Cardiac Biomarkers and Geriatric Assessment in Metastatic Castrate-Resistant Prostate Cancer During Abiraterone Acetate Therapy—A Cardio-Oncology Study

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Abstract

Background: Abiraterone acetate (AA) is a drug used in advanced prostate cancer. However, known clinical factors with predictive and prognostic value are scarce. This study evaluated cardiovascular (CV) factors and geriatric scales as potential markers of superior response during AA therapy.

Methods: This is a prospective observational study. Serum levels of high sensitivity troponin T (hsTnT), D-dimer, NT-proBNP and left ventricle ejection fraction (LVEF) were used for CV evaluation. Questionnaires of G8, VES-13, Activities of Daily Living (ADL), Instrumental Activities of Daily Living (iADL), and Geriatric Depression Scale (GDS) were included in the geriatric screening assessment. All measures were taken before AA initiation. Survival curves and Cox proportional hazard models (univariate and multivariate) were used to determine the predictors for a longer time to treatment failure (TTF).

Results: Forty nine patients were included in the study. Overall median TTF was 7.9 months (95% CI: 5.9-12.4). In univariate analysis, factors associated with inferior TTF were (P-value < .05): visceral metastases - HR 2.34; 95% CI: 1.24-4.45, history of coronary artery disease - HR 3.02; 95% CI: 1.19-7.66; LVEF < 50% - HR 2.53; 95% CI: 1.03-6.17; P = .041; age-adjusted D-dimer > upper reference limit (URL) - HR 2.3; 95% CI: 1.13-4.16; P = .016; NT-proBNP ≥ 300 pg/mL - HR 2.3; 95% CI: 1.22-4.34; P = .01; G8 score ≤ 14 points - HR 2.47; 95% CI: 1.29-4.74; P = .007. In multivariate analysis, age-adjusted D-dimer > URL, G8 score ≤ 14 points and visceral metastases remained statistically significant in prediction of inferior TTF. The number of these factors was associated with shorter median TTF: 0-1 factor – 14.1 months; 2 factors – 5.9 months; 3 factors – 2.7 months; P < .001, log-rank).

Conclusions: Age-adjusted D-dimer, and geriatric G8 scores may predict TTF in men with metastatic castration-resistant prostate cancer during AA therapy. These observations require further study in a larger population.

Keywords
abiraterone, biomarker, cardio-oncology, cardiovascular disease, D-dimer, geriatric, prostate cancer, troponin

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Introduction
According to recent epidemiological studies, prostate cancer (PCa) is the most prevalent malignancy in men. Although the disease is mainly diagnosed at an early stage, ~7-10% of men have metastases at diagnosis and require palliative treatment. The current armamentarium for metastatic PCa includes several drugs, and abiraterone acetate (AA) is one of the options. In a metastatic setting, AA has proven overall survival (OS) benefits. Nevertheless, there is an ongoing debate on which groups of patients may benefit most from AA, maximizing therapeutic effect and reducing the risks of its complications, of which cardiovascular (CV) toxicities are a significant threat. AA therapy risks inducing or exacerbating, eg, ischemic heart disease, atrial fibrillation or hypertension. Therefore, AA is an interesting subject for cardio-oncology scientific investigation.

A part of modern oncologic research is carried out to establish predictive and prognostic factors in terms of clinical outcomes, eg, drugs’ toxicity or patients’ survival. One of such tools is the use of serum biomarkers. They may aid clinicians in determining distinct subpopulations of patients, who may benefit most from specific therapies, and thus help make conscious treatment decisions. CV biomarkers, especially high sensitivity troponins, NT-pro-B-type natriuretic peptide (NT-proBNP) or D-dimer, may play a role here as they are easy, inexpensive, and the results are readily available. Troponins are regulatory proteins of cardiomyocytes and are the mainstay of cardiac injury diagnosis. Troponin has an undeniable value in diagnosing acute coronary syndromes. Nevertheless, there is increasing data on the prognostic role in other CV diseases, eg pulmonary embolism, heart failure, or atrial fibrillation or even in healthy individuals. NT-proBNP is converted from B-type natriuretic peptide secreted mainly by cardiomyocytes in response to myocardial stretch and stress. It has a significant prognostic value in heart failure, however, it may also help in death-risk assessment in patients with other unstable CV diseases. D-dimer is widely used in diagnosing venous thromboembolic disease. However, the usefulness of this biomarker may be broader and extend to other cardiac disease entities, eg as a predictor of higher mortality rate in patients with cardiac ischemia. These biomarkers are of particular interest in cardio-oncology research, but their value in metastatic PCa is scarce.

PCa incidence is closely related to age, with the highest prevalence among men aged >65 years. Frailty is an age-related syndrome associated with patients’ increased physical and mental limitations. It carries a high risk of complications following medical interventions. Comprehensive geriatric assessment is a multidimensional tool that defines the health and well-being of the elderly and helps identify frail patients. Since this assessment is time-consuming, the International Society of Geriatric Oncology recommends using screening questionnaires such as G8 or VES-13. Whether these tools are predictive for better clinical outcomes during AA therapy is an open question as no prospective trials address this issue.

To fill the gaps in knowledge, we present the prospective evaluation of the role of serum cardiac biomarkers and geriatric assessment on AA treatment.

Material and Methods
Overview
The prospective observational study included metastatic castration-resistant prostate cancer (mCRPC) patients receiving AA with prednisone before or after chemotherapy with docetaxel. Consecutive patients who agreed to participate were included between 01.03.2018 and 31.03.2021. Men received abiraterone acetate 1000 mg daily with 10 mg of oral prednisone. Signed informed consent for study participation was obtained from every individual. The Bioethical Committee at the Centre of Postgraduate Medical Education in Poland approved the study protocol (Resolution Number 83/PB/2016, date of approval 16 Nov 2016). The study was performed in accordance with the Declaration of Helsinki. Every patient signed informed consent for the treatment and data collection.

Patients
Every patient had pathological confirmation of prostate adenocarcinoma, radiologic evidence of metastases, and disease progression to mCRPC. The disease progression was defined as prostate-specific antigen (PSA) progression or radiographic disease progression in the skeletal system or soft tissues with or without the rise of PSA. All patients received androgen deprivation therapy (surgical or pharmacological). Castration was achieved if the serum testosterone level was ≤50 ng/dL (≤1.7 nmol/L). Every patient had Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 (with “0” if the patient was fully active and able to maintain all pre-cancer activities and “1” indicating that the patient has limited ability for strenuous physical activity but can carry out work of a light or sedentary nature. Both pre and post-chemotherapy patients were eligible. Every patient had no unstable CV disease or significant liver dysfunction (only Child-Pugh class A was eligible). Previous AA, enzalutamide or ketoconazole therapy was not allowed.

Clinical Measurements and Endpoint
The study’s primary endpoint was the time to treatment failure (TTF), described as the time between the start of AA therapy to its cessation (defined as the cancer progression, unaccepted toxicity, hypersensitivity to the drug or the patient’s death).

Criteria for PCa Progression Were
I. the presence of at least two of three types of progression:

1. Increase of PSA 
2. New appearance of metastasis
3. Increase in pain intensity
4. Increase of tumor volume
5. Progression of disease by radiographic assessment
6. Increase in markers of disease progression

On the day of the follow-up visit, every patient had pathological confirmation of prostate adenocarcinoma, radiologic evidence of metastases, and disease progression to mCRPC. The disease progression was defined as prostate-specific antigen (PSA) progression or radiographic disease progression in the skeletal system or soft tissues with or without the rise of PSA. All patients received androgen deprivation therapy (surgical or pharmacological). Castration was achieved if the serum testosterone level was ≤50 ng/dL (≤1.7 nmol/L). Every patient had Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 (with “0” if the patient was fully active and able to maintain all pre-cancer activities and “1” meaning that the patient has limited ability for strenuous physical activity but can carry out work of a light or sedentary nature. Both pre and post-chemotherapy patients were eligible. Every patient had no unstable CV disease or significant liver dysfunction (only Child-Pugh class A was eligible). Previous AA, enzalutamide or ketoconazole therapy was not allowed.
(1) Clinical - pain exacerbation (inclusion of a new opioid for more than two weeks), or the occurrence of a skeletal-related event or worsening of the patient’s performance status to at least Grade 2 (WHO classification).
(2) Radiological - the occurrence of at least two new metastases in bone scintigraphy.
(3) Biochemical - PSA progression (three consecutive rises, evaluated at least in weekly intervals, with two of at least 50% from AA baseline).

II. Response Evaluation Criteria In Solid Tumors version 1.1 criteria were fulfilled (regardless of the aforementioned types of progression).

OS was defined as the time from AA initiation until the Patient’s death.

Several factors were evaluated:

- ECOG performance status score, Age, body-mass index, Gleason score, metastases location, initial PSA, testosterone and hemoglobin level at AA therapy initiation;
- CV comorbidities (ie, arterial hypertension, coronary artery disease, dyslipidemia, atrial fibrillation) and diabetes;
- Concomitant CV medications;
- The serum concentration of:
  - high sensitivity troponin T – hsTnT (ng/mL) – positive when > upper reference limit (URL) of 0.014 ng/mL.
  - NT-proBNP (pg/mL) – two values were considered positive: ≥125 and ≥300 pg/mL accordingly to ESC heart failure guidelines.25
  - D-dimer (μg/mL) and age-adjusted D-dimer > URL (defined by a formula: age × 0.01 μg/mL).26
- LVEF measured by a transthoracic echocardiogram (modified Simpson method).27
- Geriatric questionnaires - G8, VES13, Activities of daily living (ADL), instrumental activities of daily living (iADL), Geriatric Depression Scale (GDS).

Statistical Analysis

Stata® Software ver. 14.1 (StataCorp LLC) was used for statistical analysis. Nominal parameters were shown as a percentage frequency. Mean values with standard deviations and medians were used in normally and not normally distributed values, respectively. The $\chi^2$ test for categorical variables (Fisher exact test for groups less than 5), the independent t-test for continuous, normally distributed variables and the Mann-Whitney U for non-normally distributed variables were used for comparisons between the groups. Survival curves and the Cox proportional hazard model (univariate and multivariate) evaluated the predictors for more prolonged TTF during AA treatment. A level of $P < 0.05$ was recognized as statistically significant.

Results

Baseline Characteristics

The baseline characteristics of the patients are presented in Table 1. Forty-nine consenting patients were included in the study. Until the database lock (31st January 2022), eight patients (16.3%) were still receiving AA. The reason for AA termination were disease progression (24 patients), unacceptable toxicity (1 patient), and death (16 patients). There were no hypersensitivity reactions to AA.

Time to Treatment Failure

Overall median TTF (mTTF) was 7.9 months (95% CI: 5.9-12.4).

Cardiovascular evaluation. The summary of CV characteristics is presented in Table 2, section A.

Table 1. Baseline Characteristics of the Study Population.

| Characteristics                              | Value         |
|----------------------------------------------|---------------|
| Age (Median [IQR] - years)                   | 71 (67-79)    |
| $\geq$ 70 yr - no. (%)                       | 31 (63.3%)    |
| ECOG performance status                      |               |
| 0 - no. (%)                                  | 15 (30.6%)    |
| 1 - no. (%)                                  | 34 (69.4%)    |
| BMI (Median [IQR])                           |               |
| $\geq$ 25 - no. (%)                          | 41 (83.7%)    |
| PSA (ng/mL)                                  |               |
| Median (IQR)                                 | 29.15 (9.12-129) |
| $\geq$ 8 - no. (%)                           | 33 (63.3%)    |
| Testosterone (ng/dL)                         |               |
| Median (IQR)                                 | 11.5 (8.23-15) |
| Location of metastases                       |               |
| Bone only - no. (%)                          | 25 (51%)      |
| Visceral metastases +/- bones - no. (%)      | 24 (49%)      |
| Reason to start AA therapy                   |               |
| PSA progression - no. (%)                    | 19 (38.78%)   |
| Radiologic progression - no. (%)             | 9 (18.37%)    |
| Both - no. (%)                               | 21 (42.86%)   |
| Prior docetaxel therapy                      |               |
| Yes – no. (%)                                | 38 (77.55%)   |
| Reason to end AA therapy                     |               |
| Disease progression - no. (%)                | 24 (58.6%)    |
| Unacceptable toxicity - no. (%)              | 1 (2.4%)      |
| Death - no. (%)                              | 16 (39%)      |
| Hypersensitivity to AA - no. (%)             | 0 (0%)        |

IQR: interquartile range; ECOG: Eastern Cooperative Oncology Group; BMI: body mass index; PSA: prostate-specific antigen; AA: abiraterone acetate.
**Table 2.** Univariate Analysis of Cardiovascular, Geriatric and Oncological Factors in Terms of Time to Treatment Failure and Overall Survival.

| Characteristic | No. (%) | TTF P-value | OS P-value |
|----------------|---------|------------|------------|
| **A. Cardiovascular evaluation** | | | |
| No comorbidities | 9 (18.37%) | .234 | .149 |
| Hypertension | 35 (71.43%) | .948 | .643 |
| Atrial fibrillation | 13 (26.53%) | .542 | .469 |
| Dyslipidemia | 12 (24.49%) | .512 | .972 |
| Coronary artery disease | 6 (12.24%) | .015* | .170 |
| Diabetes | 6 (12.24%) | .599 | .961 |
| Heart failure | 5 (10.20%) | .134 | .261 |
| **B. Medications** | | | |
| >3 drugs | 35 (71.43%) | .263 | .001* |
| B-blocker | 30 (61.22%) | .280 | .111 |
| Asi | 29 (59.18%) | .745 | .952 |
| Aspirin | 18 (36.73%) | .279 | .404 |
| Statin | 15 (30.61%) | .747 | .487 |
| Metformin | 3 (6.12%) | .780 | .606 |
| **LVEF % - Median (IQR)** | 59 (55-63) | | |
| <50% – no. (%) | 6 (12.24%) | .041* | .100 |
| **D-dimer [ug/mL]** | | | |
| Median (IQR) | .735 (46-1.29) | | |
| >age-adj. URL – no. (%) | 23 (46.94%) | <.001* | .002* |
| **hs-TnT [ng/mL]** | | | |
| Median (IQR) | .011 (0.008-0.02) | | |
| ≥0.014 – no. (%) | 20 (43.48%) | .016* | .051 |
| **NT-proBNP [pg/mL]** | | | |
| Median (IQR) | 303.8 (119.1-875.9) | | |
| ≥125 – no. (%) | 35 (71.43%) | .139 | .144 |
| ≥300 – no. (%) | 25 (51.02%) | 0.01* | .037* |
| **G8 score** | | | |
| Median (IQR) | 14.25 (12.5-15) | | |
| ≤14 – no. (%) | 23 (47%) | .007* | .018* |
| Feeling worse than people at the same age – YES | 14 (28.57%) | .031* | .036* |
| **VES13 score** | | | |
| Median (IQR) | 3 (1-7) | | |
| ≥3 points | 26 (53.06%) | .303 | .642 |
| **ADL score** | | | |

(continued)
The most common comorbidity was hypertension (71.4%). Nine patients (18.4%) had no concurrent illnesses except PCa. In the univariate analysis, only patients with the diagnosis of ischemic heart disease had shorter TTF vs those without this disease – 5.8 vs 9.8 months (P = 0.015). The use of CV concomitant medications did not affect TTF. Median LVEF was 59%. Six patients had LVEF <50%, and the mTTF was statistically shorter than in men with LVEF ≥50% (3.9 vs 8.5 months; P = 0.034).

Median D-dimer concentration was 0.735 μg/mL (IQR: 0.46-1.29). Minimal value was 0.04 μg/mL and maximum was 28.76 μg/mL. Of 49 patients, 23 (46.9%) patients had age-adjusted D-dimer > URL. mTTF was statistically shorter in men with age-adjusted D-dimer > URL (5.8 months, 95% CI: 3.44-7.21) compared to those with D-dimer concentration below age-adjusted cut-off value (14.1 months, P < .001).

Median concentration of hsTnT was 0.011 ng/mL (IQR: 0.008-0.02). Minimal value was 0.004 ng/mL and maximal 0.069 ng/mL. hsTnT > URL was detected in 20 patients. mTTF in this group was 5.1 months (95% CI: 2.78-6.97). In men with hsTnT within normal range TTF was 12.1 months (95% CI: 7.87-14.51). This difference was statistically significant (0.016).

Median NT-proBNP concentration was 303.8 pg/mL (IQR: 119.05-875.85). There were no statistical differences between the normal and abnormal values (≥125 pg/mL) of NT-proBNP in terms of TTF. Men with value ≥300 pg/mL had statistically shorter TTF than patients with NT-proBNP <300 pg/mL (5.2 vs 12.1 months; P = 0.01).

In multivariate analysis, age-adjusted D-dimer remained statistically significant. NT-proBNP ≥300 pg/mL had a positive but not significant trend in the prediction of TTF (Table 3, section A).

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**Table 2.** (continued)

| Characteristic | No. (%) | TTF P-value* | OS P-value* |
|----------------|---------|--------------|-------------|
| Comorbidities  |         |              |             |
| Median (IQR)   | 6 (5-6) |              |             |
| ADL <5 – no (%)| 0 (0%)  | NA           | NA          |
| i-ADL <9 points| 12 (11-12)| .034*        | .109        |
| GDS score      |         |              |             |
| Median (IQR)   | 4 (2-7) | .799         | .991        |
| >4 points      | 19 (43.18%) |          |             |

| Site of metastases | No. (%) | TTF P-value* | OS P-value* |
|--------------------|---------|--------------|-------------|
| Bone only vs visceral ± bones - no (%) | 25 (51%) vs 24 (49%) | .009* | .001* |
| HR 2.34 (95% CI: 1.24-4.45) | | HR 3.1 (95% CI: 1.56-6.07) |

| PSA [ng/mL] | Nominal value | ≥29.15 – no (%) | .372 | .465 |
|-------------|---------------|-----------------|------|------|
| Site of metastases | 26 (53%) | .059 | .085 |

| Gleason score | No. (%) | TTF P-value* | OS P-value* |
|---------------|---------|--------------|-------------|
| <8 vs ≥ 8 – no (%) | 14 (29.8%) vs 33 (70.2%) | .681 | .488 |

| Hgb [14.0-16.0 g/dL] | No. (%) | TTF P-value* | OS P-value* |
|----------------------|---------|--------------|-------------|
| Median (IQR)         | 12.9 (11.1-13.5) | .337 | .333 |
| < Median – no (%)    | 19 (28.7%) | .148 | .153 |
| <14.0 – no (%)       | 33 (67.4%) |             |             |

| Progression at AA start | No. (%) | TTF P-value* | OS P-value* |
|-------------------------|---------|--------------|-------------|
| PSA or Radiographic vs both | 28 (57%) vs 21 (43%) | .789 | .625 |

# - the absence of the clinical characteristics is the reference value.

ASi: angiotensin system inhibitor; IQR: interquartile range; hs-TnT: high-sensitivity troponin T; HR: hazard ratio; ADL: The Activities of Daily Living scale; i-ADL: The Instrumental Activities of Daily Living scale; GDS: The Geriatric Depression Scale; PSA: prostate-specific antigen; ECOG: Eastern Cooperative Oncology Group; Hgb: hemoglobin; adj: adjusted; TTF: time to treatment failure; OS: overall survival; *-statistically significant.
Table 3. Cardiovascular (Model A), Geriatric (Model B) and Combined (Model C) Factors and Their Influence on TTF (Multivariate Analysis).

| Characteristic                  | HR    | 95% CI     | P-value* |
|---------------------------------|-------|------------|----------|
| A. Multivariate analysis of CV factors                      |       |            |          |
| Age-adjusted D-dimer > URL     | 3.12  | 1.49-6.55  | .003*    |
| hsTnT > URL                    | 1.82  | .86-3.83   | .115     |
| NT-proBNP ≥ 300 pg/mL          | 2.09  | .98-4.49   | .058     |
| EF <50%                        | 1.98  | .76-5.18   | .165     |
| B. Multivariate analysis of geriatric factors                  |       |            |          |
| G8 score ≤14                   | 2.23  | 1.09-4.54  | .027*    |
| i-ADL score <9 points          | 1.35  | .47-3.58   | .572     |
| C. Combined multivariate analysis of significant CV, geriatric and oncological factors |       |            |          |
| Age-adjusted D-dimer > URL     | 2.77  | 1.4-5.47   | .003*    |
| G8 score ≤14                   | 3.95  | 1.84-8.5   | <.001*   |
| Bone only vs visceral ± bones  | 2.28  | 1.13-4.6   | .021*    |

URL: upper reference limit; hsTnT: high-sensitivity troponin T; EF: ejection fraction; HR: hazard ratio; CI: confidence interval; CV: cardiovascular; i-ADL: Instrumental Activities of Daily Living.
* - statistically significant; # - the absence of the clinical characteristics is the reference value.

Geriatric evaluation. The summary of the geriatric evaluation is presented in Table 2, section B. The median G8 score was 14.25 points (IQR: 12.5-15). The minimum score was 6 points, and the maximum was 16 points. Twenty-three patients (47%) scored ≤14 points and mTTF in this group 5.6 months (95% CI: 3.37-8). Men with >14 points had a mTTF of 13.2 months (95% CI: 7.2-16.9). In univariate analysis, the relative risk of treatment termination was lower in the G8 >14 points vs ≤14 points (P = 0.007). Men who claimed “feeling worse than other people at the same age” had a higher risk of treatment termination vs those who felt equally or better than their contemporaries (5.6 vs 12.1 months; P = 0.031). The median VES13 score was 3 points (IQR: 1-7). The minimum score was 0 points, maximum 10 points. Twenty-six patients (53%) scored ≥3 points. There were no statistical mTTF differences between men with <3 and ≥3 points in VES13 questionnaire (P = 0.303). ADL score did not correlate with TTF (P = .623). None of the patients had a score of <5 points. The median i-ADL score was 11 points (IQR: 9-12). Eight men (16.3%) scored <9 points and in those group mTTF was 5.1 months (95% CI: 2.1-7.6). Patients who scored ≥9 points had mTTF of 8 months (95% CI: 6.5-13.8). The difference was statistically significant, P = .034). GDS score was not correlated with TTF. In multivariate analysis, only the G8 score remained statistically significant (Table 3, section B).

Patients who scored ≤14 vs >14 points in the G8 scale had statistically higher median values of hsTnT (0.018 vs 0.008 ng/mL, respectively, P < 0.001) and NT-proBNP (218 vs 585 pg/mL, respectively, P = 0.021). No statistical difference in median D-dimer concentration was noted between these groups.

Oncological evaluation. mTTF was 6.9 and 8.0 months in the pre-chemotherapy and post-chemotherapy groups, respectively (P = .738). ECOG performance scale score, Gleason score, serum PSA level (nominal values and median-dependent), type of progression, and hemoglobin level (median-dependent value and anemia of any grade) were not predictive for superior TTF (all P-values >.05). Patients with bone-limited disease vs those with visceral metastases had longer mTTF (18.6 vs 7.7 months, respectively; P = .009).

A multivariate combined analysis of CV, geriatric and oncological factors revealed that age-adjusted D-dimer > URL, G8 score ≤14, and the presence of bone-limited vs visceral metastases remained statistically significant (Table 3, section C).

There were no differences in mTTF between men with no or only one factor – 14.1 vs 13.8 months, respectively (P = .085). mTTF in men with two factors was 5.9 months. The presence of three factors was associated with mTTF of 2.7 months (Figure 1).

Table 4 presents causes for AA termination. There were no statistical differences between the prevalence of each cause of AA cessation in clinical groups (P = .096).

Overall Survival

Median OS was 11.4 months (95% CI: 8.8-15.5). At the time of database lock, 11 patients (22.4%) were still alive. Univariate analysis of CV, geriatric and oncological factors is presented in Table 2.

Discussion

Our study aimed to assess the usefulness of CV and geriatric evaluation as potential predictors for better AA response in men with mCRPC.

In oncology, the use of CV biomarkers to assess prognosis or prediction of treatment response is subject to debate. Currently, most data seem to come from breast cancer and hematological populations. For example, Cardinale et al performed serial measurements of hsT before, during and after cardiotoxic chemotherapy for breast cancer. They found that women with increased hsT levels had a higher risk of long-lasting left ventricle dysfunction. Similarly, NT-proBNP predicted treatment-induced cardiotoxicity and LVEF reduction among breast cancer patients or predicted postoperative atrial fibrillation occurrence rate after thoracic surgery.

In hematological malignancies, eg, acute myeloid leukemia, NT-proBNP was valuable in predicting response to chemotherapy and prognosis of overall survival. D-dimer may also have a clinical value. Ay et al. report that high D-dimer levels are correlated with poor overall survival and increased mortality in cancer patients. In addition, a decrease in D-dimer concentration in lung cancer after treatment initiation strongly predicted prolonged progression-free survival and overall survival. As study by Dai et al shows, D-dimer
concentration may indicate cancer aggressiveness as high values are associated with more advanced clinical stage and the presence of metastases. The importance of CV biomarkers in oncology was underlined in the Cardio-Oncology Study Group of the Heart Failure Association and the Cardio-Oncology Council of the European Society of Cardiology in their position paper, eg in baseline cardiac assessment and thus defining patients with high CV risk during anticancer therapy, or in detection of early cardiac injury. Nevertheless, no data regarding PCa is included there. In fact, to our knowledge, there are only two studies where hsT and NT-proBNP were assessed among men with PCa. Margel et al performed a post-hoc analysis of a study which focused on CV events in men during androgen deprivation therapy. The authors found that high NTproBNP and hsT levels were associated with the risk of cardiac complications. The second study strictly refers to AA treatment. Campora et al evaluated NTproBNP and hsT serum levels at baseline, at 1 and 3 months of therapy in 17 mCRPC patients. More CV events were reported in abnormal hsT and high NTproBNP groups. In our study we draw a different hypothesis that cardiac biomarkers may predict superior response of AA treatment. In our research, D-dimer turned out to be the only marker with prognostic value and to our knowledge this is the first report of such correlation among mCRPC men treated with AA. The explanation of this correlation remains unclear, however, there are several hypothesis eg, that cancer cells promote coagulation processes by invading and damaging endothelium or via platelet activation. Therefore, serum levels of coagulation markers are increased. In our study, although nonsignificant, a positive trend in NTproBNP and hsTnT merits further evaluation in large-scale clinical trials.

The uncertainty may arise what the most appropriate cut-off value of these biomarkers is. Regarding hsTnT evaluation, our study used a binary model (negative/positive) due to the narrow difference between the upper reference level and registered values (maximum was .069 ng/mL, ie less than five times the upper reference limit). When NTproBNP is considered, we analyzed two cut-off values suggested by the European Society

| Table 4. Reasons for Abiraterone Acetate Cessation According to Clinical Group. |
|---|---|---|---|---|---|
| TTF Reason | 0-1 | 2 | 3 | Total |
| Toxicity | 0 | 1 | 0 | 1 (2.4%) |
| Progression | 13 | 7 | 4 | 24 (58.6%) |
| Death | 3 | 9 | 4 | 16 (39%) |
| Total | 16 | 17 | 8 | 41 (100%) |

*Clinical factors: Age-adjusted D-dimer > URL; G8 score ≤14; Bone only vs visceral ± bones. TTF: time to treatment failure.
of Cardiology, ie ≥125 pg/mL and ≥300 pg/mL for chronic and acute heart failure URL's, respectively. In the prediction of TTF, the 300 pg/mL value was superior in our study. Regarding D-dimer levels, ESC acute pulmonary embolism guidelines suggest using the age-adjusted value in older populations, and this value had predictive value in our study. Based on our results, we recommend using the aforementioned cut-off values for further analyses among mCRPC patients. Our study also presents several important conclusions regarding the geriatric assessment of mCRPC patients before AA therapy. First, we found that a G8 score ≤14 points indicates shorter TTF, whereas the VES-13 questionnaire did not. This observation is consistent with the Society of Geriatric Oncology geriatric screening recommendation suggesting using the G8 rather than VES-13 scale in PCa. Previous studies have reported an interdependence between frailty syndrome and CV disease in the elderly. There is also data that hsTnT and NT-proBNP have a predictive value for developing frailty in the future. Our study found that men who scored less on the G8 scale had statistically higher concentrations of hsTnT and NT-proBNP. This observation implicates that the frailty syndrome and asymptomatic CV damage at a cellular level may be two interrelated processes. To our knowledge, no previous research addressed this issue in patients with active cancer. Our study has several strengths. It is a prospective study with strict inclusion/exclusion criteria and enrolled a very homogenous population. Every patient underwent a cardiology evaluation before AA. Therefore, men with uncontrolled CV diseases were not enrolled in the study. Biomarkers and echocardiography/electrocardiography examinations were performed in one dedicated laboratory. All baseline measurements were assessed before AA initiation. However, the study also has several limitations. Due to small study population we could not perform subanalyses of clinical factors and TTF components (death, progression, hypersensitivity or toxicity). Additionally, the study sample size was not pre-calculated. Another limitations include relatively short observation time, no periodic cardiac and geriatric re-evaluation and no focus on CV complications. The last but not least, we evaluated only all-cause mortality in our survival analysis.

Conclusions

Our study is the first to suggest that a combination of clinical factors of high concentration of D-dimer, positive frailty screening on the G8 scale and metastases location may have predictive value for TTF of AA therapy in men with mCRPC who are without or have stable CV diseases. Due to limitations, the results of this study merit further validation.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: MW reports receiving speaker fees from Bayer, Janssen, Amgen, and Pfizer; conference registration fees and travel grants from Bayer, Amgen, and Pfizer. IS reports receiving speaker fees from Bayer, Janssen, and Astellas; research grants (unrelated to this study) from Janssen and Astellas. SS reports lecture fees from Janssen (unrelated to this study). AWG and CS report no conflict of interest.

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Data Availability

The study data sets are not publicly available due to the Polish National Health Fund policy. Requests to access these datasets should be directed to the Corresponding Author.

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References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin. 2021;71:7-33.
2. Siegel DA. Prostate cancer incidence and survival, by stage and race/ethnicity—United States, 2001–2017. MMWR Morb Mortal Wkly Rep. 2020;69.
3. Parker C, Castro E, Fizazi K, et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31:1119-1134.
4. Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): Final overall survival analysis of a randomized, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2015;16:152-160.
5. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: Final overall survival analysis of the COU-AA-301 randomized, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2012;13:983-992.
6. Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. NEJM. 2017;377:352-360.
7. Wilk M, Waśko-Grabowska A, Szmit S. Cardiovascular complications of prostate cancer treatment. Front Pharmacol. 2020;11:555475.
8. Karlkova M, Topolcan O, Wolfe OTJ, Barak V, Zima T. Optimal use of biomarkers in oncology. BioMed Res Int. 2015;2015:423159.
9. Collinson P. Evidence and cost effectiveness requirements for recommending new biomarkers. EJIFCC. 2015;26:183-189.
10. Thygensen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Circ. 2018;138; e618-e651.
11. Collet J-P, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2021;42:1289-1367.

12. Bajaj A, Saleeb M, Rathor P, Sehgal V, Kabak B, Hosur S. Prognostic value of troponins in acute nonmassive pulmonary embolism: A meta-analysis. *Heart Lung*. 2015;44:327-334.

13. Aimo A, Januzzi JL, Vergaro G, et al. Prognostic value of high-sensitivity troponin T in chronic heart failure: An individual patient data meta-analysis. *Circ*. 2018;137:286-297.

14. Fan Y, Zhao X, Li X, Li N, Hu X. Cardiac troponin and adverse outcomes in atrial fibrillation: A meta-analysis. *Clin Chim Acta*. 2018;477:48-52.

15. van der Linden N, Klinkenberg LJJ, Bekers O, et al. Prognostic value of basal high-sensitive cardiac troponin levels on mortality in the general population: A meta-analysis. *Medicine (Baltim)*. 2016;95:e5703.

16. Daniels LB, Maisel AS. Natriuretic peptides. *J Am Coll Cardiol*. 2007;50:2357-2368.

17. Panagopoulou V, Deftereos S, Kossyvakis C, et al. NT-proBNP: An important biomarker in cardiac diseases. *Curr Top Med Chem*. 2013;13:82-94.

18. Kelly J, Rudd A, Lewis RR, Hunt BJ. Plasma D-dimers in the diagnosis of venous thromboembolism. *Ann Intern Med*. 2002;162:747-756.

19. Akgul O, Uyarel H, Pusuroglu H, et al. Predictive value of elevated D-dimer in patients undergoing primary angioplasty for ST elevation myocardial infarction. *Blood Coagul Fibrinolysis*. 2013;24:704-710.

20. Rawla P. Epidemiology of prostate cancer. *World J Oncol*. 2019;10:63-89.

21. Lin H-S, Watts JN, Peel NM, Hubbard RE. Frailty and postoperative outcomes in older surgical patients: A systematic review. *BMC Geriatr*. 2016;16:157.

22. Decoster L, Van Puyvelde K, Mohile S, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: An update on SIOG recommendations. *Ann Oncol*. 2015;26:288-300.

23. von Elm E, Altman DG, Begg C, et al. The strengthening the report statement: Guidelines for reporting observational studies. *Ann Intern Med*. 2007;147:573-577.

24. Oken MM, Creech RH, Torney DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:469-655.

25. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2021;42:3599-3726.

26. Douma RA, Gal G, Söhne M, et al. Potential of an age adjusted D-dimer cut-off value to improve the exclusion of pulmonary embolism in older patients: a retrospective analysis of three large cohorts. *BMJ*. 2010;340:c1475.

27. Dorosz JL, Lezotte DC, Weitzenkamp DA, Allen LA, Salledo EE. Performance of 3-dimensional echocardiography in measuring left ventricular volumes and ejection fraction. *J Am Coll Cardiol*. 2012;59:1799-1808.

28. Michel L, Mincu RI, Mahabadi AA, et al. Troponins and brain natriuretic peptides for the prediction of cardiotoxicity in cancer patients: A meta-analysis. *Eur J Heart Fail*. 2020;22:350-361.

29. Cardinale D, Sandri MT, Martinoni A, et al. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. *J Am Coll Cardiol*. 2000;36:517-522.

30. Blanas I, Martin-Pérez FJ, Garrido JM, Rodriguez-Serrano F. NT-proBNP as predictor factor of cardiotoxicity during trastuzumab treatment in breast cancer patients. *Breast*. 2020;54:106-113.

31. Cai G-L, Chen J, Hu C-B, Yan M-L, Xu Q-H, Yan J. Value of plasma brain natriuretic peptide levels for predicting postoperative atrial fibrillation: A systemic review and meta-analysis. *World J Surg*. 2014;38:51-59.

32. Graf I, Greiner G, Marculescu R, et al. NT-ProBNP as personalized medicine tool and new biomarker predicting response to chemotherapy and survival in AML. *Blood*. 2021;138:3435.

33. Ay C, Dunkler A, Pirker R, et al. High D-dimer levels are associated with poor prognosis in cancer patients. *Haematologica*. 2012;97:1158-1164.

34. Zaborowska-Szmot M, Kowalski DM, Piórek A, Krzakowski M, Szmot S. A decrease in D-dimer concentration and an occurrence of skin rash as iatrogenic events and complementary predictors of survival in lung cancer patients treated with EGFR tyrosine kinase inhibitors. *Pharmacol Rep*. 2016;68:1140-1148.

35. Dai H, Zhou H, Sun Y, et al. D-dimer as a potential clinical marker for predicting metastasis and progression in cancer. *Biomed Rep*. 2018;9:453-457.

36. Pudil R, Mueller C, Celutkiené J, et al. Role of serum biomarkers in cancer patients receiving cardiotoxic cancer therapies: A position statement from the Cardio-Oncology Study Group of the Heart Failure Association and the Cardio-Oncology Council of the European Society of Cardiology. *Eur J Heart Fail*. 2020;22:1966-1983.

37. Margel D, Ber Y, Peer A, et al. Cardiac biomarkers in patients with prostate cancer and cardiovascular disease receiving gonadotropin releasing hormone agonist vs antagonist. *Prostate Cancer Prostatic Dis*. 2021;24:177-185.

38. Campora S, Campazzi E, Zanardi S, et al. Association of biomarkers with serious cardiac adverse events during abiraterone acetate treatment in castration resistant prostate cancer. *Transl Oncol*. 2016;9:600-605.

39. Heit JA. Cancer and venous thromboembolism: Scope of the problem. *Cancer Control*. 2005;12(suppl 1):5-10.

40. Kohli M, Fink LM, Spencer JH, Zent CS. Advanced prostate cancer activates coagulation: A controlled study of activation
markers of coagulation in ambulatory patients with localized and advanced prostate cancer. *Blood Coagul Fibrinolysis*. 2002;13:1–5.

41. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Heart J*. 2020;41:543-603.

42. Boyle HJ, Alibhai S, Decoster L, et al. Updated recommendations of the International Society of Geriatric Oncology on prostate cancer management in older patients. *Eur J Cancer*. 2019;116:116-136.

43. Stewart R. Cardiovascular disease and frailty: What are the mechanistic links? *Clin Chem*. 2019;65:80-86.

44. Jia Y, Li D, Yu J, et al. Subclinical cardiovascular disease and frailty risk: The atherosclerosis risk in communities study. *BMC Geriatr*. 2022;22:321.