REVIEW

5α-Reductase Inhibitors Could Prevent the Clinical and Pathological Progression of Prostate Cancer: A Meta-analysis

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Purpose: To explore the efficacy of 5-ARIs in PCA (Prostate Cancer).

Methods: Searching through the major medical databases such as PubMed, Science Citation Index, EMBASE, Medline, Web of Science, Cochrane Library for all published studies in English until 2018. The following search terms were used: "Finasteride", "dutasteride", "5α reductase inhibitors", "5-ARIs", "prostate cancer", "prostate neoplasm" and the additional related studies were manually searched. Newcastle-Ottawa Scale (NOS) assessed the qualities of studies, and the outcome measures were observed by RR or OR with 95% CIs.

Results: We included 9 eligible studies for analyses from 2011 to 2017. We found that 5-ARIs group may have fewer progression (OR = 0.48 95%CI: 0.37-0.61 $P < 0.00001$, I2=4% $p = 0.39$) and lower pathological progression (OR = 0.46; 95%CI: 0.29-0.73; $p = 0.001$, I2=0% $p = 0.45$), compared with control groups. However, the OS did not show significant difference between two groups (OR=1.10; 95%CI:0.90-1.35; $P = 0.35$, I2 = 93% $P < .00001$).

Conclusion: The use of 5-ARIs could prevent progression in PCA patients both clinical and pathological.

Keywords: 5α-reductase inhibitors, prostate cancer, clinical progression, pathological progression, meta-analysis

INTRODUCTION

Inhibitors of 5a-reductase(5-ARIs), such as finasteride and dutasteride, are widely used in the medical treatment of benign prostatic hyperplasia (BPH)[(1)], and these drugs inhibit the conversion of testosterone to dihydrotestosterone(DHT) to reduce the prostate size and alleviate the lower urinary obstruction. Blocking DHT leads to a lower level of androgen, which is involved in the development of prostate cancer, thus we may wonder that 5-ARIs may have an effect on prostate cancer or not. The Prostate Cancer Prevention Trial (PCPT)[(2)], a large, phase III and double-blind placebo-control trial, reported that finasteride may decrease the risk of new prostate cancer through changes in intraprostatic androgen. The data was impressive, however, some other studies[(3)] also pointed out that there were no strong pieces of evidence that showed the benefit of the finasteride and analogous 5-ARIs. Therefore, researchers have a furious conflict about the efficacy of 5-ARIs in prostate cancer, and we did this meta-analysis to quantify the effect of 5-ARI on PCA patients.

METHODS

Search Strategy

We searched Pubmed, Embase, and the Cochrane Library(until May 6, 2018). In addition, we searched potentially relevant trials from the references of selected studies by hand. The search strategy was followed by using all possible combinations of medical subject headings(MeSH) or non-MeSH terms: "finasteride", "dutasteride", "5α reductase inhibitors", "5-ARIs", "prostate cancer", "prostate neoplasm" and the additional related studies were manually searched. Each search strategy met each database. (**Figure 1**)

Selection Criteria

Studies that were published in English were selected if they met the following criteria: (1) All patients should be diagnosed with prostate cancer(PCA) in pathology. (2) All patients' clinical and pathological parameters were covered (3) All studies should be controlled trials which compared 5-ARIs with placebo (4) The observations should report at least one of our outcomes: progression of cancer and overall survival(OS). (5) The same trial that was reported by different articles should be excluded. (6) Case reports, letters, systematic reviews, comments, and animals trial should be excluded.

Data extraction

Two reviewers independently assessed all eligible publications, and disagreements were resolved by discussion with a third reviewer. Data from all full-text studies that accorded with selection criteria were independently extracted by each reviewer using a standardized ex-

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Table 1. Demographic and clinical data of DM and non-DM patients in different studies.

Reference	Country	Center	Design	Period	Sample		Age		Follow-up (years)	Event	Quanity
					5-ARI	Placebo	5-ARI	Placebo			
Aners Kjellman 2013 ********	Denmark	M	T	1989-2001	199	2806	73.9+8.3	73.6+8.5	3	1,2	
Antonio Finalli 2011	Canada	S	T	1995-2010	70	218	65.6+6.4	63.8+7.8	4	3,4	*******
Ashley E.Ross 2011	USA	M	T	1994-2010	47	540	66	65	4	3,4	******
Charles Dai 2017	Egypt	S	T	2002-2015	70	301	66+7	64+7	3	1,3	*******
Fritz Schroder 2013	USA	S	R	N	147	146	69.7	68.6	2	3	******
Laurent Azoulay 2015 ********	Canada	M	T	1999-2009	574	13318	76.2+8.2	71.9+9.2	5	3,5	
Neil E Fleshner 2012	Canada	S	R	2006-2007	147	155	N	N	3	3,4	*****
Rodolfo Monotironi 2013	Italy	S	R	N	41	42	64+4	63+7	2	3,4	******
Teemu J.Murtola 2013	Finland	S	T	1995-2009	24	901	N	N	4	1,3,4	*****

Center: M: multiple centers, S: single center ;Event: 1:Overall survival,2:Prostate-cancer specific surviva, 3:Progression, 4:Pathologic progression, 5:All cause mortality;T:Retropective, R:Rondomized;N: not mentioned

traction form. All the data extracted from the studies included details on the first author name, publication year, country, study design, study period, number of patients, duration of follow-up (**Table 1**).

Outcome Measures

The primary outcome measures were a progression of cancer, defined as the number of the patients who got disease progressing including clinical and pathological progression. Secondary outcome measures in this meta-analysis were overall survival (OS), defined as the time from observation to death during the research.

Statistical Analysis

Differences were expressed as RR with 95% CIs for the primary outcome and OR for the secondary outcome. The RR below 1 meant an advantage of 5-ARIs better than the placebo such as none of the analogy. I^2 statistics were used to quantify the heterogeneity across trials, which is a standardized measure of inconsistency and chi-square(Cochrane Q statistic) test. If I^2 statistics < 50% and as a *p*-value > 0.05 for chi-square test, it indicted to have a low level of heterogeneity. A fix-effects model was used to pool estimates in a low level of heterogeneity. A random-effects model was used to pool estimates in a high level of heterogeneity. Patient characteristics and other confounding factors in all the studies didn't have significant heterogeneity. Meanwhile, Subgroup analyses were planned to assess the effect of different progression of the tumor. A *P* value <.05 was affirmed as statistically significant.

Quality Assessment

The methodological quality of each controlled trial was evaluated by using the Newcastle-Ottawa Scale (NOS) [4] which was recommended for assessing the qualities of studies and a study with >= 7 awarded stars was considered as a high-quality study.

RESULTS

After removing 122 duplicates, 209 potential studies were identified through reviewing abstracts and articles, 42 studies were excluded due to no combination therapy, incomplete outcome data, no comparison group, or not in English. The final set of eligible studies included 9 studies[5-13], published from 2011 to 2017. The selection strategy is shown in **Figure 1**. The characteristics of 9 included studies are summarized in **Table 1**. A to-

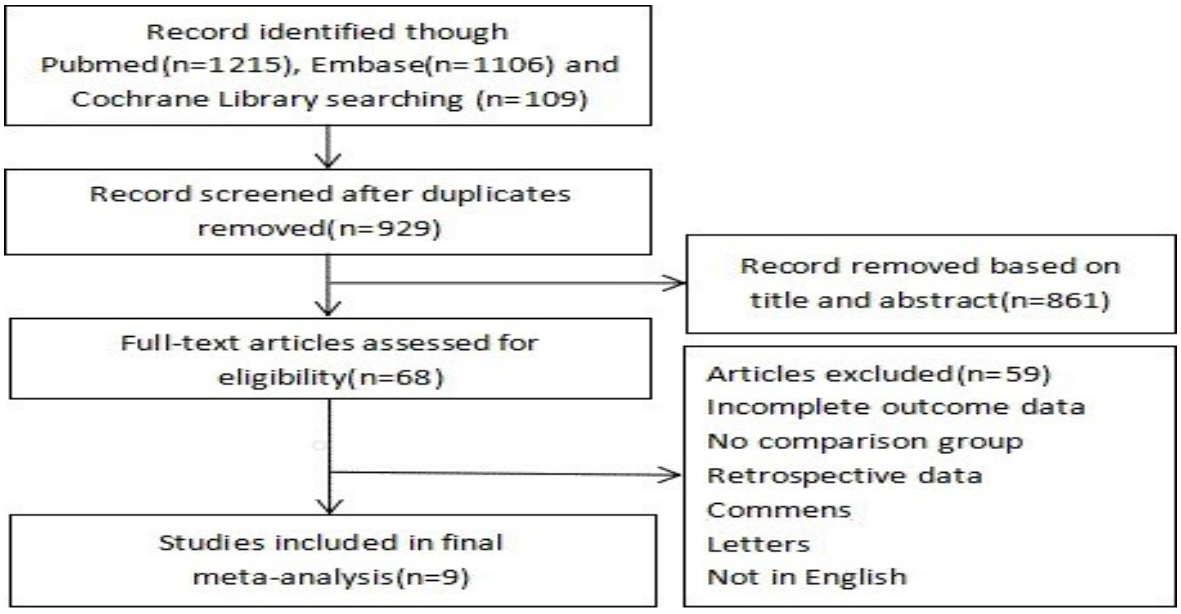
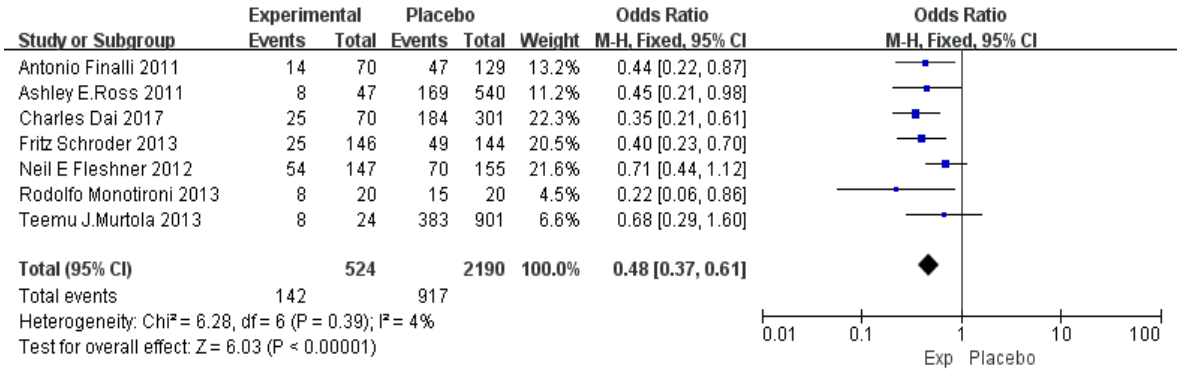


Figure 1. Selecting flowchat for included studies in the meta-analysis



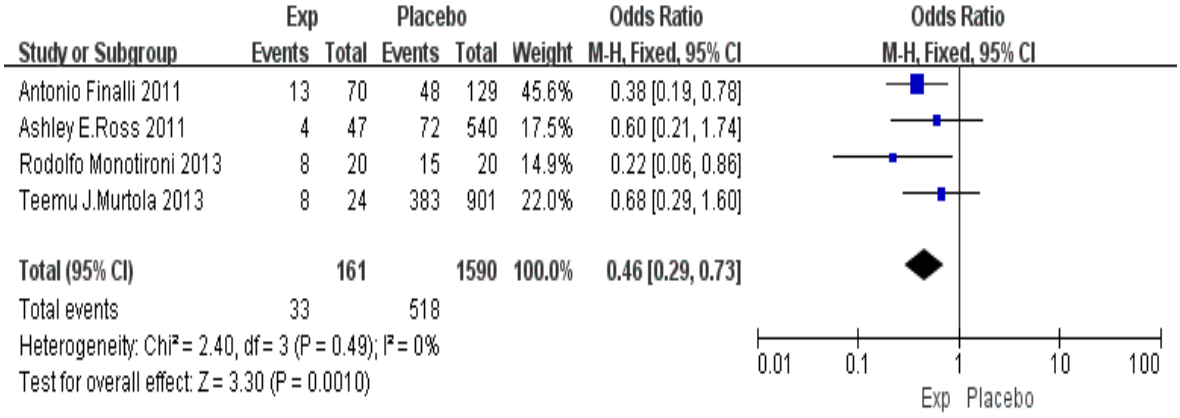
tal of 19764 patients were included in this meta-analysis. 1319 patients were treated with 5-ARIs.

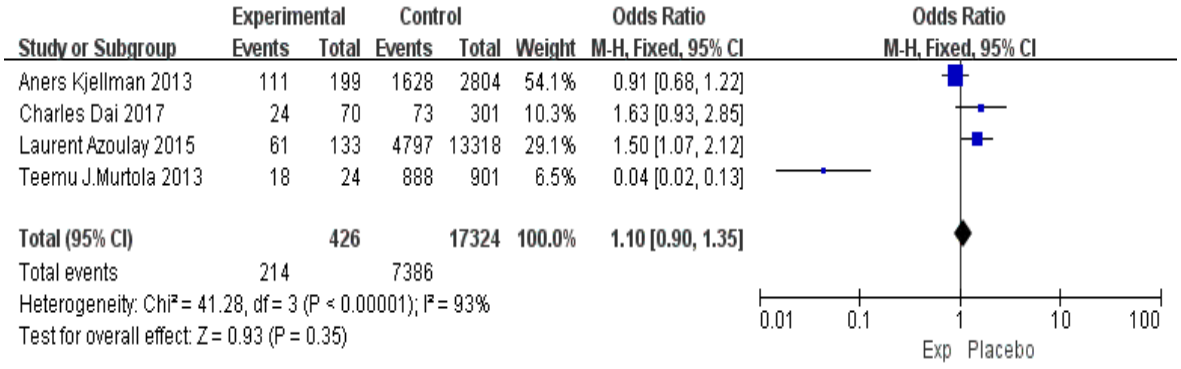
Effect of interventions on the primary outcome measure Progression (both clinical and pathological progression) was the primary outcome measure in this meta-analysis. Using a random-effects model, the pooled OR was 0.48(95%CI: 0.37-0.61; $p < 0.00001$, **Figure 2**). This represented significantly fewer progression in patients with 5-ARIs, and no heterogeneity was observed (I^2=4%, $p = 0.39$).

Furthermore, the subgroup analyses were conducted and shown in **Figure 3**. The pathological progression also decreased in 5-ARIs groups (OR=0.46; 95%CI: 0.29-0.73; $p = 0.001$, heterogeneity $p = 0.45$, $I^2 = 0\%$), thus PCA patients gained more benefit from 5-ARIs. The second outcome, Overall survival(OS) did not show significant difference between two groups (OR=1.10; 95%CI, 0.90-1.35; $p = 0.35$, heterogeneity $p < 0.00001$, I^2=93%, **Figure 4**).No significant publication bias existed in the funnel plots.

DISCUSSION

We present this meta-analysis to assess the effect of 5-ARIs in treatment with PCA, and the results showed an inspiring outcome that 5-ARIs may prevent the progression of PCA. In our study, less progression was observed in the 5-ARIs groups (5-ARIs vs Placebo OR=0.48 95%CI:0.37-0.61; $p < 0.00001$). Furthermore, the subgroup analysis was also undertaken and we identified a positive effect of 5-ARIs in pathological progression(5-ARIs vs Placebo, OR=0.46, 95%CI: 0.29-0.73, $p = 0.001$, I^2=0%). Moreover, the results were coincident with recent researches, and increasing evidence suggested that there may be a close affinity between PCA and 5-ARIs. In the Prostate Cancer Prevention Trial(PCPT), a total of 18882 patients were assigned to finasteride or placebo for PCA with 7 years follow-up, and the study showed that the finasteride could reduce the risk of prostate cancer by 25%[14]. Meanwhile, Fritz Schroder.et[10]also conducted a randomized, placebo-controlled Avodart after radical therapy for prostate cancer study(ARTS), which included 294 subjects with dutasteride treatment over 2 years and they concluded that dutasteride could delay the progression of PCA, even in patients with biochemical failure after radical therapy for clinically localized disease. In fact, the drugs, such as finasteride, dutasteride, and other 5-ARIs, inhibited testosterone to DHT, which played an important role in the PCA mechanism. The progression of PCA could perform in a clinical or pathological way. The clinical progression may behave as tumor metastasis, a higher level of PSA, or biochemical progression after therapies. Studies demonstrated that PCA was an androgen-relative tumor, thus impeding the original substrate of translation to androgen should prevent the progression of PCA somehow. Besides, pathological progression can be defined as an increased





grade, increased number of scores to more than three, or any core involvement over 50%. Noticeably, the trial[13] reported that those taking 5-ARIs could bring an approximate 50% reduction in the rate of pathological progression. However, many conflicts[15] also pointed out that the finasteride contributed to the increase in high-grade cancers. Long-term 5-ARIs treatment had been proposed to alter the histologic appearance of prostate cancer tissue, which would falsely lead to high Gleason grades in a low-grade tumor[5], but larger prostates are more likely to be undergraded at initial diagnostic biopsy, thus patients who took 5-ARIs might theoretically be likely to be detected with a higher grade with subsequent biopsies[16] and it might not be ascribed the higher Gleason score in a low-grade tumor to a pathologic progression. Eventually, as the aspect of the amount of observation[12], 5-ARIs appeared to diminish the progression of PCA patients.

Counting for the overall survivals, our study found there was no significant difference between 5-ARIs and placebo (OR=1.10; 95%CI, 0.90-1.35; p = 0.35). A recent Finnish Prostate Cancer Screening trial[18] similarly implicated that 5-ARIs use didn't have an impact on survival (HR=1.51, p = 0.8). Meanwhile, a larger study[18], which included over 3 million patients from Denmark, reported that 5-ARIs were associated with an increased risk of PCA-specific mortality(HR=2.1, 95%CI: 1.97-2.30). However, even more, studies should be needed to definitely prove this in the future. To our knowledge, this is the first meta-analysis to systemically assess the efficiency of 5-ARIs in the progression of the PCA patients. The present meta-analysis carries few limitations that must be taken into account. The main limitation is that our meta-analysis contains few randomized data, most of the studies included were observational. Although the heterogeneity of studies was not obvious, all the patients in different groups were not possible to match for age, BMI, preoperative therapy, and these biases may affect the primary outcome. All these factors may have contributed to a higher heterogeneity between studies. Because of these limitations, larger and randomized control trials were needed to confirm these results.

CONCLUSIONS

The use of 5-ARIs could prevent progression in PCA patients both in clinical and pathological terms.

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CONFLICT OF INTEREST

None of the authors have a conflict of interest to declare.

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