Heart failure is a common complication of advanced heart failure, with a prevalence of approximately 5% to 7% in patients with moderate heart failure and 10% to 15% in patients with severe heart failure. The 1-year survival rate for patients with heart failure is approximately 50%. The 5-year survival rate for patients with heart failure is approximately 25%. The 10-year survival rate for patients with heart failure is approximately 15%.

Androgen deprivation therapy (ADT), a hormone treatment, is recommended for advanced prostate cancer but is increasingly being used for localised prostate cancer treatment (Sharifi et al, 2005). In parallel, localised prostate cancer diagnosis has tremendously increased, reaching 90% in the United States, given the widespread prostate screening antigen (PSA) testing (Thompson et al, 2007). ADT lowers male hormone to castration testosterone levels within 3 weeks after treatment (Burton et al, 2013). Several randomised clinical trials suggest that radiation therapy plus ADT improves overall survival among patients with locally advanced disease (i.e., extracapsular or node positive) vs radiation therapy alone, but
findings remain controversial (Bolla et al, 1997, 2002, 2009; Horwitz et al, 2008). Despite certain benefits of ADT, it is associated with problematic side effects similar to those experiencing testosterone deficiency due to other causes, such as gynaecomastia and erectile dysfunction (Sharifi et al, 2005; Cattabiani et al, 2012; Nguyen et al, 2015). Additionally, androgen deficiency has been linked to cardiovascular disease (CVD) risk factors. For example, low bioavailable testosterone may increase atherosclerosis risk (Hak et al, 2002; Jones et al, 2005; Khaw et al, 2007). However, these studies mainly included much older men.

Conflicting evidence exists regarding the association between ADT and CVD, and prior studies have not been able to sufficiently adjust for a comprehensive set of confounders (Bolla et al, 2002; Keating et al, 2006; D’Amico et al, 2007; Van Hemelrijck et al, 2010; Nguyen et al, 2011; O’Farrell et al, 2015). A meta-analysis of observational studies found a 40% increased risk of non-fatal CVD in men with prostate cancer who used ADT, specifically gonadotropin-releasing hormone (GnRH) agonists (Bosco et al, 2015). By contrast, ADT was not associated with CVD mortality in an earlier report (Punnen et al, 2015). The cardiotoxicity of ADT was confirmed in a population-based study suggesting a slightly elevated myocardial infarction risk regardless of existing CVD history (Keating et al, 2013), though other studies suggested that CVD-specific and all-cause mortality only occurred in patients with preexisting CVD (Nanda et al, 2014; Ziehr et al, 2015). Thus, given the mixed cohorts of both patients with and without existing CVD, distinguishing whether ADT is associated the development of CVD or accelerating the progression of the existing disease remains unclear. Although studies based on both SEER-Medicare and VA databases found moderate associations between ADT and non-fatal CVD events, they did not have access to a broad set of covariates, such as CVD medications, which are commonly used by men with localised prostate cancer (Keating et al, 2006, 2010).

Given this background, our goal was to assess the association of ADT and important incident CVD outcomes in a cohort that also included younger men with localised prostate cancer initially conservatively managed. We accounted for important confounders, including prior CVD history, PSA levels, CVD medications, and CVD risk factors. Additionally, we assessed whether ADT only has effect on new-onset CVD or also on the progression of preexisting cardiovascular conditions. To our knowledge, this is the first study to comprehensively account for CVD medications, including antiarrhythmic medications, anticoagulants, antihypertensive medications, calcium channel blockers, digoxin, nitrates, and antidiabetics.

MATERIALS AND METHODS

Study design and setting. We conducted a prospective cohort study of men with newly diagnosed localised prostate cancer using electronic health records from Kaiser Permanente Southern California (KPSC) health-care delivery system. KPSC includes a network of 6600 physicians who serve 14 hospitals, over 220 outpatient clinics, and nearly 4.3 million members. The health plan’s database includes comprehensive information from prospectively recorded inpatient and outpatient diagnoses, clinical encounters, laboratory test values, pharmacy data and cancer registry data.

Participants. We identified 30,092 men diagnosed with prostate cancer between 1998 and 2008 from the health plan’s NCI SEER-affiliated tumour registry (Potosky et al, 2014). Men were excluded if they had advanced stage prostate cancer at diagnosis (T4/nodal involvement/distant metastasis, N = 3352); received other therapies, including radiation, radical prostatectomy, or chemotherapy, within 1 year after prostate cancer diagnosis (N = 18,904); underwent orchiectomy within 1 year after diagnosis (N = 59); received neoadjuvant ADT (N = 120); or were missing date of death and other data errors (N = 16). Four men who died on the cohort entry date were further excluded from the study, resulting in a final cohort of 7637 men with clinically localised prostate cancer who initially were under active surveillance.

Androgen deprivation therapy. The main independent variable was exposure to any ADT after prostate cancer diagnosis. ADT was ascertained from electronic pharmacy dispensing records and outpatient procedures. This included men who might have received ADT as their sole primary therapy for clinically localised disease or as salvage therapy anytime thereafter. ADT was defined as a GnRH analogist (leuprolide, goserelin, or triptorelin) with or without an oral antiandrogen (flutamide, bicalutamide, or nilutamide for combined androgen blockade). ADT was treated as dichotomous (ever/never) time-dependent variable. During the study period, ADT antagonists (abarelix and degarelix) were not available in the KPSC formulary. Men contributed information to the exposed group only after the drug initiation and were categorised as exposed to ADT once initiated until reaching one of the study’s end points.

Study outcomes. The cohort was followed through death or 31 December 2010 for the study endpoints. We identified first occurrence of CVD outcomes based on hospitalisation with a primary diagnoses of a CVD event (using ICD9 and ICD10 discharge diagnosis codes; see Supplementary Appendix 1). We focussed on CVD outcomes that were serious enough to require hospitalisation using a previously published algorithm with demonstrated validity of diagnosis codes in the electronic health records (Haque et al, 2011). Men with multiple primary CVD diagnoses on the same date were assigned to one outcome group according to this algorithm: (1) acute myocardial infarction, (2) cardiac arrest, (3) stroke, (4) heart failure (HF), (5) hypertensive heart disease with HF, (6) cardiomyopathy, (7) arrhythmias; (8) valvuopathy, (9) angina pectoris; and (10) conduction disorder. Furthermore, we combined the individual events and grouped them into three major categories based on the mechanism of disease: cardiac ischaemia, stroke, and other heart disease (Haque et al, 2011). The CVD outcomes were treated as a binary variable. Information on the date of death for health plan members were derived from a combination of clinical databases, linkages with California death certificate records, and linkage with the national Social Security Administration data. There were 178 patients who died owing to CVD but with no specified CVD diagnoses during their health plan membership. We handled such patients in two ways. First, patients were combined with those who died owing to any other causes and were censored at the death date. Second, we excluded the 178 men in sensitivity analysis and compared the HR results with those of the full cohort.

Covariates. Because ADT users and non-users could have been systematically different in prognostic factors of prostate cancer that may also affect the risk of CVD, we compared tumour characteristics (year of diagnosis, Gleason score, prostate cancer risk group, baseline PSA level) between the two groups and adjusted those factors in the multivariable analyses. In addition, we extracted other covariates, including patients’ demographics (age, race/ethnicity), prior history of CVD, risk factors for CVD (hypertension, diabetes), Charlson comorbidity score, and CVD medications. The CVD medications included antiarrhythmics, anticoagulants, antilipemics, calcium channel blockers, digoxin/lanoxin, nitrates, and antidiabetic drugs. As the antihypertensive medication use did not differ by exposure status, we excluded it
from the covariate set. The demographic information and tumour characteristics were gathered from electronic health records around the prostate cancer diagnosis date while CVD risk factors and comorbidity scores were captured 1 year before diagnosis. CVD medications were extracted from pharmacy dispensing and coded as time-dependent variables. History of preexisting CVD conditions (at least two records) were ascertained from inpatient and outpatient electronic health records up to 2 years before prostate cancer diagnosis. Men must have had at least two consecutive prescriptions within 90 days during the follow-up period to be counted as exposed to a particular CVD medication.

Statistical analyses. Differences in demographic characteristics, tumour status, CVD risk factors, and medications were first examined by comparing frequency distributions by ADT use status. Because subjects had varying lengths of follow-up, we examined the person-year rates of each of the CVD outcomes. To estimate the associations between ADT and each of the 10 cardiovascular outcomes, we fit 10 separate time-dependent Cox-proportional hazards models. For each model, the follow-up years began on prostate cancer diagnosis date and ended on the date of the incident CVD as the outcome event or censoring event corresponding to termination of health plan membership, death, or end of the study period (31 December 2010), whichever occurred first. In the Cox models, ADT and the prescription medications were treated as time-dependent variables (i.e., 0 up to start date; 1 after drug initiation). The multivariable Cox proportional hazards models were adjusted for all potential confounders deemed to be clinically or statistically significant (P<0.05). These confounders included demographics, tumour characteristics (stage at prostate cancer diagnosis, Gleason score, risk group), and CVD medications. In sensitivity analyses, we further adjusted for BMI and smoking. The proportional hazards assumption was tested via graphic plots and Schoenfeld residuals. Because a proportion of cases were missing at least one or more of the key clinical prognostic variables (clinical stage, Gleason score, or baseline PSA), we performed multiple imputations using all other covariates. We constructed five imputed data sets, each having estimates for the missing values for PSA, Gleason score, and T-stage. We then pooled the estimates and corresponding s.e. across the five imputations using Rubin’s method (Rubin, 2008).

All model results used these imputed data sets; multivariable models using only the complete cases did not show any significant deviations from the results presented here. To distinguish the effect on newly diagnosed CVD from the effect on the progression on preexisting CVDs, we also conducted a sensitivity analysis to assess whether preexisting CVD was an important confounder by performing analyses stratified by the presence or absence of preexisting CVD. In another sensitivity analysis, we repeated the Cox model excluding the men who died of CVD without having a prior CVD diagnosis (N=178). Because these outcomes were studied in prior reports, we decided not to make adjustments in the P-values for multiple comparisons per Rothman (1990). All statistical analyses were conducted using SAS (Version 9.4, SAS institute Inc., Cary, NC, USA).

RESULTS

Of the 7637 men with localised prostate cancer who did not undergo curative intent therapy (initially conservatively managed), nearly 30% (n=2170) were exposed to ADT during a median of 3.4 years of follow-up (interquartile range: 1.6–6.0 years). The cohort includes both men with (N=1665, 22%) and without (N=5972, 78%) preexisting CVD. Of the 2170 exposed to ADT, 36% began treatment within 6 months after prostate cancer diagnosis, 32% between 6–24 months, and 32% after 2 years. Thus ADT might have been prescribed as primary or salvage therapy. There were 2061 men who experienced CVD events over 31255 person-years, which translated to 65.9 event per 1000 PY. The average time to a CVD event was 3.2 years (s.d. 2.6 years). The ADT group had significantly longer follow-up compared with the non-user group (average of 3.6 vs 5.3 years).

Comparison of patients by ADT status. Demographics, comorbidities, CVD risk factors, and tumour characteristics are displayed in Table 1 by ADT status. The ADT group was more likely to be older, have hypertension, diabetes, and more comorbid conditions 1 year before prostate cancer diagnoses. Prevalence of preexisting CVD was 22.5% among men who used ADT and 21.5% among non-users. ADT use was strongly associated with patients’ tumour characteristics. Compared with the ADT group, a larger proportion of the non-user group was diagnosed after 2006 (31.9 vs 20.5%), had lower Gleason scores (69.0 vs 42.3% for Gleason score <7), at less advanced tumour stage (69.1 vs 55.8% for T1), and were in the lower-risk group (47.7 vs 19.2% for low risk). In the ADT group, a larger proportion of patients had higher baseline PSA level (17.3 vs 36.1% for PSA > 10 units).

Use of CVD and antidiabetic medications by ADT status. Table 2 shows patients’ CVD medication use by ADT use. Significantly more patients in the ADT group used anticoagulants, antilipemics, calcium channel blockers, digoxin/lanoxin, nitrates, and antidiabetic drugs than patients in the non-user group. Thus ADT users were more likely to be treated for CVD.

CVD occurrence by ADT status. The person-year incidence rates, adjusted HRs and 95% CIs of each CVD event, and HRs stratified by history of preexisting CVD are shown in Table 3 and Figure 1. Generally, the unadjusted person-year absolute CVD rates were higher for men treated with ADT than for non-users. The crude CVD rates were higher among men with more advanced age at cancer diagnosis and with worse tumour characteristics, that is, higher T-stage, Gleason score, and recurrence risk group (Supplementary Appendix 2). After adjusting for all other covariates including CVD medications in the multivariate models, men exposed to ADT were 27% more likely to develop HF than non-exposed men (adjusted HR = 1.27, 95% CI: 1.06–1.51); this association was seen in men without preexisting CVD (adjusted HR = 1.81, 95% CI: 1.40–2.32) but not in men with preexisting CVD (adjusted HR = 1.00, 95% CI: 0.78–1.29). ADT users with preexisting CVD were at increased risk of developing arrhythmia (adjusted HR = 1.44, 95% CI: 1.02–2.01) and conduction disorders (adjusted HR = 3.11, 95% CI: 1.22–7.91; Figure 1). We did not find increased risks for ischaemic heart disease, stroke, or the other conditions. To assess the potential confounding effect of BMI and smoking, we performed a sensitivity analysis comparing models with and without additional adjustment for these factors in a subset of the cohort (N=1983) with complete information of the two lifestyle factors; there was little change in the hazard ratios for the three major CVD groups (Table 4). After multiple imputations for missing data (PSA level: (N=1270, 15.8%), Gleason score: (N=709, 9.3%), and T-stage (N=96, 1.3%), the HR results did not substantially change. In the sensitivity analysis, excluding those 178 patients who died of CVD, the HRs were approximately the same as in the full cohort (data not shown). In stratified analysis among African-American patients (data not shown), the magnitude of association was greater in arrhythmia (HR = 1.46, 95% CI: 0.87–2.45) and HF (HR = 1.65, 95% CI: 1.09–2.50). We also found increased risks in angina (HR = 4.37, 95% CI: 0.99–13.36) and cardiomyopathy (HR = 7.86, 95% CI: 1.22–50.62) in African-American men, although confidence intervals were wide.
In this prospective population-based study of insured men with localised prostate cancer who were initially conservatively managed and followed a maximum of 13 years, we found associations between ADT and certain CVD outcomes after adjustment for multiple confounder variables, including hypertension, diabetes, age and stage of prostate cancer diagnosis, Gleason score, prostate cancer risk score, race/ethnicity, and covariate CVD medications. The increased risk of other heart diseases (e.g., arrhythmia, HF, and conduction disorder) among ADT users persisted even in the sensitivity analysis that controlled for BMI and smoking. ADT use was associated with an increased risk of HF; this finding was similar to a study in UK General Practice Research Database but they observed a slightly smaller effect size (Martin-Merino et al, 2011). ADT was also associated with arrhythmia and conduction disorders but only among men with preexisting CVD. A major advantage of our study was that we were able to consider the influence of cardiovascular medications and examine a comprehensive set of outcomes.

Given the pharmacological functions of ADT, our findings may be explained by possible mechanisms pertaining to testosterone deficiency and CVD risk factors. For example, testosterone deficiency increases fat mass, a risk factor of CVDs, such as HF and arrhythmia. Men with androgen deficiency also have abnormal lipid profiles, elevated pro-inflammatory factors, endothelial function, and hypertension (Traish et al, 2009). In the Caperhilly Study, Smith et al (2005) suggested that the cortisol/testosterone ratio was related with ischaemic heart disease, mediated through insulin resistance, which may exacerbate conduction disorders (Traish et al, 2009; Keating et al, 2010). Therefore, the negative impact of testosterone deficiency may derive from its influencing cardiac and cardiovascular medications and examine a comprehensive set of outcomes. The observed increased risk of arrhythmia among ADT users in our study is consistent with the confirmed inverse association between testosterone level and prolonged QT interval, a strong risk factor of fatal arrhythmias (van Noord et al, 2010).
We also found an increased risk of conduction disorder among patients with preexisting CVD (HR = 3.11, 95% CI: 1.22–7.91) but not in those without CVD history (HR = 1.08, 95% CI: 0.57, 2.03). Reasons for this are not clear, but it is possible that those with preexisting CVD may be more susceptible to developing conduction disorders or that individuals with certain preexisting conditions are more likely to have greater health-care utilisation, be monitored more frequently, and hence, more likely to be diagnosed with other CVD conditions. This observation requires additional confirmation.

The adjusted hazard ratios of ischaemic heart disease and stroke were > 1.00 (1.15 and 1.09) but not significantly different between the ADT use and non-use. The lack of elevated risks in our study may be attributed to higher proportion of younger men in our study compared with the rates in a SEER-Medicare study (33% of men in our cohort were aged ≤65 years; Keating et al, 2006), the
Additional adjustment for smoking

Table 4. Hazard ratio estimates of incident CVD outcomes from different models (N = 1983)

| CVD                      | Multivariable models | Additional adjustment for smoking | Additional adjustment for BMI + smoking |
|--------------------------|----------------------|-----------------------------------|---------------------------------------|
|                          | Adjusted HR          | 95% CI                            | Adjusted HR                           | 95% CI                                 |
| Cardiovascular disease   |                      |                                   |                                       |                                       |
| Cardiac ischaemia        | 1.15                 | 0.94, 1.40                        | 1.14                                  | 0.93, 1.39                            |
| Stroke                   | 1.04                 | 0.60, 1.80                        | 1.01                                  | 0.58, 1.76                            |
| Other heart diseases     | 1.24                 | 1.10, 1.40                        | 1.24                                  | 1.10, 1.40                            |

Abbreviations: ADT = androgen deprivation therapy, CI = confidence interval, CVD = cardiovascular disease, HR = hazard ratio, PY = person-years.

In this population-based study, ADT was associated with greater risk of HF and arrhythmia and conduction disorder in men with preexisting CVD. These conditions affect patients’ quality of life and morbidity and can possibly compromise survival. This study provides the basis for identifying susceptible individuals for regular cardiac check-up, including identifying subclinical signs, monitoring hypertension, diabetes, and encouraging physical activity.

CONCLUSIONS

In this population-based study, ADT was associated with greater risk of HF and arrhythmia and conduction disorder in men with preexisting CVD. These conditions affect patients’ quality of life and morbidity and can possibly compromise survival. This study provides the basis for identifying susceptible individuals for regular cardiac check-up, including identifying subclinical signs, monitoring hypertension, diabetes, and encouraging physical activity.
and healthy dietary habits. Indeed, emerging evidence exists that recommending diet and exercise to patients receiving ADT for prostate cancer treatment benefits the cardiometabolic profile (Galvao et al., 2009); such efforts may indirectly help lower the risk of non-fatal CVD in men with localised prostate cancer treated with ADT.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Kaiser IRB approved this study and written informed consent was waived as we were using secondary data.

AUTHOR CONTRIBUTIONS

Study concept and design, acquisition of data and drafting of the manuscript: RH, XX. Analysis and interpretation of data and critical revision of the manuscript for important intellectual content: all authors. All authors read and approved the final manuscript.

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