart catheterization with stent (admitted to hospital due to unstable angina, referred to emergency percutaneous transluminal coronary angioplasty, which revealed occlusion of 2 coronary vessels, underwent drug eluting stent insertion to distal lt anterior descending coronary artery, mid to distal rt coronary artery)	169
Ca related emergency room visits (admitted to hospital due to dyspnea, diagnosed with new cardiac related atrial fibrillation)	1

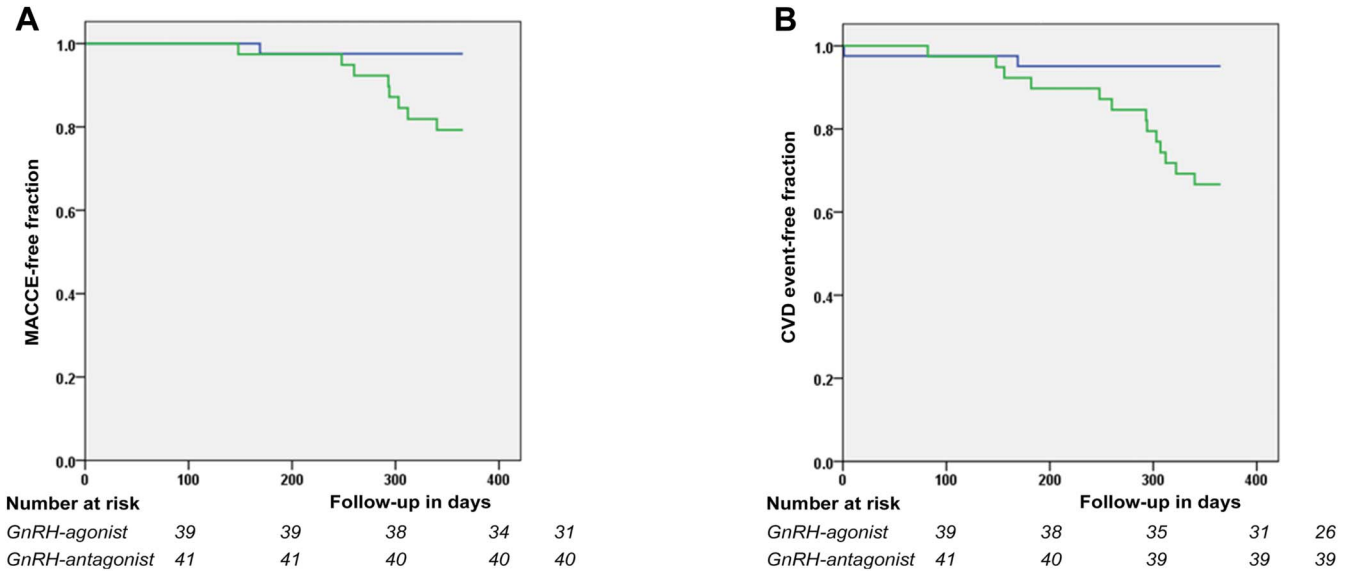

Figure 2. Kaplan-Meier estimated time to first events in GnRH antagonist (blue curve) and agonist (green curve) arms. *A,* MACCE-free followup (log rank test p=0.013). *B,* CVE-free followup (log rank test p=0.001).

and it is essential to normal vascular wall homeostasis. One of the earliest indicators of cardiovascular impairment is endothelial dysfunction.[9,20]

Our cohort consisted of men with a history of CVD, which was demonstrated in the severe endothelial dysfunction measured at baseline in 48% of the trial population.[21] This may have resulted in the null effect of ADT on the primary outcome, which was changes in endothelial function. However, the selected population was enriched with patients at high risk for CVEs. Thus, despite the modest sample size a clinically and statistically significant effect on cardiac outcome was achieved.

The most obvious link between ADT and CVEs is low testosterone, which causes metabolic changes similar to those of metabolic syndrome, including low high density lipoprotein cholesterol, hypertriglyceridemia and insulin resistance.[22] However, in our study castrate levels of testosterone were achieved equally by GnRH agonists and GnRH antagonists.

Acute CVEs such as MI and CVA are caused by plaque instability and rupture.[23] Although plaque stability was beyond the scope of this study, it may explain the observed differences between GnRH agonist and antagonist. Plaque rupture is mediated by infiltrating macrophages releasing matrix degrading proteases.[24] These macrophages are recruited by T-helper 1 cells, which express GnRH receptors.[25] Activation of these receptors by GnRH agonist may promote plaque destabilization.[26]

GnRH antagonists suppress LH and follicle-stimulating hormone as opposed to GnRH agonists, which predominantly suppress LH. Follicle-stimulating hormone receptors expressed on endothelial cells may regulate endothelial cell function, which may increase the CVD risk.[27] In our study we did not observe a difference in endothelial function.

Brain natriuretic peptide is a hormone which regulates myocardial function. NTproBNP was reported to be a significant cardiac biomarker.[28] In our study baseline NTproBNP was predictive of MACCE. Moreover, on repeated measures analyses NTproBNP levels differed among subjects with a cardiac event. NTproBNP levels continuously increased and reached maximal levels at 6 months in men with a CVE or a MACCE, corresponding to median CVE and MACCE time. In contrast, NTproBNP remained stable in patients without a CVE. These analyses further contribute to the credibility of the cardiovascular outcomes in our series.

Our study has several limitations. It was a phase II study and included only 80 subjects. The primary end point of endothelial function was negative and the main findings of CVEs were secondary outcomes. Thus, our results must be further confirmed in a large-scale trial. The similar phase III PRONOUNCE study (A Trial Comparing Cardiovascular Safety of Degarelix Versus Leuprolide in Patients with Advanced Prostate Cancer and Cardiovascular Disease, ClinicalTrials.gov NCT02663908) was recently launched.

The generalizability of our findings may be hampered because we included only patients with preexisting CVD. However, about 30% of men with

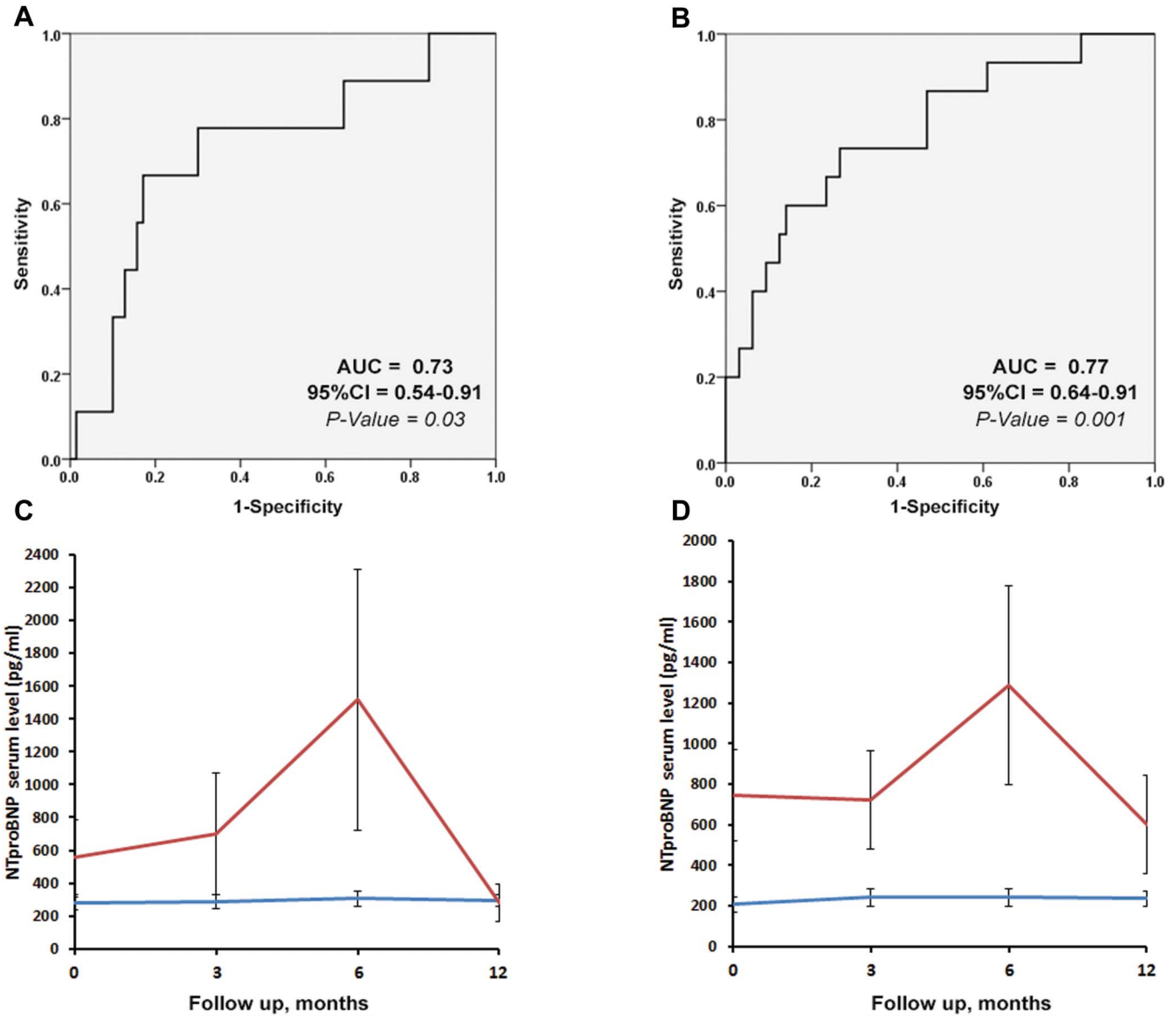

Figure 3. *A* and *B*, ROC curve analysis of baseline serum NTproBNP in all randomized subjects. Blue curve indicates no event. *A*, MACCE. *B*, all CVEs. *C* and *D*, repeated measures analysis of NTproBNP at baseline, and at 3, 6 and 12 months of treatment using conservative F-test for interaction between time and CVE, and F-test Greenhouse-Geisser correction to adjust degrees of freedom for deviation from sphericity. *C*, stratified by MACCE (red curve) (p=0.03). *D*, stratified by all CVEs (red curve) (p=0.014).

advanced prostate cancer also have preexisting CVD and many others have CVD risk factors.[29] In this open label study patients and study personnel were aware of the treatment allocation. However, the study was designed to look at cardiovascular side effects and not treatment effects. All CVEs were treated by medical personnel blinded to study outcomes. MACCEs were adjudicated by an expert cardiologist who was blinded to treatment allocation. All analyses were performed in intent to treat fashion and no patient was lost to followup during the study period.

While accounting for these limitations, we clearly found that a high proportion of MACCEs may be prevented. ADT was clinically mandated in all of our patients due to prostate cancer characteristics. However, GnRH antagonists reduced the risk of a MACCE.

CONCLUSIONS

ADT did not alter endothelial function in patients with prostate cancer who had preexisting CVD but it was associated with a high incidence of CVEs. Patients treated with GnRH antagonist had significantly fewer CVEs within the first year of ADT compared to those treated with GnRH agonist. These results are now being tested in the larger, phase III PRONOUNCE study.

REFERENCES

1. Shahinian VB, Kuo YF and Gilbert SM: Reimbursement policy and androgen-deprivation therapy for prostate cancer. N Engl J Med 2010; **363:** 1822.
2. Hu JC, Williams SB, O'Malley AJ et al: Androgen-deprivation therapy for nonmetastatic prostate cancer is associated with an increased risk of peripheral arterial disease and venous thromboembolism. Eur Urol 2012; **61:** 1119.
3. Jespersen CG, Nørgaard M and Borre M: Androgen-deprivation therapy in treatment of prostate cancer and risk of myocardial infarction and stroke: a nationwide Danish population-based cohort study. Eur Urol 2014; **65:** 704.
4. FDA Drug Safety Communication: Update to Ongoing Safety Review of GnRH Agonists and Notification to Manufacturers of GnRH Agonists to Add New Safety Information to Labeling Regarding Increased Risk of Diabetes and Certain Cardiovascular Diseases. 2010. Available at https://www.fda.gov/Drugs/DrugSafety/ucm229986.htm. Accessed July 17, 2018.
5. Nguyen PL, Je Y, Schutz FA et al: Association of androgen deprivation therapy with cardiovascular death in patients with prostate cancer: a meta-analysis of randomized trials. JAMA 2011; **306:** 2359.
6. Klotz L, Boccon-Gibod L, Shore ND et al: The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. BJU Int 2008; **102:** 1531.
7. Albertsen PC, Klotz L, Tombal B et al: Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. Eur Urol 2014; **65:** 565.
8. Scailteux LM, Vincendeau S, Balusson F et al: Androgen deprivation therapy and cardiovascular risk: no meaningful difference between GnRH antagonist and agonists—a nationwide population-based cohort study based on 2010-2013 French Health Insurance data. Eur J Cancer 2017; **77:** 99.
9. Quyyumi AA: Endothelial function in health and disease: new insights into the genesis of cardiovascular disease. Am J Med, suppl., 1998; **105:** 32S.
10. McCrea CE, Skulas-Ray AC, Chow M et al: Test-retest reliability of pulse amplitude tonometry measures of vascular endothelial function: implications for clinical trial design. Vasc Med 2012; **17:** 29.
11. Bonetti PO, Pumper GM, Higano ST et al: Noninvasive identification of patients with early coronary atherosclerosis by assessment of digital reactive hyperemia. J Am Coll Cardiol 2004; **44:** 2137.
12. Rubinshtein R, Kuvin JT, Soffler M et al: Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. Eur Heart J 2010; **31:** 1142.
13. U.S. Food and Drug Administration: Guidance for Industry. Diabetes Mellitus Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. 2008. Available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf. Accessed September 12, 2018.
14. Hijazi Z, Oldgren J, Siegbahn A et al: Biomarkers in atrial fibrillation: a clinical review. Euro Heart J 2013; **34:** 1475.
15. Matsuzawa Y, Sugiyama S, Sumida H et al: Peripheral endothelial function and cardiovascular events in high-risk patients. J Am Heart Assoc 2013; **2:** e000426.
16. Evans S, Royston P and Day S: Minim: Allocation by Minimisation in Clinical Trials, version 1.5. Available at http://www-users.york.ac.uk/~mb55/guide/minim.htm. Accessed September 27, 2018.
17. Freemantle N: Interpreting the results of secondary end points and subgroup analyses in clinical trials: should we lock the crazy aunt in the attic? BMJ 2001; **322:** 989.
18. Smith MR, Klotz L, van der Meulen E et al: Gonadotropin releasing hormone blockers and cardiovascular disease risk: analysis of prospective clinical trials of degarelix. J Urol 2011; **186:** 1835.
19. Zareba P, Duivenvoorden W, Leong DP et al: Androgen deprivation therapy and cardiovascular disease: what is the linking mechanism? Ther Adv Urol 2016; **8:** 118.
20. Poredos P: Endothelial dysfunction and cardiovascular disease. Pathophysiol Haemost Thromb 2002; **32:** 274.
21. Syvänen K, Korhonen P, Partanen A et al: Endothelial function in a cardiovascular risk population with borderline ankle-brachial index. Vasc Health Risk Manag 2011; **7:** 97.
22. Brand JS, van der Tweel I, Grobbee DE et al: Testosterone, sex hormone-binding globulin and the metabolic syndrome: a systematic review and meta-analysis of observational studies. Int J Epidemiol 2011; **40:** 189.
23. Hansson GK: Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005; **352:** 1685.
24. Kolodgie FD, Virmani R, Burke AP et al: Pathologic assessment of the vulnerable human coronary plaque. Heart 2004; **90:** 1385.
25. Hansson GK and Hermansson A: The immune system in atherosclerosis. Nat Immunol 2011; **12:** 204.
26. Tanriverdi F, Gonzalez-Martinez D, Hu Y et al: GnRH-I and GnRH-II have differential modulatory effects on human peripheral blood mononuclear cell proliferation and interleukin-2 receptor gamma-chain mRNA expression in healthy males. Clin Exp Immunol 2005; **142:** 103.
27. Crawford ED, Schally AV, Pinthus JH et al: The potential role of follicle-stimulating hormone in the cardiovascular, metabolic, skeletal, and cognitive effects associated with androgen deprivation therapy. Urol Oncol 2017; **35:** 183.
28. Schouten O, Hoeks SE, Goei D et al: Plasma N-terminal pro-B-type natriuretic peptide as a predictor of perioperative and long-term outcome after vascular surgery. J Vasc Surg 2009; **49:** 435.
29. Pinthus JH, Klotz L, Lukka H et al: Cardiovascular disease characteristics of newly diagnosed prostate cancer patients: findings from the pilot phase of RADICAL PC: a prospective study of cardiovascular disease in men with prostate cancer (abstract MP14-04). J Urol, suppl., 2017; **197:** e163.

EDITORIAL COMMENT

In this randomized phase II study the authors report that of men with preexisting CVD those treated with a LH releasing hormone agonist had significantly more MACCEs than men treated with a LH releasing hormone antagonist (20% vs 3%). There are 2 important issues. The first is the increased MACCE rate in men on ADT and the second is the cause or causes. We have known for years that men on ADT have a higher rate, especially when they have preexisting CVD (reference 4 in article). There has been recent speculation as to the etiology of these increased risks. Several retrospective studies as well as this current prospective trial suggest that MACCEs are more prevalent with

agonists than antagonists. This could be secondary to variations in follicle-stimulating hormone levels and other factors.

There are a number of challenges in this study, the most significant being that this is a small, randomized, phase II trial and not a phase III trial. Many biostatisticians believe that it is not appropriate to compare the arms of phase II trials. The selection of men with a CVD history enriches the study for events so that this study does not apply to men without preexisting CVD. Other issues relate to twice as many patients with diabetes in the agonist arm, which could have influenced the findings. Were the men with a MACCE highly represented because of this imbalance? Also, it is not clear how well these men with known CVD were treated in the study. The authors report similar use of agents to control lipids, blood pressure and coagulation but not how well. Stay tuned—I believe that there may be an association between the type of ADT and MACCEs but we need definitive evidence.

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REPLY BY AUTHORS

To our knowledge this is the first prospective evidence of the link between ADT and cardiovascular events. In this phase II study we found that among patients with preexisting CVD a simple choice between 2 equally effective therapies may affect cardiovascular outcomes.

We acknowledge that more confirmation is needed in a larger scale clinical study and it is necessary to determine the mode of action. Our group is already working on proteomic analyses of the biobank samples collected during the study to help unveil some underlying biological processes. In addition, the larger, phase 3 PRONOUNCE study is under way, which may provide definitive clinical data. In the meantime we believe that the accumulating evidence from retrospective data (reference 7 in article) and now our prospective data are consistent. All suggest an advantage for GnRH antagonist, at least in patients with preexisting CVD.

We cautiously recommend that men with prior CVD should be informed of these data before commencing ADT. After all, various lines of evidence, although yet not level 1, point to a similar direction, so why take the risk?