Two-Year Outcomes of Prostatic Artery Embolization for Symptomatic Benign Prostatic Hyperplasia: An International, Multicenter, Prospective Study

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Materials and Methods

This was an international, multicenter, prospective trial of males with BPH with lower urinary tract symptoms (LUTS) or acute urinary retention (AUR) treated with PAE. The primary outcome was the 12 month change in the International Prostate Symptom Score (IPSS) for patients referred for bothersome LUTS, or urinary catheter independence for patients treated for AUR. Secondary outcome measures included changes in IPSS at 3 and 24 months, changes in quality of life (QoL), changes in the Sexual Health Inventory for Men (SHIM) questionnaire, technical success rate, and adverse events (AEs). Data were summarized using descriptive statistics.

Results

Four hundred seventy-eight consecutive patients underwent PAE (bothersome LUTS: N = 405; AUR: N = 73), mean age was 70 years. For patients treated for bothersome LUTS, mean total IPSS at baseline was 21.8 and decreased to 9.3, 10.6, and 11.2 at 3, 12, and 24 months following PAE, respectively (all $p < 0.001$); QoL at baseline was 4.7 and decreased to 2.0, 2.1, and 2.3 at 3, 12, and 24 months, respectively (all $p < 0.001$). The mean SHIM score at baseline and 12 months following PAE was 13.8 and 13.9, respectively. Of the 73 patients treated for AUR, 48 (65.8%) had their indwelling catheter removed within 3 months of PAE and remained catheter free at 24 months. Fifty-five patients (11.5%) experienced ≥ 1 AE and 10 (2.1%) experienced a serious AE.

Conclusion

PAE is a safe and effective treatment for symptomatic BPH and LUTS.

Nonstatin Therapy for Dyslipidemia

Current and Future Directions

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HMG Co-A (β-hydroxy β-methylglutaryl-coenzyme A) reductase inhibitors (statins) were introduced in 1987 and have revolutionized the prevention and treatment of cardiovascular disease (CVD). However, for the next 37 years, the treatment of dyslipidemia stagnated with no truly pivotal new therapies introduced until 2015 when the first PCSK9 (proprotein convertase subtilisin kexin 9) inhibitor was approved by the Food and Drug Administration. PCSK9 inhibitors are undoubtedly the most effective lipid-lowering therapy ever developed and have been demonstrated to prevent coronary artery plaque progression and cardiovascular events in well-controlled randomized trials. Despite that, they remain drastically underutilized in clinical practice. In this article, we discuss the barriers that have led to underutilization and propose ways to avoid such pitfalls with other emerging lipid therapies, such as antisense oligonucleotide inhibitors and small interfering RNA addressing novel targets.

widespread acceptance for the prevention of CVD. Yet, that has not been the case. Despite the impressive results in clinical trials, PCSK9 inhibitors are grossly underutilized. Recent data shows that a shocking <0.5% of eligible patients (based on the American College of Cardiology Expert Consensus Decision Pathway) are actually prescribed PCSK9 inhibitors.[6] This drastic underutilization is a consequence of critical flaws in trial design, marketing, and drug pricing, all of which have significantly undermined the success of these drugs.

How Did We Get Here?

The FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) was the first large cardiovascular outcomes trial of PCSK9 inhibitors in patients with known CVD.[4] This trial enrolled 27 564 subjects with established CVD from 49 countries. Subjects were randomized to evolocumab versus pla-

Lessons Moving Forward

With emerging lipoprotein targets, such as ApoA and ApoCIII, and with the advent of novel strategies for silencing gene expression, such as antisense oligonucleotide inhibitors and small interfering RNA, it is more important than ever to learn from the PCSK9 inhibitor trials. We propose the following key points that industry and trialists should consider to facilitate successful bench to bedside delivery:

1. We must size clinical trials correctly. Studies that are too small will be underpowered, and those that are too large (eg. FOURIER) will be too expensive, resulting in higher drug costs.
2. There is no substitute for good trial design. Even the most powerful lipid-lowering drugs can appear less effective if trial participants do not receive the drug (eg, ODYSSEY Outcomes).
3. Cardiovascular outcomes studies must be continued for adequate durations. In an era when most cardiovascular patients are already on statins, it is increasingly difficult to show rapid separation in event curves. Despite the pressures to cut costs, sometimes ending a trial just a few months early can lead to unsatisfactory results and undermine confidence in the therapy.
4. The drug has to be priced wisely. Overpricing can be fatal to the drug's long-term success. For example, even if the price of PCSK9 inhibitors is reduced, it remains unclear how long it will take for these drugs to recover from initial disappointment. With multiple competing

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Improving HCC surveillance with abbreviated MRI: A call to integrate and innovate?

axime Ronot[1,2,*]

Table 1. Ongoing trials testing abbreviated MRI for HCC surveillance.

Trial identification	Country	Patients phenotype	Planned inclusion	Randomization	Comparison	Health economic endpoint	HCC risk stratification	Completion date
	USA	High risk cirrhosis	4,700	Yes	US + AFP	No	Yes	2031
NCT03731923	South Korea	High risk HBV or HCV	257	No (single arm	US	No	No	2031
NCT05095714	France	High risk cirrhosis (non-viral, viral inactive)	944	Yes	US	Yes	Yes	2028
NCT05657249	South Korea	High risk HBV or HCV	199	No (single arm	US	No	Yes	2028
NCT06312826	South Korea	High risk cirrhosis	806	Yes	US	No	Yes	2027
NCT05828446	Switzerland	Cirrhosis, high risk HBV	330	No (single arm)	US	No	No	2027
NCT04455932	Australia, New Zealand	Cirrhosis (and poor US visualization)	476	No (single arm)	US	No	No	2027
NCT05429190	Netherlands	Cirrhosis/ACLD	470	No (single arm)	US	Yes	No	2026
NCT04539717	USA	Cirrhosis	820	No (single arm)	US	Yes	No	2025
NCT05716620	India	High risk cirrhosis	320	No (single arm)	US	No	No	2025
NCT04288323	USA	Cirrhosis	150	No (single arm)	US	No	No	2023

In conclusion, while this study marks a significant step forward in the quest for optimal HCC surveillance, it is merely the beginning of what must be a sustained, collaborative effort to refine and implement strategies that will ultimately reduce the burden of this deadly disease.

Liver AMRI will undoubtedly be included in future surveillance strategies, but a thorough and accurate evaluation of its accessibility, acceptability and cost-benefit ratio is needed before considering its widespread implementation in clinical practice. The ongoing trial will further provide valuable and much needed evidence.

Blood tests for colorectal cancer: practical or premature?

On July 26, 2024, the US Food and Drug Administration (FDA) approved the Shield blood-based test (Guardant Health [Palo Alto, CA, USA]) for colorectal cancer (CRC) screening of average-risk individuals aged 45 years or older. The approval positions the test as a direct alternative to established screening options, including colonoscopy once every 10 years, annual faecal immunochemical tests (FIT), or stool DNA testing every 1–3 years. A blood-based test has several benefits that might improve screening uptake or adherence compared with existing options, such as avoiding invasive colonoscopy or stool handling and enabling testing to be nested within routine blood draws.

Shield detects genomic and epigenomic alterations associated with CRC in circulating cell-free DNA, producing a qualitative positive or negative test result. Patients with a positive test result must then receive a timely diagnostic colonoscopy. How effective is Shield? In the pivotal study of an average-risk population of US adults who underwent testing with Shield and colonoscopy, the test had an overall sensitivity for detection of CRC developed by Freenome (South San Francisco, CA, USA). In data from the PREEMPT CRC study presented at Digestive Disease Week 2024, the test had a sensitivity of 79·2% (95% CI 68·4–86·9) for CRC of any stage, but sensitivity for advanced adenomas was just 12·5% (95% CI 11·3–13·8). Notably, modelling also suggests that even a much-improved hypothetical blood-based test with 90% sensitivity for CRC and 70% sensitivity for advanced precancerous lesions would produce clinical outcome benefits similar to annual FIT or colonoscopy every 10 years.

A number of crucial considerations emerge from these data. First, although Shield provides better clinical outcomes compared with no screening, populations already partaking in screening using established effective methods would have worse clinical outcomes and higher costs if they substitute these tests for a blood test of similar performance to Shield. Moreover, despite some evidence that people who do not partake in other screening methods are receptive to blood-based screening, there is an urgent need for real-world data to

colonoscopy-detected CRC of 83·1% (95% CI 72·2–90·3), exceeding minimum performance characteristics set by the US Centers for Medicare and Medicaid Services for reimbursing a triennial CRC blood-based screening test (sensitivity ≥74%, specificity ≥90%). All stage II, III, and IV cancers were picked up by Shield, although ten of 22 stage I cancers were missed.

However, data for the detection of advanced precancerous lesions were less impressive. 1116 participants had such lesions on colonoscopy, of which Shield identified only 147 (sensitivity 13·2% [95% CI 11·3–15·3]). Notably, sensitivity appeared to increase with age, from just 7·9% (5·8–10·8) in those aged 45–59 years to 19·0% (14·7–24·2) in those aged 70 years or older. As detection of these lesions enables cancer prevention, this is a critical limitation.

Comparison of this effectiveness with existing screening options is not favourable. In modelling studies, FIT (done every 1 or 2 years) prevented more CRC cases and mortality and was more cost-effective than Shield, a result driven by lower cost and the greater sensitivity of FIT for advanced precancerous lesions. Similar disappointing performance for advanced adenoma detection was seen with another blood test for early

assess how blood tests might be taken up and used in practice, and on adherence to follow-up colonoscopy, to better understand the risks of offering costly tests with poor sensitivity for advanced precancerous lesions within existing screening programmes. Screening coverage providers considering blood-based tests must account for the risks of this test substitution. Second, the detection of advanced precancerous lesions is a key determinant of blood-based test effectiveness, and this aspect should receive much greater priority in test development if blood-based tests are to achieve comparable clinical outcomes to existing tests. Finally, the high cost of Shield (before FDA approval, it was available out of pocket for US$895) and the likely high cost of other blood-based tests might exacerbate rather than reduce screening disparities.

Screening for CRC and advanced precancerous lesions is an effective tool for reducing the disease's incidence and mortality. Cheap blood-based tests might one day revolutionise screening for CRC. But to get there, industry, regulators, and coverage providers must prioritise test characteristics that produce net clinical benefit for patients in the context of current screening behaviours and programmes. ■ *The Lancet Gastroenterology & Hepatology*

A New Class of Drugs Approved in the United States for Hypertension: Endothelin Antagonists

Globally, hypertension is estimated to affect 1.28 billion adults aged 30-79 years, the majority of whom have uncontrolled hypertension.[1] In the United States, almost half of adults have blood pressure (BP) >130/80 mmHg or are taking an antihypertensive medicine; hypertension is estimated to have caused or contributed to 691,095 deaths in 2021.[2] Systemic hypertension results from a mosaic of interdigitating pathophysiological mechanisms, hence a combination of antihypertensive drugs is necessary to lower BP levels.[3] Despite optimal adherence and therapy, approximately 5% of hypertensive patients have a BP >140/90 mmHg (ie, true-resistant hypertension), equating to approximately 6 million people in the United States.[2,3] It was therefore with cautious optimism that on March 19, 2024, the US Federal Drug Administration (FDA) approved aprocitentan (TRYVIO™) an endothelin (ET) receptor antagonist (ETRA) for resistant hypertension. This is the first new class of oral antihypertensive medicines to be approved by the FDA in almost 40 years.

The mechanisms responsible for BP elevation are multiple and complex: however, ET-mediated effects (directly or via the sympathetic nervous system and renin-angiotensin-aldosterone activation) are detrimental to cardiovascular homeostasis. Overexpression of ET-1 causes adverse vascular remodelling.[7] Patients with hypertension have exaggerated vascular ET activity which triggers intense vasoconstriction that can be reversed by the nonselective blockade of ET_A and ET_B receptors.[8] This dual blockade, in addition to causing vasodilation, may exert anti-inflammatory and anti-fibrotic effects and promote reversal of cardiac hypertrophy.[9,10]

Overall, ET receptor antagonists (ETRAs) are associated with some side effects such as headaches, flushing, edema, and anemia.[6] Endothelin receptor antagonists are also classified as pregnancy category X because studies in knockout mice have demonstrated the potential for teratogenic effects.[11]

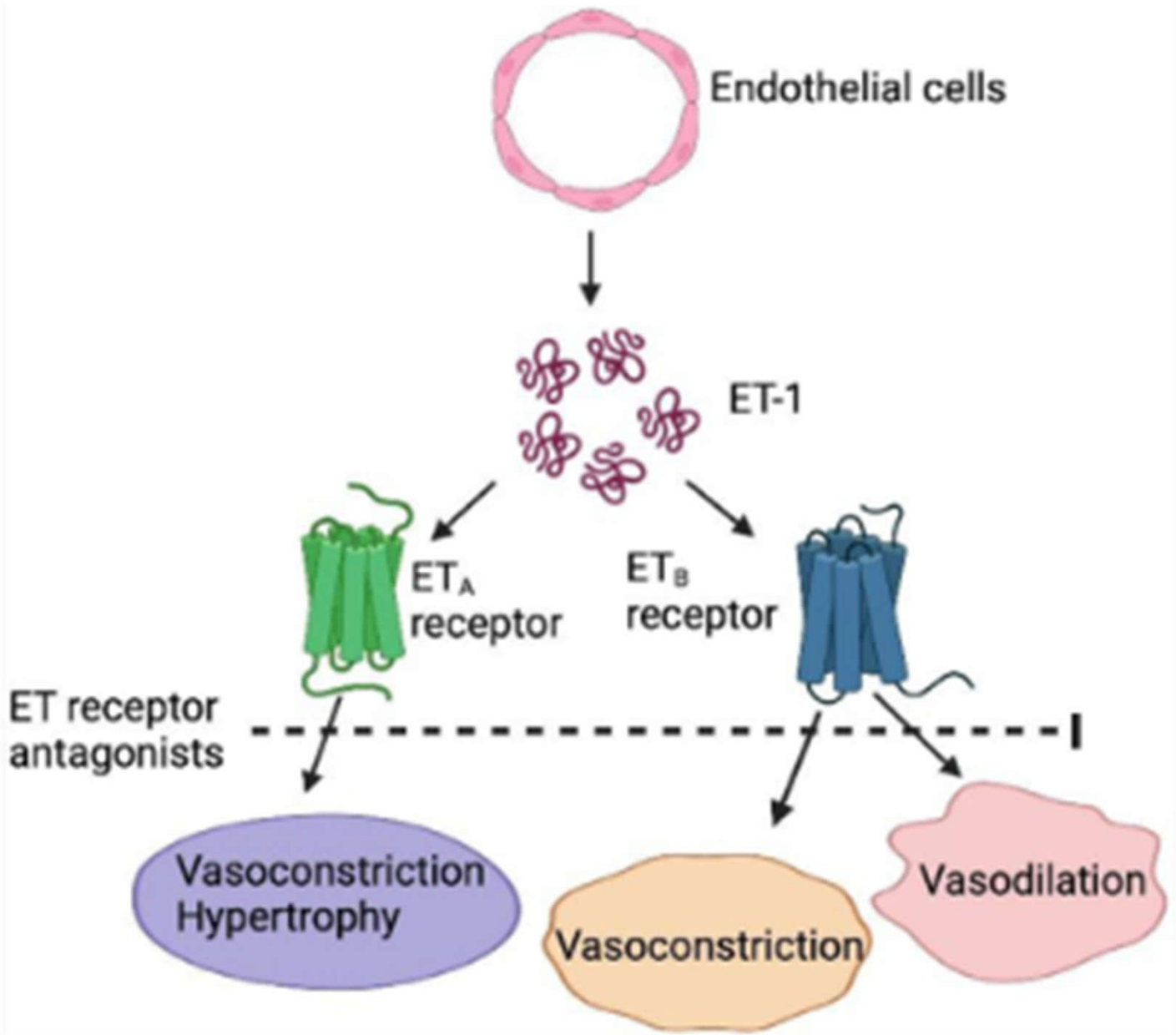

Figure 2 The endothelin system and action of endothelin receptor antagonists. Created in BioRender.com.

with once-daily dosing likely to optimize treatment adherence. Although the FDA has approved aprocitentan for resistant hypertension, its ultimate place in the antihypertensive armamentarium can only be revealed when the drug is available for all grades of hypertension. Further studies are also required to determine whether aprocitentan-induced ankle edema is a local cosmetic (benign) phenomenon or mediated by the cardio-renal axis. Certainly, the improvement in urine albumin-creatinine ratio compared with placebo is intriguing, and the possibility that aprocitentan is synergistic with renin-angiotensin-system inhibitors suggests an additional benefit may be possible for patients with hypertension and kidney disease who require careful monitoring if they are prescribed spironolactone. Endothelin receptor antagonists are therefore a welcome novel option to improve hypertension control rates; however, this optimistic premise awaits evidence from prospective clinical experience and additional studies.

THE END