Fall Injury Among Community-Dwelling Older Adults: Effect of a Multifactorial Intervention and a Home Hazard Removal Program

Bhasin S, Gill TM, Reuben DB, et al; STRIDE Trial Investigators. A randomized trial of a multifactorial strategy to prevent serious fall injuries. N Engl J Med. 2020;383:129-140. doi:10.1056/NEJMoa2002183

Stark S, Keglovits M, Somerville E, et al. Home hazard removal to reduce falls among community-dwelling older adults: a randomized clinical trial. JAMA Netw Open. 2021;4(8):e2122044. doi:10.1001/jamanetworkopen.2021.22044

Study 1 Overview (Bhasin et al)

Objective: To examine the effect of a multifactorial intervention for fall prevention on fall injury in community-dwelling older adults.

Design: This was a pragmatic, cluster randomized trial conducted in 86 primary care practices across 10 health care systems.

Setting and participants: The primary care sites were selected based on the prespecified criteria of size, ability to implement the intervention, proximity to other practices, accessibility to electronic health records, and access to community-based exercise programs. The primary care practices were randomly assigned to intervention or control.

Eligibility criteria for participants at those practices included age 70 years or older, dwelling in the community, and having an increased risk of falls, as determined by a history of fall-related injury in the past year, 2 or more falls in the past year, or being afraid of falling because of problems with balance or walking. Exclusion criteria were inability to provide consent or lack of proxy consent for participants who were determined to have cognitive impairment based on screening, and inability to speak English or Spanish. A total of 2802 participants were enrolled in the intervention group, and 2649 participants were enrolled in the control group.

Intervention: The intervention contained 5 components: a standardized assessment of 7 modifiable risk factors for fall injuries; standardized protocol-driven recommendations for management of risk factors; an individualized care plan focused on 1 to 3 risk factors; implementation of care plans, including referrals to community-based programs; and follow-up care conducted by telephone or in person. The modifiable risk factors included impairment of strength, gait, or balance; use of medications related to falls; postural hypotension; problems with feet or footwear; visual impairment; osteoporosis or vitamin D deficiency; and home safety hazards. The intervention was

delivered by nurses who had completed online training modules and face-to-face training sessions focused on the intervention and motivational interviewing along with continuing education, in partnership with participants and their primary care providers. In the control group, participants received enhanced usual care, including an informational pamphlet, and were encouraged to discuss fall prevention with their primary care provider, including the results of their screening evaluation.

Main outcome measures: The primary outcome of the study was the first serious fall injury in a time-to-event analysis, defined as a fall resulting in a fracture (other than thoracic or lumbar vertebral fracture), joint dislocation, cut requiring closure, head injury requiring hospitalization, sprain or strain, bruising or swelling, or other serious injury. The secondary outcome was first patient-reported fall injury, also in a time-to-event analysis, ascertained by telephone interviews conducted every 4 months. Other outcomes included hospital admissions, emergency department visits, and other health care utilization. Adjudication of fall events and injuries was conducted by a team blinded to treatment assignment and verified using administrative claims data, encounter data, or electronic health record review.

Main results: The intervention and control groups were similar in terms of sex and age: 62.5% vs 61.5% of participants were women, and mean (SD) age was 79.9 (5.7) years and 79.5 (5.8) years, respectively. Other demographic characteristics were similar between groups. For the primary outcome, the rate of first serious injury was 4.9 per 100 person-years in the intervention group and 5.3 per 100 person-years in the control group, with a hazard ratio of 0.92 (95% CI, 0.80-1.06; $P = .25$). For the secondary outcome of patient-reported fall injury, there were 25.6 events per 100 person-years in the intervention group and 28.6 in the control group, with a hazard ratio of 0.90 (95% CI, 0.83-0.99; $P = 0.004$). Rates of hospitalization and other secondary outcomes were similar between groups.

Conclusion: The multifactorial STRIDE intervention did not reduce the rate of serious fall injury when compared to enhanced usual care. The intervention did result in lower rates of fall injury by patient report, but no other significant outcomes were seen.

Study 2 Overview (Stark et al)

Objective: To examine the effect of a behavioral home hazard removal intervention for fall prevention on risk of fall in community-dwelling older adults.

Design: This randomized clinical trial was conducted at a single site in St. Louis, Missouri. Participants were community-dwelling older adults who received services from the Area Agency on Aging (AAA). Inclusion criteria included age 65 years and older, having 1 or more falls in the previous 12 months or being worried about falling by self report, and currently receiving services from an AAA. Exclusion criteria included living in an institution or being severely cognitively impaired and unable to follow directions or report falls. Participants who met the criteria were contacted by phone and invited to participate. A total of 310 participants were enrolled in the study, with an equal number of participants assigned to the intervention and control groups.

Intervention: The intervention included hazard identification and removal after a comprehensive assessment of participants, their behaviors, and the environment; this assessment took place during the first visit, which lasted approximately 80 minutes. A home hazard removal plan was developed, and in the second session, which lasted approximately 40 minutes, remediation of hazards was carried out. A third session for home modification that lasted approximately 30 minutes was conducted, if needed. At 6 months after the intervention, a booster session to identify and remediate any new home hazards and address issues was conducted. Specific interventions, as identified by the assessment, included minor home repair such as grab bars, adaptive equipment, task modification, and education. Shared decision making that enabled older adults to control changes in their homes, self-management strategies to improve awareness, and motivational enhancement strategies to improve acceptance were employed. Scripted algorithms and checklists were used to deliver the intervention. For usual care, an annual assessment and referrals to community services, if needed, were conducted in the AAA.

Main outcome measures: The primary outcome of the study was the number of days to first fall in 12 months. Falls were defined as unintentional movements to the floor, ground, or object below knee level, and falls were recorded

through a daily journal for 12 months. Participants were contacted by phone if they did not return the journal or reported a fall. Participants were interviewed to verify falls and determine whether a fall was injurious. Secondary outcomes included rate of falls per person per 12 months; daily activity performance measured using the Older Americans Resources and Services Activities of Daily Living scale; falls self-efficacy, which measures confidence performing daily activities without falling; and quality of life using the SF-36 at 12 months.

Main results: Most of the study participants were women (74%), and mean (SD) age was 75 (7.4) years. Study retention was similar between the intervention and control groups, with 82% completing the study in the intervention group compared with 81% in the control group. Fidelity to the intervention, as measured by a checklist by the interventionist, was 99%, and adherence to home modification, as measured by number of home modifications in use by self report, was high at 92% at 6 months and 91% at 12 months. For the primary outcome, fall hazard was not different between the intervention and control groups (hazard ratio, 0.9; 95% CI, 0.66-1.27). For the secondary outcomes, the rate of falling was lower in the intervention group compared with the control group, with a relative risk of 0.62 (95% CI, 0.40-0.95). There was no difference in other secondary outcomes of daily activity performance, falls self-efficacy, or quality of life.

Conclusion: Despite high adherence to home modifications and fidelity to the intervention, this home hazard removal program did not reduce the risk of falling when compared to usual care. It did reduce the rate of falls, although no other effects were observed.

Commentary

Observational studies have identified factors that contribute to falls,[1] and over the past 30 years a number of intervention trials designed to reduce the risk of falling have been conducted. A recent Cochrane review, published prior to the Bhasin et al and Stark et al trials, looked at the effect of multifactorial interventions for fall prevention across 62 trials that included 19,935 older adults living in the community. The review concluded that multifactorial interventions may reduce the rate of falls, but this conclusion was based on low-quality evidence and there was significant heterogeneity across the studies.[2]

The STRIDE randomized trial represents the latest effort to address the evidence gap around fall prevention, with the STRIDE investigators hoping this would be the definitive trial that leads to practice change in fall prevention. Smaller trials that have demonstrated effectiveness were brought to scale in this large randomized trial that included 86 practices and more than 5000 participants. The investigators used risk of injurious falls as the primary outcome, as this outcome is considered the most clinically meaningful for the study population. The results, however, were disappointing: the multifactorial intervention in STRIDE did not result in a reduction of risk of injurious falls. Challenges in the implementation of this large trial may have contributed to its results; falls care managers, key to this multifactorial intervention, reported difficulties in navigating complex relationships with patients, families, study staff, and primary care practices during the study. Barriers reported included clinical space limitations, variable buy-in from providers, and turnover of practice staff and providers.[3] Such implementation factors may have resulted in the divergent results between smaller clinical trials and this large-scale trial conducted across multiple settings.

The second study, by Stark et al, examined a home modification program and its effect on risk of falls. A prior Cochrane review examining the effect of home safety assessment and modification indicates that these strategies are effective in reducing the rate of falls as well as the risk of falling.[4] The results of the current trial showed a reduction in the rate of falls but not in the risk of falling; however, this study did not examine outcomes of serious injurious falls, which may be more clinically meaningful. The Stark et al study adds to the existing literature showing that home modification may have an impact on fall rates. One noteworthy aspect of the Stark et al trial is the high adherence rate to home modification in a community-based approach; perhaps the investigators' approach can be translated to real-world use.

Applications for Clinical Practice and System Implementation

The role of exercise programs in reducing fall rates is well established,[5] but neither of these studies focused on

exercise interventions. STRIDE offered community-based exercise program referral, but there is variability in such programs and study staff reported challenges in matching participants with appropriate exercise programs.[3] Further studies that examine combinations of multifactorial falls risk reduction, exercise, and home safety, with careful consideration of implementation challenges to assure fidelity and adherence to the intervention, are needed to ascertain the best strategy for fall prevention for older adults at risk.

Given the results of these trials, it is difficult to recommend one falls prevention intervention over another. Clinicians should continue to identify falls risk factors using standardized assessments and determine which factors are modifiable.

Practice Points

- Incorporating assessments of falls risk in primary care is feasible, and such assessments can identify important risk factors.
- Clinicians and health systems should identify avenues, such as developing programmatic approaches, to providing home safety assessment and intervention, exercise options, medication review, and modification of other risk factors.
- Ensuring delivery of these elements reliably through programmatic approaches with adequate follow-up is key to preventing falls in this population.

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Coronary CT Angiography Compared to Coronary Angiography or Standard of Care in Patients With Intermediate-Risk Stable Chest Pain

SCOT-HEART Investigators, Newby DE, Adamson PD, Berry C, et al. Coronary CT angiography and 5-year risk of myocardial infarction. N Engl J Med. 2018;379(1):924-933. doi:10.1056/NEJMoa1805971

DISCHARGE Trial Group, Maurovich-Horvat P, Bosserdt M, Kofoed KF, et al. CT or invasive coronary angiography in stable chest pain. N Engl J Med. 2022;386(17):1591-1602. doi:10.1056/NEJMoa2200963

Study 1 Overview (SCOT-HEART Investigators)

Objective: To assess cardiovascular mortality and nonfatal myocardial infarction at 5 years in patients with stable chest pain referred to cardiology clinic for management with either standard care plus computed tomography

angiography (CTA) or standard care alone.

Design: Multicenter, randomized, open-label prospective study.

Setting and participants: A total of 4146 patients with stable chest pain were randomized to standard care or standard care plus CTA at 12 centers across Scotland and were followed for 5 years.

Main outcome measures: The primary end point was a composite of death from coronary heart disease or nonfatal myocardial infarction. Main secondary end points were nonfatal myocardial infarction, nonfatal stroke, and frequency of invasive coronary angiography (ICA) and coronary revascularization with percutaneous coronary intervention or coronary artery bypass grafting.

Main results: The primary outcome including the composite of cardiovascular death or nonfatal myocardial infarction was lower in the CTA group than in the standard-care group at 2.3% (48 of 2073 patients) vs 3.9% (81 of 2073 patients), respectively (hazard ratio, 0.59; 95% CI, 0.41-0.84; $P = .004$). Although there was a higher rate of ICA and coronary revascularization in the CTA group than in the standard-care group in the first few months of follow-up, the overall rates were similar at 5 years, with ICA performed in 491 patients and 502 patients in the CTA vs standard-care groups, respectively (hazard ratio, 1.00; 95% CI, 0.88-1.13). Similarly, coronary revascularization was performed in 279 patients in the CTA group and in 267 patients in the standard-care group (hazard ratio, 1.07; 95% CI, 0.91-1.27). There were, however, more preventive therapies initiated in patients in the CTA group than in the standard-care group (odds ratio, 1.40; 95% CI, 1.19-1.65).

Conclusion: In patients with stable chest pain, the use of CTA in addition to standard care resulted in a significantly lower rate of death from coronary heart disease or nonfatal myocardial infarction at 5 years; the main contributor to this outcome was a reduced nonfatal myocardial infarction rate. There was no difference in the rate of coronary angiography or coronary revascularization between the 2 groups at 5 years.

Study 2 Overview (DISCHARGE Trial Group)

Objective: To compare the effectiveness of computed tomography (CT) with ICA as a diagnostic tool in patients with stable chest pain and intermediate pretest probability of coronary artery disease (CAD).

Design: Multicenter, randomized, assessor-blinded pragmatic prospective study.

Setting and participants: A total of 3667 patients with stable chest pain and intermediate pretest probability of CAD were enrolled at 26 centers and randomized into CT or ICA groups. Only 3561 patients were included in the modified intention-to-treat analysis, with 1808 patients and 1753 patients in the CT and ICA groups, respectively.

Main outcome measures: The primary outcome was a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke over 3.5 years. The main secondary outcomes were major procedure-related complications and patient-reported angina pectoris during the last 4 weeks of follow up.

Main results: The primary outcome occurred in 38 of 1808 patients (2.1%) in the CT group and in 52 of 1753 patients (3.0%) in the ICA group (hazard ratio, 0.70; 95% CI, 0.46-1.07; $P = .10$). The secondary outcomes showed that major procedure-related complications occurred in 9 patients (0.5%) in the CT group and in 33 patients (1.9%) in the ICA group (hazard ratio, 0.26; 95% CI, 0.13-0.55). Rates of patient-reported angina in the final 4 weeks of follow-up were 8.8% in the CT group and 7.5% in the ICA group (odds ratio, 1.17; 95% CI, 0.92-1.48).

Conclusion: Risk of major adverse cardiovascular events from the primary outcome were similar in both the CT and ICA groups among patients with stable chest pain and intermediate pretest probability of CAD. Patients referred for CT had a lower rate of coronary angiography leading to fewer major procedure-related complications in these patients than in those referred for ICA.

Commentary

Evaluation and treatment of obstructive atherosclerosis is an important part of clinical care in patients presenting with angina symptoms.[1] Thus, the initial investigation for patients with suspected obstructive CAD includes ruling out acute coronary syndrome and assessing quality of life.[1] The diagnostic test should be tailored to the pretest probability for the diagnosis of obstructive CAD.[2]

In the United States, stress testing traditionally has been used for the initial assessment in patients with suspected

CAD,[3] but recently CTA has been utilized more frequently for this purpose. Compared to a stress test, which often helps identify and assess ischemia, CTA can provide anatomical assessment, with higher sensitivity to identify CAD.[4] Furthermore, it can distinguish nonobstructive plaques that can be challenging to identify with stress test alone.

Whether CTA is superior to stress testing as the initial assessment for CAD has been debated. The randomized PROMISE trial compared patients with stable angina who underwent functional stress testing or CTA as an initial strategy.[5] They reported a similar outcome between the 2 groups at a median follow-up of 2 years. However, in the original SCOT-HEART trial (CT coronary angiography in patients with suspected angina due to coronary heart disease), which was published in the same year as the PROMISE trial, the patients who underwent initial assessment with CTA had a numerically lower composite end point of cardiac death and myocardial infarction at a median follow-up of 1.7 years (1.3% vs 2.0%, $P = .053$).[6]

Given this result, the SCOT-HEART investigators extended the follow-up to evaluate the composite end point of death from coronary heart disease or nonfatal myocardial infarction at 5 years.[7] This trial enrolled patients who were initially referred to a cardiology clinic for evaluation of chest pain, and they were randomized to standard care plus CTA or standard care alone. At a median duration of 4.8 years, the primary outcome was lower in the CTA group (2.3%, 48 patients) than in the standard-care group (3.9%, 81 patients) (hazard ratio, 0.58; 95% CI, 0.41-0.84; $P = .004$). Both groups had similar rates of invasive coronary angiography and had similar coronary revascularization rates.

It is hypothesized that this lower rate of nonfatal myocardial infarction in patients with CTA plus standard care is associated with a higher rate of preventive therapies initiated in patients in the CTA-plus-standard-care group compared to standard care alone. However, the difference in the standard-care group should be noted when compared to the PROMISE trial. In the PROMISE trial, the comparator group had predominantly stress imaging (either nuclear stress test or echocardiography), while in the SCOT-HEART trial, the group had predominantly stress electrocardiogram (ECG), and only 10% of the patients underwent stress imaging. It is possible the difference seen in the rate of nonfatal myocardial infarction was due to suboptimal diagnosis of CAD with stress ECG, which has lower sensitivity compared to stress imaging.

The DISCHARGE trial investigated the effectiveness of CTA vs ICA as the initial diagnostic test in the management of patients with stable chest pain and an intermediate pretest probability of obstructive CAD.[8] At 3.5 years of follow-up, the primary composite of cardiovascular death, myocardial infarction, or stroke was similar in both groups (2.1% vs 3.0; hazard ratio, 0.70; 95% CI, 0.46-1.07; $P = .10$). Importantly, as fewer patients underwent ICA, the risk of procedure-related complication was lower in the CTA group than in the ICA group. However, it is important to note that only 25% of the patients diagnosed with obstructive CAD had greater than 50% vessel stenosis, which raises the question of whether an initial invasive strategy is appropriate for this population.

The strengths of these 2 studies include the large number of patients enrolled along with adequate follow-up, 5 years in the SCOT-HEART trial and 3.5 years in the DISCHARGE trial. The 2 studies overall suggest the usefulness of CTA for assessment of CAD. However, the control groups were very different in these 2 trials. In the SCOT-HEART study, the comparator group was primarily assessed by stress ECG, while in the DISCHARGE study, the comparator group was primary assessed by ICA. In the PROMISE trial, the composite end point of death, myocardial infarction, hospitalization for unstable angina, or major procedural complication was similar when the strategy of initial CTA was compared to functional testing with imaging (exercise ECG, nuclear stress testing, or echocardiography).[5] Thus, clinical assessment is still needed when clinicians are selecting the appropriate diagnostic test for patients with suspected CAD. The most recent guidelines give similar recommendations for CTA compared to stress imaging.[9] Whether further improvement in CTA acquisition or the addition of CT fractional flow reserve can further improve outcomes requires additional study.

Applications for Clinical Practice and System Implementation

In patients with stable chest pain and intermediate pretest probability of CAD, CTA is useful in diagnosis compared to stress ECG and in reducing utilization of low-yield

ICA. Whether CTA is more useful compared to the other noninvasive stress imaging modalities in this population requires further study.

Practice Points

- In patients with stable chest pain and intermediate pretest probability of CAD, CTA is useful compared to stress ECG.
- Use of CTA can potentially reduce the use of low-yield coronary angiography.

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Overall Survival Gain With Adding Darolutamide to ADT and Docetaxel in Metastatic, Hormone-Sensitive Prostate Cancer

Smith MR, Hussain M, Saad F, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. N Engl J Med. 2022;386(12):1132-1142. doi:10.1056/NEJMoa2119115

Study Overview

Objective: To evaluate whether the addition of the potent androgen-receptor inhibitor (ARA) darolutamide to the standard doublet androgen-deprivation therapy (ADT) and docetaxel in metastatic, hormone-sensitive prostate cancer (mHSPC) would increase survival.

Design: A randomized, double-blind, placebo-controlled, multicenter, phase 3 study. The results reported in this publication are from the prespecified interim analysis.

Intervention: Patients with mHSPC were randomly assigned to receive either darolutamide 600 mg twice daily or placebo. All patients received standard ADT with 6 cycles of docetaxel 75 mg/m^2 on day 1 every 21 days along with prednisone given within 6 weeks after randomization. Patients receiving luteinizing hormone–

releasing hormone (LHRH) agonists as ADT were bridged with at least 4 weeks of first-generation antiandrogen therapy, which was discontinued before randomization. Treatments were continued until symptomatic disease progression, a change in neoplastic therapy, unacceptable toxicity, patient or physician decision, death, or nonadherence.

Setting and participants: Eligible patients included those newly diagnosed with mHSPC with metastases detected on contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) and bone scan. Patients were excluded if they had regional lymph node–only involvement or if they had received more than 12 weeks of ADT before randomization. Between November 2016 and June 2018, 1306 patients (651 in the darolutamide group and 655 in the placebo group) were randomized in a 1:1 manner to receive darolutamide 600 mg twice daily or placebo in addition to ADT and docetaxel. Randomization was stratified based on the TNM staging system (M1a—nonregional lymph node–only metastasis, M1b—bone metastasis with or without lymph node, or M1c—bone metastases) as well as baseline alkaline phosphatase levels.

Main outcome measures: The primary end point for the study was overall survival. Other meaningful secondary end points included time to castration resistance, time to pain progression, time to first symptomatic skeletal event, symptomatic skeletal event-free survival, time to subsequent systemic antineoplastic therapy, time to worsening of disease-related physical symptoms, initiation of opioid therapy for ≥7 days, and safety.

Results: The baseline and demographic characteristics were well balanced between the 2 groups. Median age was 67 years. Nearly 80% of patients had bone metastasis, and approximately 17% had visceral metastasis. At the data cutoff date for the primary analysis, the median duration of therapy was 41 months for darolutamide compared with 16.7 months in the placebo group; 45.9% in the darolutamide group and 19.1% in the placebo group were receiving the allotted trial therapy at the time of the analysis. Six cycles of docetaxel were completed in approximately 85% of patients in both arms. Median overall survival follow-up was 43.7 months (darolutamide) and 42.4 months (placebo). A significant improvement in overall survival was observed in the darolutamide group. The risk of death was 32.5% lower in the darolutamide cohort than in the placebo cohort (hazard ratio [HR], 0.68; 95% CI, 0.57-0.80; $P < .001$). The overall survival at 4 years was 62.7% (95% CI, 58.7-66.7) in the darolutamide arm and 50.4% (95% CI, 46.3-54.6) in the placebo arm. The overall survival results remained favorable across most subgroups.

Darolutamide was associated with improvement in all key secondary endpoints. Time to castration-resistance was significantly longer in the darolutamide group (HR, 0.36; 95% CI, 0.30-0.42; $P < .001$). Time to pain progression was also significantly longer in the darolutamide group (HR, 0.79; 95% CI, 0.66-0.95; $P = .01$). Time to first symptomatic skeletal events (HR, 0.71; 95% CI, 0.54-0.94; $P = .02$) and time to initiation of subsequent systemic therapy (HR, 0.39; 95% CI, 0.33-0.46; $P < .001$) were also found to be longer in the darolutamide group.

Safety: The risk of grade 3 or higher adverse events was similar across the 2 groups. Most common adverse events were known toxic effects of docetaxel therapy and were highest during the initial period when both groups received this therapy. These side effects progressively decreased after the initial period. The most common grade 3 or 4 adverse event was neutropenia, and its frequency was similar between the darolutamide and placebo groups (33.7% and 34.2%, respectively). The most frequently reported adverse events were alopecia, neutropenia, fatigue, and anemia and were similar between the groups. Adverse events of special significance, including fatigue, falls, fractures, and cardiovascular events, were also similar between the 2 groups. Adverse events causing deaths in each arm were low and similar (4.1% in the darolutamide group and 4.0% in the placebo group). The rates of discontinuation of darolutamide or placebo were similar (13.5% and 10.6%, respectively).

Conclusion: Among patients with mHSPC, overall survival was significantly longer among patients who received darolutamide plus ADT and docetaxel than among those who received ADT and docetaxel alone. This was observed despite a high percentage of patients in the placebo group receiving subsequent systemic therapy at the time of progression. The survival benefit of darolutamide was maintained across most subgroups. An improvement was also observed in the darolutamide arm in

terms of key secondary end points. The adverse events were similar across the groups and were consistent with known safety profiles of ADT and docetaxel, and no new safety signals were identified in this trial.

Commentary

The results of the current study add to the body of literature supporting multi-agent systemic therapy in newly diagnosed mHSPC. Prior phase 3 trials of combination therapy using androgen-receptor pathway inhibitors, ADT, and docetaxel have shown conflicting results. The results from the previously reported PEACE-1 study showed improved overall survival among patients who received abiraterone with ADT and docetaxel as compared with those who received ADT and docetaxel alone.[1] However, as noted by the authors, the subgroup of patients in the ENZAMET trial who received docetaxel, enzalutamide, and ADT did not appear to have a survival advantage compared with those who received ADT and docetaxel alone.[2] The results from the current ARASENS trial provide compelling evidence in a population of prospectively randomized patients that combination therapy with darolutamide, docetaxel, and ADT improves overall survival in men with mHSPC. The survival advantage was maintained across subgroups analyzed in this study. Improvements were observed in regards to several key secondary end points with use of darolutamide. This benefit was maintained despite many patients receiving subsequent therapy at the time of progression. Importantly, there did not appear to be a significant increase in toxicity with triplet therapy. However, it is important to note that this cohort of patients appeared largely asymptomatic at the time of enrollment, with 70% of patients having an Eastern Cooperative Oncology Group performance status of 0.

Additionally, the average age in this study was 67 years, with only about 15% of the population being older than 75 years. In the reported subgroup analysis, those older than 75 years appeared to derive a similar benefit in overall survival, however. Whether triplet therapy should be universally adopted in all patients remains unclear. For example, there is a subset of patients with mHSPC with favorable-risk disease (ie, those with recurrent metastatic disease, node-only disease). In this population, the risk-benefit analysis is less clear, and whether these patients should receive this combination is not certain. Nevertheless, the results of this well-designed study are compelling and certainly represent a potential new standard treatment option for men with mHSPC. One of the strengths of this study was its large sample size that allowed for vigorous statistical analysis to evaluate the efficacy of darolutamide in combination with ADT and docetaxel.

Application for Clinical Practice

The ARASENS study provides convincing evidence that in men with mHSPC, the addition of darolutamide to docetaxel and ADT improves overall survival. This combination appeared to be well tolerated, with no evidence of increased toxicity noted. Certainly, this combination represents a potential new standard treatment option in this population; however, further understanding of which subgroups of men benefit from enhanced therapy is needed to aid in proper patient selection.

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