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Review

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Real-world use of androgen-deprivation therapy intensification for metastatic hormone-sensitive prostate cancer: a systematic review

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Objective

To conduct a systematic literature review of real-world data (RWD) studies to summarise treatment patterns among men with metastatic hormone-sensitive prostate cancer (mHSPC). While androgen-deprivation therapy (ADT) is a primary treatment strategy for mHSPC, ADT intensification with androgen receptor pathway inhibitors (ARPIs) and/or chemotherapy is recommended by current guidelines and has improved clinical outcomes in the last decade.

Methods

We searched electronic databases (PubMed; Excerpta Medica dataBASE [EMBASE]) for eligible studies (retrospective or prospective observational RWD studies examining mHSPC treatment patterns) between database inception and July 2023, and manually screened the past 2 years of relevant conference proceedings.

Results

Of 2336 retrieved citations, 29 studies met the inclusion criteria, covering North America (United States, n = 21; Canada, n = 2), Europe (n = 8), and Asia (n = 6). Most studies utilised retrospective cohorts (n = 26) and included men with a median age of ≥70 years (n = 20). ADT monotherapy was predominantly used across geographies, followed by ADT + ARPI and ADT + docetaxel in the United States and Europe but not in Asia, where use of each combination remained low. Studies with recent electronic medical record data from cancer centres/registries showed >40% use of ADT + ARPI in the United States and Europe. Abiraterone was the most frequently used ARPI, followed by enzalutamide. Quantitative factors associated with ADT intensification were high disease burden, younger age, Eastern Cooperative Oncology Group performance status score of 0 to 1, fewer comorbidities, and oncologist physician specialty; qualitative factors were patient preference, unsatisfactory response to ADT, ability to tolerate adverse events, and absence of cost barriers.

Conclusion

While there was an increasing trend in ADT intensification for mHSPC over the study period across geographies, use remained suboptimal considering the high proportion of patients who were still receiving ADT monotherapy only. These findings highlight the need for interventions to further optimise current mHSPC therapies with high guideline concordance.

Keywords

androgen-deprivation therapy, androgen receptor pathway inhibitors, metastatic hormone-sensitive prostate cancer, real world, treatment patterns

Introduction

According to recent United States estimates, 288 300 new cases of prostate cancer were projected to be diagnosed in 2023, and 3.5 million cancer survivors were living with prostate cancer in 2020 [1,2]. As such, prostate cancer is the most common solid cancer and the second leading cause of cancer-related death among men in the United States. Every year, nearly 6–8% of newly diagnosed prostate cancer cases present with *de novo* metastases (i.e., at diagnosis of prostate cancer) [2,3]. As of 2018, among the 120 368 cases of metastatic hormone-sensitive prostate cancer (mHSPC), 55% were *de novo* and 45% were men with recurrent mHSPC (i.e., progressing from non-metastatic to metastatic prostate cancer, but prior to castration resistance) [4]. In general, men with metastatic prostate cancer have lower overall survival

compared with those with non-metastatic prostate cancer, with a 5-year relative survival rate of >99% vs 32% in men with localised/regional prostate cancer vs distant prostate cancer, respectively [2]. Furthermore, metastatic prostate cancer represents attributable costs of $5.2–$8.2 billion United States dollars per year [5]. Thus, mHSPC represents a stage of prostate cancer with high unmet clinical needs and financial burden.

Historically, androgen-deprivation therapy (ADT; through medication or surgical procedures) was the main treatment option for men with mHSPC. Since 2015, there have been several randomised controlled trials (RCTs) demonstrating prolonged progression-free survival and, more importantly, overall survival benefits of ADT intensification with either docetaxel (DOC; Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer [CHAARTED, 2015] and Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy [STAMPEDE, 2016]) [6,7], abiraterone (STAMPEDE Arm G, 2017 and A study of abiraterone acetate plus low-dose prednisone plus ADT vs ADT alone in newly diagnosed participants with high-risk metastatic hormone-naïve prostate cancer [LATITUDE, 2017]) [8,9], enzalutamide (Enzalutamide in First Line Androgen Deprivation Therapy for Metastatic Prostate Cancer [ENZAMET, 2019] and a study of enzalutamide plus ADT vs placebo plus ADT in patients with mHSPC [ARCHES, 2019]) [10,11], or apalutamide (a study of apalutamide [JNJ-56021927, ARN-509] plus ADT vs ADT in participants with mHSPC [TITAN, 2019]) [12], as well as with combinations of abiraterone and ADT + DOC (Phase III study for patients with metastatic hormone-naïve prostate cancer [PEACE-1, 2022]) [13] or darolutamide and ADT + DOC (Darolutamide in addition to standard androgen deprivation therapy and docetaxel in metastatic hormone-sensitive prostate cancer [ARASENS, 2022]) [14]. Thus, given the benefits of ADT intensification, current clinical guidelines recommend the use of androgen receptor pathway inhibitors (ARPIs) and/or chemotherapy for men with mHSPC as the standard of care, except for men who are unable to tolerate intensified therapy [15–17]. In light of the existing evidence and recommendations from the guidelines, various studies around the globe have been undertaken to assess the translation of clinical evidence into real-world clinical practice by studying the utilisation/uptake of guideline-based recommendations. However, to the best of our knowledge, data on real-world treatment patterns in mHSPC, specifically ADT intensification, have not been summarised systematically at the global level. Therefore, we conducted a systematic literature review (SLR) to summarise real-world treatment utilisation patterns among men with mHSPC using data from published real-world data (RWD) studies.

Methods

This analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to conduct this SLR [18].

Eligibility Criteria

This analysis included retrospective or prospective observational RWD studies, including registries, claims, electronic medical records (EMRs) structured data, and chart reviews, to examine treatment patterns with ADT monotherapy and ADT intensification with ARPIs/chemotherapy among men with mHSPC. Given recent RCTs and guideline recommendations on ADT intensification, studies covering a data period from 2015 onwards were further selected. Studies were excluded if they examined treatment patterns for metastatic castration-resistant prostate cancer (mCRPC) or metastatic prostate cancer in general without specific information on mHSPC, or if they only examined one or two treatment options and outcomes for mHSPC.

Information Sources and Search Strategy

Electronic databases such as PubMed and the Excerpta Medica dataBASE (EMBASE) were searched for eligible studies published from database inception to July 2023 using keywords for prostate cancer, metastases, and RWD (see Table S1 for details on search strategy). Additionally, conference proceedings (e.g., the American Society of Clinical Oncology [ASCO], the European Society for Medical Oncology [ESMO], the AUA) were searched to identify additional abstracts. While all major relevant conferences, including ASCO, ESMO, and AUA, are indexed in EMBASE, for more recent conferences (within the past 2 years) the conference proceedings were manually screened for eligible abstracts/posters. In addition, the reference lists of included studies were checked to confirm the identification of relevant studies not captured in the literature database search.

Data Screening and Data Extraction

A first-pass screening of the titles and abstracts of all retrieved citations was conducted to determine eligibility according to defined criteria. Subsequently, a second-pass screening was conducted by retrieving and independently reviewing all full-text articles to determine their final inclusion in the analysis.

All relevant data from eligible studies were extracted into a template designed in Microsoft Excel (Microsoft, Redmond, WA, USA). The extracted data were validated by a second review. In the case of multiple citations for the same study, information from the latest and most comprehensive source

was extracted. For example, for a study cited as both a poster and peer-reviewed publication, the latter was used for extraction of necessary data. Elements for data extraction included study characteristics (study design, data source, sample size, study period, and country) and baseline characteristics of the study populations (age, race, mHSPC type [*de novo* vs recurrent], PSA level, tumour volume, risk of progression, performance status, and local treatment). In the real world, mHSPC treatment patterns could include palliative management or local treatment in addition to ADT with or without intensification. We planned to summarise all given treatments for mHSPC in the included studies. However, we noted significant heterogeneity in the reporting of treatment patterns. To compare the distributions of ADT monotherapy and intensification with ARPI or DOC across the studies in a uniform manner, treatment utilisation data were restricted to a total population treated with three mutually exclusive categories of ADT monotherapy, ADT intensification with ARPIs (ADT + ARPI; including enzalutamide, apalutamide, darolutamide, or abiraterone), and ADT intensification with DOC (ADT + DOC). Further, ADT monotherapy was defined as the use of ADT with or without first-generation ARPIs (bicalutamide, flutamide, or nilutamide) given the limited efficacy of these agents in patients with mHSPC. Further, given the relative recency of clinical evidence (2022 onwards) on triplet combination with ADT + ARPI + DOC in men with mHSPC, very few studies examined intensification with triplet therapy. Among those that did, utilisation was shown to be limited during this timeframe (0.1–4.8%; Table S2). In an effort to focus on primary treatment modalities across reported countries, triplet use was not detailed within the main analysis. Regarding the quality of included studies, the operational definitions were examined to identify disease condition and treatment of interest, as well as representativeness of the included study populations. Furthermore, information on qualitative or quantitative factors associated with ADT intensification with ARPIs or chemotherapy were extracted from the included studies.

Statistical Analysis

Characteristics of the included studies and their study populations were summarised through narrative synthesis. In addition, the distribution of ADT monotherapy, ADT + ARPI, and ADT + DOC were reported for various subgroups, including by race, mHSPC status (*de novo* vs recurrent), and treating physician specialty (urologist vs oncologist) across calendar years, as well as tumour volume (high vs low). Given the heterogeneity across studies, a formal meta-analysis to estimate the pooled proportion of men with ADT monotherapy or ADT intensification was not conducted. Data are therefore presented separately for each RWD source. Data on the utilisation of individual ARPI agents are also reported.

Results

Eligible Studies from the Systematic Literature Search

Figure S1 depicts the PRISMA flow diagram for study selection. Of 2325 retrieved citations, 1952 were eligible for the first-pass screening after removing duplicates. In the second-pass screening, 128 citations were identified as potentially eligible; out of these, 99 citations were removed because the studies reported treatment patterns for men with mCRPC, only examined one or two types of mHSPC treatment options, or did not include any information on treatment patterns in men with mHSPC. The 29 real-world studies that met the inclusion criteria were analysed in this SLR [19–47], collectively representing a total of 344 473 men with mHSPC and covering the period from 2014 to 2021.

Characteristics of the Included Studies

Table 1 [19–47] provides details on the characteristics of the included studies. Most studies utilised a retrospective cohort design (n = 26), while three studies presented a cross-sectional snapshot of mHSPC treatment through syndicated survey/chart reviews [37–39].

With respect to RWD sources, the most frequently used data sources were EMRs and/or chart reviews (n = 18). Most studies utilised RWD from the United States (n = 21), followed by Europe (n = 8) and Asia (n = 6). Among the studies, most RWD were country specific, whereas four studies included data from multiple continents/regions, spanning North America, Europe, Asia, and Oceania [37–40].

With respect to quality in terms of population representativeness of the included studies, these collectively represented almost 92% of the United States population with mHSPC; four studies utilised claims data representing United States private insurance providers (IQVIA and Optum) with large sample sizes (range: 4675–131 200), and two studies used claims data from United States public insurance (Medicare). With respect to EMR origin and representativeness, six studies represented the United States veteran population, three studies represented United States community oncologist practices, and two studies represented tertiary care cancer centre databases. Most RWD studies in Europe or Asia were EMR-based, using a sample of selected academic medical institutes/hospitals, or were syndicated chart reviews of patients treated by clinicians who agreed to participate in commercial surveys. A total of 20 studies utilised highly precise methods such as chart review or clinical decision-based claims algorithm to identify men with

Table 1 Characteristics of included studies.

Reference	Design	Data type	Database	Study period	Country	Sample size
Mar and Forsyth 2021 [19]	Cohort	Claims	IQVIA	2015–2020	United States	131 200
Heath et al., 2022 [20]	Cohort	Claims	IQVIA	2015–2021	United States	109 607
Freedland et al., 2021-m [21]	Cohort	Claims	Medicare 100%	2018	United States	35 195
Ryan et al., 2021-M* [22]	Cohort	Claims	Medicare 100%	2014–2017	United States	13 324
Ryan et al., 2021-C [22]	Cohort	Claims	Optum	2014–2019	United States	6517
Swami et al., 2022 [23]	Cohort	Claims	Optum	2014–2020	United States	4675
Conner et al., 2023 [24]	Cohort	EMR	CTCA (5 cancer centres)	2015–2021	United States	523
Dhillon et al., 2023 [25]	Cohort	EMR	Cleveland Cancer Clinic	2017–2021	United States	449
George et al., 2021 [26]	Cohort	EMR	ConcertAI Oncology	2014–2019	United States	858
Swami et al., 2021 [27]	Cohort	EMR	Flatiron	2011–2019	United States	9747
Shore et al., 2022 [28]	Cohort	EMR	Flatiron	2016–2020	United States	4753
Freedland et al., 2021-b [29]	Cohort	EMR	VHA	2006–2019	United States	7340
Schoen et al., 2023 [30]	Cohort	EMR	VHA	2012–2021	United States	5006
Freedland et al., 2021-a [31]	Cohort	EMR	VHA	2013–2018	United States	1395
De Jesus Pizarro et al., 2023 [32]	Cohort	EMR	VHA	2014–2022	United States	4283
Freedland et al., 2023 [33]	Cohort	EMR	VHA	2018–2020	United States	380
Gong et al., 2023 [34]	Cohort	EMR/chart review	VHA	2015–2021	United States	400
Gotto et al., 2023 [35]	Cohort	Claims + EMR	Alberta Claims/EMR	2010–2020	Canada	1779
Wallis et al., 2021 [36]	Cohort	Claims + EMR	Ontario Claims/EMR	2014–2019	Canada	3556
Barata et al., 2023 [37]	Cross-sectional	Chart review	Adelphi PCDSP	2016–2020	Global†	1321
Leith et al., 2022 [38]	Cross-sectional	Chart review	Adelphi PCDSP	2020	Global†	1195
Partridge et al., 2022 [39]	Cross-sectional	Chart review	IPSOS GOMD	2018–2020	Global‡	3893
Mucci et al., 2023 [40]	Cohort	Registry	IRONMAN global registry	2017–2021	Global§	1184
de Velasco Oria de Rueda et al., 2022 [41]	Cohort	EMR	BIG-PAC/Atrys Health	2015–2019	Spain	379
Lambert et al., 2022 [42]	Cohort	Chart review	Ghent University	2014–2021	Belgium	243
Lambert et al., 2021 [43]	Cohort	Chart review	21 hospitals	2017–2018	Belgium	93
Uemura et al., 2022 [44]	Cohort	Registry	J-ROCK Registry¶	2019–2021	Japan	410
Wang et al., 2023 [45]	Cohort	EMR	3 medical centres	2014–2021	China	1086
Uemura et al., 2020 [46]	Cohort	Registry	UFO	2015–2017	Asia**	1038
Yang et al., 2023 [47]	Cohort	Registry-EMR	PC Registry-EMR	2016–2020	Singapore	585

*While 29 studies were included in the final analysis, the above list presents 30. This is due to Ryan et al. 2021 [22] utilising two varied databases (Optum [C], Medicare [M]). CTCA, Cancer Treatment Centers of America; EMR, electronic medical record; GOMD, Global Oncology Monitor Database; PCDSP, Prostate Cancer Disease Specific Programme; PCF, Prostate Cancer Foundation; UFO, United in Fight against Prostate Cancer Registry; VHA, Veterans Health Administration. *Ryan et al. [22] utilised two databases including Medicare and Optum Database within the United States. †Barata et al. [37] included data from the United States, UK, France, Germany, Spain, and Italy; Leith et al. [38] included data from Japan as an additional country. ‡ISPOS GODM database had data for the United States, Germany, France, China, and Japan. §IRONMAN global registry had data for the United States, Canada, Spain, UK, Australia, Switzerland, Sweden, Ireland, and Brazil. ¶J-ROCK Registry included data from 77 medical sites in Japan. **Uemura et al., 2020 [46] had data from China, India, Japan, Malaysia, Singapore, South Korea, Taiwan, and Thailand.*

mHSPC, whereas nine studies utilised a diagnostic code-based operational with consistency across the codes, although they are likely to have coding-related biases. All studies could accurately capture medication use; however, the timeline to measure ADT varied from 1 month pre-mHSPC to 3 months post-mHSPC. Use of ADT, DOC, and abiraterone was captured in all included studies; 26, 19, and six studies examined enzalutamide, apalutamide, and darolutamide use, respectively. Three studies only examined ADT, DOC, and abiraterone to study treatment patterns (Table S3).

Characteristics of the Study Populations Among the Included Studies

Table 2 [21–47] presents available details on study population characteristics of the included studies. The median age in most studies was ≥70 years (n = 20); however, two studies reported a lower median age of 63 years [24,25]. Nine studies included a cohort of men with *de novo* mHSPC only [27,30,32–36,43,47]. In all, 12 studies reported baseline PSA levels, with mean values varying widely from 5 to 800 ng/mL [22,27,29,31,33,34,36,38,42–44,46]. Six studies reported a distribution of high-volume mHSPC, ranging from 34% to 67% [37,38,41–43,47]. Eight studies reported the distribution of functional status at baseline, with five out of eight

Table 2 Reported characteristics of the study populations among the included studies.

Reference	Sample size	Median age, years	Race, %				Prostate cancer–related characteristics					ECOG PS score, %		Local treatment, %	
			White	Black	Hispanic	Asian	*De novo*, %	PSA at diagnosis	PSA >20 ng/mL	High volume, %	High risk, %	0–1	≥2	RT	RP
Freedland et al., 2021-m [21]	35 195	77 (8)	79	12	5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ryan et al., 2021-M* [22]	13 324	75 (8)	75	18	2	N/A	34	5 (12)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ryan et al., 2021-C [22]	6517	75 (9)	N/A	N/A	N/A	N/A	36	8 (32)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Swami et al., 2022 [23]	4675	73–76	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Conner et al., 2023 [24]	523	63 (9)	60	33	N/A	N/A	73	N/A	N/A	N/A	N/A	75	N/A	N/A	N/A
Dhillon et al., 2023 [25]	449	63 (43–96)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
George et al., 2021 [26]	858	69	70	16	3	N/A	63	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Swami et al., 2021 [27]	9747	74 (67–80)	64	9	6	N/A	100	49.8 (12.5–218.2)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Shore et al., 2023 [28]	4753	73	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Freedland et al., 2021-b [29]	7340	73 (10)	N/A	N/A	N/A	N/A	N/A	28.2 (6.1–140.2)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Schoen et al., 2023 [30]	5006	73.1	N/A	27	N/A	N/A	100	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Freedland et al., 2021-a [31]	1395	66–75	66	26	N/A	N/A	N/A	256–338	N/A	N/A	N/A	N/A	N/A	N/A	N/A
De Jesus Pizarro et al., 2023 [32]	4248	73.3	73	27	N/A	N/A	100	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Freedland et al., 2023 [33]	380	75	66	34	N/A	N/A	100	74–153	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Gong et al., 2023 [34]	400	77	N/A	N/A	N/A	N/A	100	147 (35.8–530.4)	N/A	N/A	N/A	N/A	N/A	5	N/A
Gotto et al., 2023 [35]	1779	N/A	N/A	N/A	N/A	N/A	100	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Wallis et al., 2021 [36]	3556	72–78	N/A	N/A	N/A	N/A	100	12–152	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Barata et al., 2023-Europe [37]	1321	70 (44–88)	93	3	N/A	N/A	N/A	N/A	N/A	45	N/A	83	17	N/A	N/A
Barata et al., 2023-United States [37]	239	68 (48–89)	67	21	N/A	N/A	N/A	N/A	N/A	43	N/A	88	12	N/A	N/A
Leith et al., 2022 [38]	1195	72.1 (8.01)	N/A	N/A	N/A	N/A	N/A	21.1 (60.42)	N/A	34	36	79	21	N/A	N/A
Partridge et al., 2022 [39]	3893	N/A	63	24	9	N/A	N/A	N/A	N/A	N/A	N/A	84	16	N/A	N/A
Mucci et al., 2023 [40]	1184	70 (32–97)	87	9	4	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
de Velasco Oria de Rueda et al., 2022 [41]	379	71 (12)	N/A	N/A	N/A	N/A	9	N/A	N/A	67	N/A	N/A	N/A	16	0
Lambert et al., 2022 [42]	243	70 (62–78)	N/A	N/A	N/A	N/A	100	45 (15–196)	N/A	50	52	90	10	N/A	N/A
Lambert et al., 2021 [43]	93	73 (68–79)	N/A	N/A	N/A	N/A	23	59.5 (24.7–236.8)	N/A	66	N/A	N/A	N/A	8	2
Uemura et al., 2022 [44]	410	70–74	N/A	N/A	N/A	100	N/A	250–370	N/A	N/A	100	88	12	N/A	N/A
Wang et al., 2023 [45]	1086	72 (9)	N/A	N/A	N/A	100	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Uemura et al., 2020 [46]	1038	69 (8)	N/A	N/A	N/A	100	N/A	200–800	N/A	N/A	N/A	90–100	0–10	12	8
Yang et al., 2023 [47]	585	73	N/A	N/A	N/A	100	100	N/A	N/A	55	N/A	78	22	N/A	N/A

*Data on reported mean and SD are presented using mean (SD) format, whereas median and interquartile range are presented as median (Q1–Q3). ECOG PS, Eastern Cooperative Oncology Group performance status; N/A, not available; Q, quartile; RP, radical prostatectomy; RT, radiation therapy. *Ryan et al. [22] utilised two varied databases (Optum [C], Medicare [M]).*

reporting >80% of men with mHSPC having a fully active functional status without restriction or without restriction in strenuous physical activity (Eastern Cooperative Oncology Group performance status [ECOG PS] of 0–1) [37,39,42,44,46]. Of the 29 eligible studies, only four reported on primary localised treatment utilisation. In these studies, the reported use of baseline radical prostatectomy ranged from 0% to 8% and the use of radiation therapy ranged from 5% to 16% [34,41,43,46].

Treatment Patterns Among Included Studies by Geographical Region

North America (United States and Canada)

Overall, in the United States and Canada, most studies reported predominant use of ADT monotherapy (>50%), followed by ADT + ARPI (20–40%), and ADT + DOC (10–20%). Of note, the absolute utilisation rate varied by RWD source and across calendar years. Of the 14 studies reporting data on United States treatment patterns using EMR or registry data (Fig. S2A) [24–34,37–39], the reported use of ADT monotherapy ranged from 24% to 80%, covering study periods from 2015 to 2021. While most studies (10 out of 14) reported ≥50% use of ADT monotherapy, four studies reported a bit lower use, ranging from 24% to 47% (the Flatiron EMR, the Adelphi Prostate Cancer Disease Specific Programme [PCDSP], and the Cleveland Cancer Clinic databases). While the reported use of ADT + ARPI ranged widely from 9% to 66%, most studies (11 out of 14) reported the use of ADT + ARPI as ≤40%. The use of ADT + DOC was consistently low, ranging from 1% to 23% (≤20% in 12 out of 14 studies). Interestingly, among the subset of studies using only United States claims, all showed a greater use of ADT monotherapy (range: 73–96%), with only a minor fraction using ADT intensification with ARPIs (2–16%) or chemotherapy (4–12%; Fig. S3) [21–23].

Nine studies reported on ADT intensification trends in the United States, each using claims or EMR/registry data (Fig. 1A). All studies showed an increasing trend in the use of ADT + ARPI from 2015 to 2021, although the magnitude of the increase varied by RWD source. The use of ADT + DOC remained relatively consistent over time, with only a slight decrease, most likely offsetting the observed rise in the use of ADT + ARPI. Regardless of these latest trends, until 2020, ADT monotherapy was the most commonly utilised option in the majority of United States populations across database types.

Two studies reported treatment patterns in Canada (Fig. S2B) [35,36] and found ADT monotherapy to be the primary option for >60% of the treated mHSPC population. While utilisation of ADT + DOC was similar between studies (11–12%), use of ADT + ARPI was higher in the Gotto et al. [35] study from 2023 (24%) in comparison to the previously reported study by Wallis et al. [36] from 2021 (2–3%).

Europe

Six studies reported data on treatment patterns across Europe [37–39,41–43] utilising RWD from Belgium, France, Germany, Italy, Spain, and the UK (Fig. S2C). Three studies reported data from multiple countries using syndicated chart review. Treatment patterns varied greatly across countries and databases. While the reported use of ADT monotherapy was ≥40% in most study cohorts, three studies reported use of <40% in Belgium, Germany, and Spain [38,41,43]. In regard to ADT + ARPI, most study cohorts reported a range of use from 13% to 38%, with one study from Belgium reporting a higher use of 52% [43]. Similarly, the use of ADT + DOC generally ranged from 12% to 36%, except one study from the UK (40%) [38] and another study from Spain (61%) [41].

One study reported on usage trends for ADT intensification across Europe, covering five countries (France, Germany, Italy, Spain, and the UK) [37]. Similar to the trend seen in the United States, data from all included countries showed an increasing trend in the use of ADT + ARPI, with reported use of ADT + DOC remaining relatively consistent over time (Fig. 1B).

Asia

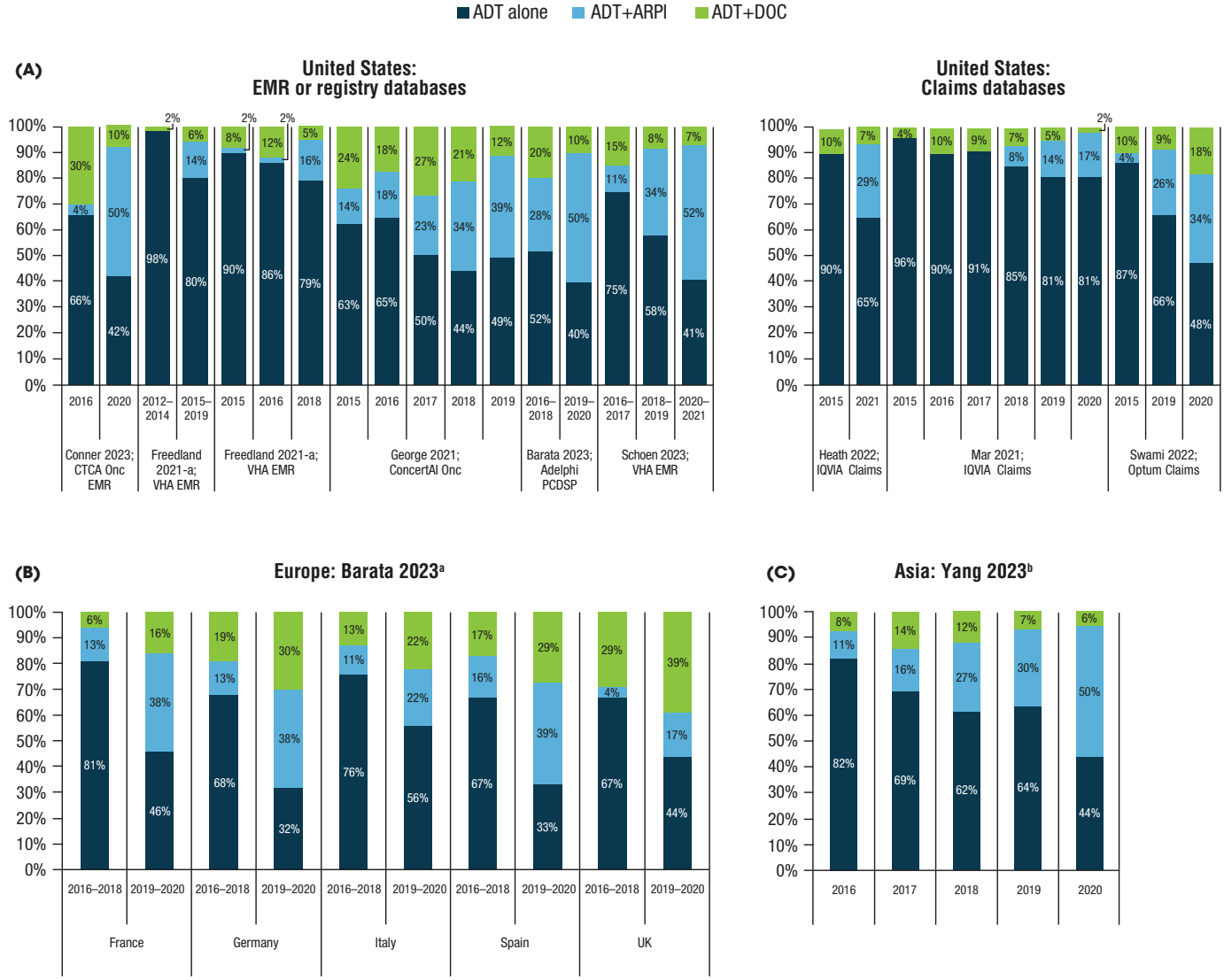
Six studies reported treatment utilisation patterns in Asian countries (Fig. S2D) [38,39,44–47]. All studies reported a high proportion of ADT monotherapy use, ranging from 41% to 89%. Intensification of ADT with ARPI also varied considerably—while most studies reported use of ≤20%, two studies of men specifically with high-risk mHSPC reported 27% and 59% use of ADT + ARPI [44,47]. Use of ADT + DOC was less frequent (<15%) across all studies. As reported by the Japanese Adelphi PCDSP database, 80% of men with mHSPC were treated with ADT monotherapy, with the remaining 20% being treated with ADT + ARPI; no use of chemotherapy was reported [38].

Only one study from Asia found use of ADT intensification from 2016 to 2020 [47]. While the use of ADT monotherapy did decrease, it was more gradual than the decreasing trend observed from other geographical regions. Reported use of ADT + ARPIs increased over time, while the use of ADT + DOC remained consistently low (Fig. 1C).

Global Registry

Mucci et al. [40] utilised the International Registry for Men with Advanced Prostate Cancer (IRONMAN), which aimed to examine mHSPC and CRPC treatment patterns and

Fig. 1 Trends in ADT intensification by RWD types in (**A**) the United States, (**B**) Europe, and (**C**) Asia. [a]Barata et al. [37] reported data from European countries such as the UK, France, Germany, Spain, and Italy. [b]Yang et al. [47] reported data from Singapore, Asia. ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; CTCA, Cancer Treatment Centers of America; DOC, docetaxel; EMR, electronic medical records; RWD, real-world data; VHA, Veterans Health Administration.



outcomes from centres in Australia, the Bahamas, Barbados, Brazil, Canada, Ireland, Jamaica, Kenya, Nigeria, Norway, South Africa, Spain, Sweden, Switzerland, the UK, and the United States. Treatment patterns within continental North America, namely the United States and Canada, were comparable [40]. Intensification of ADT with ARPI was found to be the leading treatment in both the United States (58%) and Canada (67%), whereas use of ADT monotherapy (United States, 25%; Canada, 17%) and ADT + DOC (United States, 17%; Canada, 16%) were substantially lower. In Europe, the reported use of ADT monotherapy was also low (<33%) in all included European countries (Ireland, Spain, Sweden, Switzerland, and the UK) [40]. Instead, ADT + ARPI (30–48%) and ADT + DOC (28–50%) composed the majority of treatment choices (Fig. S4).

Treatment Patterns by Specific Subgroups

Three studies reported treatment patterns by physician specialty (urologist vs oncologist) [20,23,37]. The use of ADT intensification was lower for men with mHSPC who were treated by urologists vs oncologists (ADT + ARPI, 8–28% vs 18–48%, respectively; ADT + DOC, 0–18% vs 11–23%; Fig. S5).

Two studies reported on treatment patterns by tumour volume, and both noted a directional trend of high use of

ADT intensification (ADT + ARPI or ADT + DOC) with high-volume disease, but to various extents [33,41]. Furthermore, four studies reported data on tumour volume in which the use of ADT intensification corresponded to the proportion of men with high tumour volume [38,41–43]. Nine studies reported treatment patterns in men with *de novo* mHSPC [27,30,33–36,41,42,47]. ADT monotherapy remained the predominant choice in men with *de novo* mHSPC, with one exception: the de Velasco Oria de Rueda et al. [41] study from 2022, which used data from the BIG-PAC EMR database, found that the use of ADT intensification in men with *de novo* vs recurrent mHSPC was mixed.

Reported Findings on Factors Associated with ADT Intensification

We additionally captured reported data, where available (n = 13 studies), on the potential quantitative factors associated with ADT intensification in the real world (Table 3) [20,21,23,25,26,30,35–39,42,43,46,47]. Some of the

Table 3 Trends on factors associated with ADT intensification use in the real world.

Reference	Type of evidence	Reason for no intensification	Factors associated with ADT intensification with ARPI	Factors associated with ADT intensification with chemotherapy
Barata et al., 2023 [37]	Descriptive	• Descriptive subgroups	• Oncologist vs urologist • Black vs White race • High- vs low-volume disease	• Oncologist vs urologist • Black patients received more intensification compared with White patients • High- vs low-volume disease
Dhillon et al., 2023 [25]	Qualitative	• Patient preference (33%) • Poor functional status/comorbidities (10%) • Cost (5%)		
Freedland et al., 2021 [21]	Regression		• ADT + abiraterone vs ADT • Older age • Fewer cardiovascular comorbidities • Higher disease burden in terms of PSA and metastases (other sites including bone) • Metastatic lymph node	• Compared with ADT alone, patients who received ADT + DOC were younger and had fewer comorbidities, and had greater disease burden in terms of higher PSA and metastases (respiratory and digestive, and other sites including bone)
Partridge et al., 2022 [39]	Descriptive			• Younger age • High disease burden (bone metastases, Gleason score) • ECOG PS score
George et al., 2021 [26]	Regression			• Younger age • High PSA • *De novo* metastases
Gotto et al., 2023 [35]	Regression		• Any intensification • Younger age • Low CCI • High number of metastatic sites • Shorter time to ADT initiation • Referral to a specialist/ cancer care • Prior treatment (TURP/ radiation) • More recent year of diagnosis	
Heath et al., 2022 [20]	Descriptive		• Oncologist vs urologist	• Oncologist vs urologist
Lambert et al., 2021 [43]	Descriptive			• Younger age

Table 3 (continued)

Reference	Type of evidence	Reason for no intensification	Factors associated with ADT intensification with ARPI	Factors associated with ADT intensification with chemotherapy
Lambert et al., 2022 [42]	Qualitative	• Compliance for the time period (60%) • Unfit for additional systemic treatment (8%) • Not considered by treating physician (8%) • Low volume disease (3%) • Local therapy (6%) • Local therapy followed by MDT (7%) • Refused by the patient (6%) • Satisfactory response with monotherapy (<0.2%)		
Leith et al., 2022 [38]	Descriptive	• Bone-only disease • Poor functional status • Not able to tolerate adverse events • Maintain QoL • Compliance challenges	• Younger age • Patient preference to maintain or improve QoL • Top priority of overall survival • High disease burden	• Younger age • Performance status • Maximum PFS • Rapid onset of action • High disease burden (visceral disease)
Schoen et al., 2023 [30]	Descriptive			• Younger age
Swami et al., 2022 [23]	Descriptive		• Oncologist vs urologist	• Oncologist vs urologist
Uemura et al., 2020 [46]	Descriptive			
Wallis et al., 2021 [36]	Descriptive		• High CCI score • Rural area	• Younger age • Low CCI
Yang et al., 2023 [47]	Regression		• CCI 0–2 (OR 4) • ECOG PS score 0–1 (OR 1.8) • Age <65 years (OR 2.5) • PSA level >400 ng/mL (OR 2.0) • High-volume disease (OR 1.7) • Development of systemic complications (OR 2.190) • Primary physician being urologist-oncologist (OR 9.0) and medical oncologist (OR 18)	

ADT, androgen deprivation therapy; AE, adverse event; ARPI, androgen receptor pathway inhibitor; CCI, Charlson Comorbidity Index; DOC, docetaxel; ECOG, Eastern Cooperative Oncology Group; MDT, metastasis-directed therapy; OR, odds ratio; PFS, progression-free survival; QoL, quality of life.

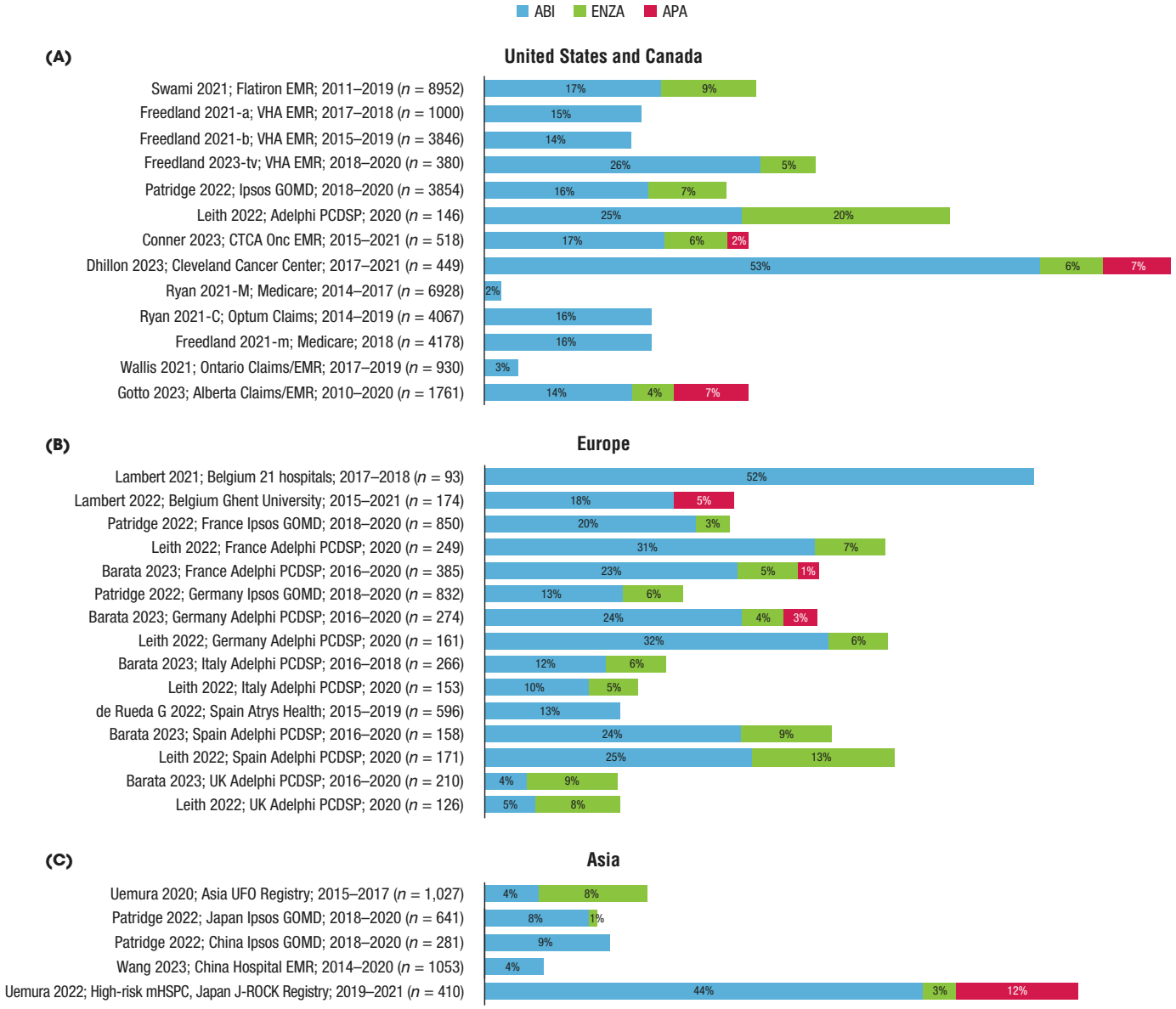
key factors reported in these studies were the presence of high disease burden (e.g., the spread of metastases and/or a high number of lesions; definitions varied by study), younger patient age, ECOG PS score of 0 to 1, the presence of fewer comorbidities, and a treating physician specialty of oncology. In addition to quantitative factors, two studies reported qualitative factors, which included patient preferences, an unsatisfactory response to prior ADT treatment, the ability to tolerate adverse events, and an absence of economic barriers, such as cost (Table 3).

Types of ARPIs Used Around the Globe

Figure 2A depicts studies with available data on the distribution of individual ARPI use in men with mHSPC across North America (United States and Canada). Across the majority of studies, abiraterone was the primary ARPI used in combination with ADT (0–53%). Enzalutamide use was low (0–20%), while any apalutamide use was low (0–7%) and reported in only a few studies. Darolutamide use (2%) was reported by only one study. While the use of abiraterone (United States, 49%; Canada, 35%) and enzalutamide (United States, 8%; Canada, 9%) was comparable between the United States and Canada in the IRONMAN global registry, the reported use of apalutamide was much lower in the United States (3%) compared with Canada (26%) (40).

Similarly, abiraterone remained the most common ARPI in combination with ADT in Europe (4–52%), followed by enzalutamide (0–13%; Fig. 2B). Apalutamide use (0–39%) was

Fig. 2 Utilisation patterns of ARPI in (**A**) the United States and Canada, (**B**) Europe, and (**C**) Asia. ABI, abiraterone; APA, apalutamide; ARPI, androgen receptor pathway inhibitor; DARO, darolutamide; ENZA, enzalutamide; GOMD, Global Oncology Monitor Database; VHA, Veterans Health Administration.



reported in fewer databases and ranged more widely than that of enzalutamide. European data from the IRONMAN global registry were comparable, with abiraterone being the most utilised agent (9–37%), followed by enzalutamide (7–30%) and apalutamide (3–10%). The use of darolutamide was reported only in Switzerland (2%) [40].

In Asia, only abiraterone and enzalutamide were reported as commonly used therapies (Fig. 2C), with abiraterone tending to be the leading choice (4–9%) and enzalutamide being the secondary choice (0–8%), which was consistent with global trends.

Discussion

Utilisation of appropriate therapy is critical to improving clinical outcomes, including survival, in men with mHSPC. This SLR summarises the treatment patterns of men with mHSPC, including data from 29 real-world studies with a variety of RWD sources around the globe, covering a pivotal period following publication of key clinical trials; the approval of novel therapeutic agents for mHSPC (e.g., abiraterone, apalutamide, enzalutamide) in the United States, Europe, and

Japan [48–55]; and updates to guideline recommendations on the use of ADT intensification.

This SLR presents several noteworthy findings, including the variability in ADT intensification treatment patterns across geographical regions and RWD sources.

First, although there was an increasing trend in the use of ADT intensification with ARPIs across different data sources over the years, ADT monotherapy was still used in 40–50% of men with mHSPC in most included studies, with data up to 2021. We also noted differences in the absolute proportion of ADT intensification use across studies, which could be attributed to differences in the RWD sources. The provenance of the RWD and its ability to accurately capture treatment and disease information, in addition to the depth and quality of the dataset (e.g., patient sample size included) are critical to the generalisability of findings. For example, within the United States, both private and public insurance-based claims databases are of a large volume and thus have more generalisability to the United States population. In contrast, chart-review and registry-based data may have less generalisability but are more precise in terms of disease identification. The data sources may nevertheless be comparable in terms of capture of medication use. Large claims databases showed a gradual increase in the uptake of ADT + ARPI over the study period, up to 34% in 2020 [23], whereas community oncologist–based data showed an uptake of up to 50% in 2020 within tertiary care centres [24]. More specifically, we noted a relatively higher use of chemotherapy among studies with RWD sources originating from oncologists or shared-decision settings, including ConcertAI and Cancer Treatment Centers of America. Furthermore, three studies (two based in the United States and one globally) reported that men with mHSPC who were treated by oncologists were more likely to receive ADT intensification compared with those managed by urologists. This may reflect the disease progression and transition of care patterns among men with mHSPC, especially those with recurrent mHSPC, given that individuals with early-stage disease are generally managed by urologists; transition of care patterns may also impact the setting of care (office-based vs clinic/hospital). Factors such as the variation in medical education between oncologists and urologists, academic vs community settings, respective board approvals and guidelines, and accessibility of specialties across geographical regions may further contribute to clinical differences in how the mHSPC population is managed by different physician specialties. As further data on the characteristics of populations as managed by varying physician specialties were limited, this topic therefore warrants further investigation.

Second, ADT + DOC use was much more commonly reported in Europe compared with the United States. Of note, most of these data originate from two global studies using the Adelphi PCDSP, where physicians are invited to contribute the de-identified data of their treated patients. These data showed relatively high use of ADT + ARPI and ADT + DOC across both the United States and Europe. Furthermore, ADT + DOC use was much greater in European studies compared with United States–based studies. Third, ADT with or without first-generation ARPIs remained the predominant choice in Asia. There were a few exceptions, as reported by two studies showing high use of ADT + ARPI, which may be attributable to the inclusion either largely or exclusively of men with high-risk mHSPC. The variation in treatment patterns could be due, in part, to differences in healthcare systems (private vs public), treatment funding or out-of-pocket costs, guidelines, and treatment approval status across geographical regions. For example, almost all ARPI agents were approved (and available) in the United States between 2018 and 2019, whereas approval and reimbursement decisions were made more than a year later in European or Asian countries [56] (Table S4 for regulatory and reimbursement details). In the Asia-Pacific region, along with the cost and accessibility of newer medications, reimbursement may indeed be an additional barrier on top of regional-specific dynamics, such as heightened concern over the potential toxicity of DOC, and accepted practice standards may further influence treatment selection [57,58].

The IRONMAN global registry data represented an outlier with respect to ADT monotherapy use in mHSPC compared with other studies from similar geographical regions. The IRONMAN global registry aims to understand treatment patterns and outcomes of novel therapies in men with mHSPC or CRPC across North America, Europe, and Oceania using post-clinical trial findings on the benefits of ADT intensification. All countries that contributed to this data source showed highly prevalent use of ADT intensification with ARPIs or chemotherapy, with only one in five patients treated with ADT monotherapy in the IRONMAN global registry compared with one in two patients in the majority of United States studies. Apart from country-level data, data on disease characteristics of mHSPC were not reported in preliminary findings, and sample sizes were low in centres outside the United States, thereby limiting our understanding of potential drivers of the highly guideline-consistent care reported within this registry.

Along with regional or data source variations, we also reported quantitative clinical or patient-related characteristics associated with the use of ADT intensification independent of data source, geographical region, or provider-level factors, such as younger age, higher tumour volume or disease burden, and better performance status. While we were not able to perform subgroup analyses on treatment patterns by key patient and disease characteristics, we did note that ADT intensification was proportionate to high tumour volume, but

not proportionate to performance status. This may indicate a higher preference given to tumour volume or disease burden in comparison to ECOG PS scores when identifying patients who are fit to receive ADT intensification. Apart from data source, geographical region, provider-level factors, and disease characteristics, a few studies also reported access issues to therapies as a barrier, in addition to perceived drug tolerability, perceived lack of clinical benefit, cost constraints, and lack of clarity on timing of treatment intensification within the disease journey to optimise treatment outcomes. These qualitative findings highlight the need for reducing access barriers and improving evidence generation and education across disciplines, as well as the education of patients and patient advocate groups regarding the benefits and safety of ADT intensification for men with mHSPC. Given the recency of available RCTs, critical steps would be to evaluate real-world safety, clinical outcomes, and cost-effectiveness in the future to globally understand the uptake of ADT intensification in men with mHSPC.

Among the ARPI regimens used for ADT intensification, abiraterone was observed as a leading choice across geographical regions. The use of enzalutamide was limited to ≤20% of the mHSPC population in most studies globally, and the use of apalutamide was lower yet. As approval, accessibility, and reimbursement statuses for ARPIs evolve, most recently with triplet therapy combinations of ADT + ARPI + DOC, new trends in treatment patterns, especially in further treatment intensification for patients with high disease burden, may begin to emerge. Indeed, prostate cancer treatment guidelines at both international and national levels have updated to include a triplet therapy recommendation for appropriate patients with mHSPC.

To the best of our knowledge, this is the most comprehensive and up-to-date SLR summarising treatment patterns in a total of 344 473 men with mHSPC, using 29 studies with global representation. Subgroup analyses were performed to better understand the impact of population-based or external policy factors on real-world ADT intensification practices. Due to some inherent limitations associated with SLRs, such as data reporting inconsistencies between studies, findings are summarised qualitatively. As data were either not available or limited to a very minor fraction of the mHSPC population, it was not possible to assess the use of ADT + ARPI + DOC given that RCTs for ADT + ARPI + DOC combinations post-dated the analysis period of this SLR.

Conclusion

Findings of this SLR show an increasing trend toward treatment intensification for men with mHSPC over the study period across geographical regions; however, a high proportion of patients are still receiving ADT monotherapy globally, particularly in the United States. There is a remaining unmet need for translational research to help bridge the gap between clinical trial evidence and real-world practice. Further studies are needed to develop interventions to overcome clinical inertia by optimising the adoption of guideline-concordant therapies and to foster greater awareness and educational intervention of current therapies in mHSPC.

Author Contributions

Amit D. Raval, Stephanie Chen, Natasha Littleton, Niculae Constantinovici, and Peter J. Goebell contributed to the study concept and design and the analysis and interpretation of the data. Amit D. Raval and Niculae Constantinovici contributed to the acquisition of data and provided administrative and technical support. Amit D. Raval contributed to the statistical analyses. Natasha Littleton, Niculae Constantinovici, and Peter J. Goebell provided supervision. Amit D. Raval participated in drafting the manuscript, and all authors critically reviewed and revised the manuscript.

Disclosure of Interests

This analysis was sponsored by Bayer HealthCare Pharmaceuticals Inc. (Whippany, NJ, USA). Amit D. Raval, Stephanie Chen, and Natasha Littleton are employees of Bayer HealthCare Pharmaceuticals Inc., and Niculae Constantinovici is an employee of Bayer Consumer Care; these authors were involved in the study design, data collection and analysis, manuscript preparation, and publication decisions. Peter J. Goebell has participated in advisory boards for and received honoraria for educational talks and travel support from Accord, Apogepha, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Clinsol, Eisai, EUSA Pharma, Gilead, iOMedico, Ipsen, Janssen, Merck, MSD, Novartis, Pfizer, Recordati, Roche, and Sanofi. The studies included in this systematic review noted funding by Janssen, Bayer, Astellas/Pfizer, and the Prostate Cancer Foundation or were independent studies.

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Data Availability Statement

All studies included in this systematic literature review are in the public domain.

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Abbreviations: ADT, androgen-deprivation therapy; ARPI, androgen receptor pathway inhibitor; ASCO, American Society of Clinical Oncology; (m)CRPC, (metastatic) castration-resistant prostate cancer; DOC, docetaxel; ECOG PS, Eastern Cooperative Oncology Group performance status; EMBASE, Excerpta Medica dataBASE; EMR, electronic medical record; ESMO, European Society for Medical Oncology; IRONMAN, International Registry for Men with Advanced Prostate Cancer; mHSPC, metastatic hormone-sensitive prostate cancer; PCDSP, Prostate Cancer Disease Specific Programme; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial; RWD, real-world data; SLR, systematic literature review.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Electronic database searches.

Table S2. Utilisation of triplet combination among included studies.

Table S3. Assessment of quality of RWD studies in terms of representativeness and accuracy of disease and treatment pattern identification.

Table S4. Regulatory and reimbursement approvals for novel therapies in mHSPC within the United States, Europe and Asia.

Figure S1. The PRISMA flow diagram for study selection.

Figure S2. The mHSPC treatment patterns in (A) United States, (B) Canada, (C) Europe, and (D) Asia.

Figure S3. The mHSPC treatment patterns within the United States using claims databases.

Figure S4. The IRONMAN global registry mHSPC treatment patterns.

Figure S5. The ADT intensification treatment subgroup: urologists vs oncologists.

