

Use of Aprocitentan and Spironolactone in Resistant Hypertension Management

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ABSTRACT

Aprocitentan was approved by the United States Food and Drug Administration (U.S. FDA) in March 2024 as the first oral agent of a new drug class to treat resistant hypertension. The endothelin receptor antagonist, which is not registered in Hong Kong, is indicated as an add-on therapy in the treatment of hypertension in combination with other antihypertensive agents. Spironolactone, on the other hand, has a much longer history since its FDA approval in 1960 and currently has the role of treating resistant hypertension with other antihypertensive agents of different mechanisms of action. Both spironolactone and aprocitentan were found to be efficacious in reducing blood pressure and their safety profiles were characterised in medical literature. However, there is a lack of head-to-head comparison between the two antihypertensives. This article reviews the two old and new antihypertensive agents in terms of their distinctive mechanisms of action, approved indications, as well as their efficacy and safety profiles with evidence from the results of major clinical trials.

Keywords: *Aprocitentan, Spironolactone, Resistant Hypertension, Endothelin receptor antagonist, Aldosterone antagonist*

INTRODUCTION

Hypertension is a highly prevalent disease and its rate of control is suboptimal globally. It is well known for its association with an increased risk of various cardiovascular and kidney outcomes,

and different target organ damages can occur. In Hong Kong, hypertension is a significant public health issue due to its high prevalence. According to data from the Population Health Survey 2020-2022 conducted by the Department of Health, the prevalence of hypertension was 29.5% among the age group 15-84 years, and the prevalence increased with age accounting for 57.4% in those aged 65-84 years, highlighting that there is a higher risk in elderly⁽¹⁾.

Individuals with poorly uncontrolled hypertension despite the use of multiple antihypertensives may lead one to suspect the possibility of resistant hypertension. Currently, resistant hypertension can be defined as blood pressure (BP) above goal despite treatment with three antihypertensive drugs with different mechanisms of action, including a diuretic at maximally tolerated doses; alternately it also refers to the phenomenon in which use of four or more antihypertensives are required for controlling BP at goal⁽²⁾. This three-drug regimen commonly includes an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB), a long-acting calcium channel blocker (CCB), and a thiazide-like diuretic. To confirm the diagnosis of resistant hypertension, pseudo-resistance has to be excluded, and common causes such as inaccurate BP measurement, poor adherence to antihypertensive therapy, and white-coat effect should be evaluated^(2, 3).

Resistant hypertension is not uncommon around the world. For example, based on BP goal of 130/80 mm Hg, the prevalence of resistant hypertension is approximately 8.5% to 20% among hypertensive adults in the United States⁽⁴⁾. Common comorbidities such as obesity, chronic kidney diseases, and diabetes were identified as risk factors for resistant

hypertension in multiple cohort studies⁽⁵⁾. In the Hong Kong local population, a cross-sectional descriptive study examining the clinical profile of patients aged 30 years or above reflects that the prevalence of resistant hypertension is around 7.4% in the primary care setting of Hong Kong⁽⁶⁾.

Patients with resistant hypertension can have more than 50% higher risk of stroke, myocardial infarction, end-stage renal disease, and cardiovascular death than their hypertensive counterparts without treatment resistance^(7, 8). Therefore, effective BP management is critical to minimize the risk of such complications. Resistant hypertension requires high doses and/or higher number of antihypertensives for BP control, but safety and efficacy of the add-on (non-first-line) drugs is a concern and generates much interest in this research area. Currently, aprocitentan and spironolactone are two drugs that are indicated to treat hypertension in patients who are unresponsive to or whose BP is not adequately controlled on other antihypertensive medications. Comparing these two drugs can also provide insights about their clinical use in hypertensive patients with different comorbidities such as those with hyperkalaemia and renal failure. Therefore, this article aims to provide a discussion about these two add-on drugs in the management of resistant hypertension.

OVERVIEW OF APROCITENTAN

Tryvio (aprocitentan) has been approved by the U.S. FDA on 19 March 2024 and its European counterpart, Jeraygo, has been authorized in European Union by European Medicines Agency (EMA) on 27 June 2024 for combination with other antihypertensives to lower BP in adults who are not adequately controlled on other drugs^(9, 10). Aprocitentan is approved to be taken 12.5mg orally once daily⁽¹¹⁾. In Hong Kong, aprocitentan is not yet registered and listed in Hospital Authority Drug Formulary.

Pharmacology

Aprocitentan is an active metabolite of macitentan, a drug used for treating pulmonary artery hypertension. Aprocitentan functions as a dual endothelin receptor antagonist (ERA) that blocks endothelin-1 (ET-1) binding to both ETA and ETB receptor subtypes, with an inhibitory potency ratio of 1:16 [12]. ET-1 has caught the attention of researchers as its expression is enhanced in endothelium in patients with severe hypertension. ET-1, as one of the most

potent vasoconstrictors in human body, is a 21-amino acid peptide mainly produced by endothelial cells, and it exerts harmful effects in the pathogenesis of hypertension including vasoconstriction, fibrosis, cellular proliferation, and inflammation through ETA and ETB receptors found on vascular endothelial and smooth muscle cells. Notably, in hypertension, ET-1 contributes to endothelial dysfunction, vascular hypertrophy, remodeling, sympathetic activation, and elevated aldosterone production⁽¹³⁾. Aprocitentan achieves its antihypertensive effect by inhibiting ET-1 signaling in these pathophysiological processes.

Aprocitentan is a highly protein-bound drug (>99%) and is eliminated in both urine and feces⁽¹⁴⁾. As the drug's main elimination pathways are independent of CYP enzymes, there is low potential for interactions with drugs that inhibit or induce CYP enzymes. Indeed, no significant interaction with commonly used drugs have been reported as of today. The drug's long elimination half-life of about 41 hours enables it to be administered on an once-daily basis⁽¹¹⁾. Aprocitentan can be taken without regard to food, and no clinically significant differences in its pharmacokinetics were observed following administration of a high-fat, high-calorie meal⁽¹¹⁾. A recent double-blind study supported that the pharmacokinetics of aprocitentan is unlikely to be different between Caucasian and Japanese subjects, and suggested that dose adjustment may not be necessary in patients of different ethnicity⁽¹⁵⁾.

Efficacy

PRECISION was a 4-year, multicenter, blinded, randomized, parallel-group, phase 3 trial examining the effect of aprocitentan in patients with sitting systolic blood pressure (SiSBP) $\geq$ 140 mmHg despite taking three standardized antihypertensive drugs, including a diuretic⁽¹⁶⁾. This trial consisted of a 4-week placebo run-in period and was followed by three parts. Before the placebo run-in period, all patients were transitioned to standard background antihypertensive therapy (SBAT) consisting of valsartan (ARB) 160 mg, amlodipine (long-acting CCB) 5 or 10 mg, and hydrochlorothiazide (diuretic) 25 mg, which was maintained consistently throughout the whole trial period. After the 4-week placebo run-in period, part 1 started with a total of 730 participants with uncontrolled SiSBP ($\geq$ 140 mmHg) using the unattended automated office blood pressure measurement (uAOBPM), and they were randomized to receive either aprocitentan 12.5 mg, aprocitentan 25 mg, or placebo once daily in a 1:1:1 ratio during the initial 4-week double-blind treatment phase. In part 2, all participants transitioned

to a 32-week single (patient)-blind phase where they received apocritentan 25 mg daily. After that, for part 3, participants underwent re-randomization to either continue apocritentan 25 mg or switch to placebo in a 1:1 ratio for a 12-week double-blind withdrawal period. The study concluded with a 30-day safety follow-up assessment for all enrolled participants. The primary endpoint was the change in mean trough SiSBP from baseline to week 4 (part 1), while the key secondary endpoint assessed the change in mean trough SiSBP from withdrawal baseline from week 36 to week 40 (part 3).

For primary endpoint, the least-squares mean (LSE) changes were -15.3 (0.9) mmHg for the 12.5 mg dose, -15.2 (0.9) mmHg for the 25 mg dose, and -11.5 (0.9) mmHg for placebo. The treatment differences versus placebo were -3.8 (1.3) mmHg (97.5% CI -6.8 to -0.8, $p=0.0042$) for apocritentan 12.5 mg and -3.7 (1.3) mmHg (97.5% CI -6.7 to -0.8, $p=0.0046$) for the 25 mg dose. For the key secondary endpoint, the mean difference of SiSBP with placebo compared to apocritentan 25 mg after 4 weeks of treatment withdrawal was 5.8 mmHg (95% CI 3.7 to 7.9; $p < 0.0001$). The between-group differences in SiSBP persisted through week 48.

Safety

Mild-to-moderate fluid retention or edema including peripheral edema and face edema emerged represented the most common adverse event in a dose-dependent manner during the entire study and occurred mainly in part 1. Incidence rates were 9.1% with apocritentan 12.5 mg, 18.4% with apocritentan 25 mg, and 2.1% with placebo. In part 2, edema adverse events were reported in 17% of participants, with differential incidence rates based on prior treatment allocation: 23% among placebo-switched subjects, 16% for those transitioning from apocritentan 12.5 mg, and 12% for patients maintained on apocritentan 25 mg. Two severe adverse events of pulmonary edema occurred in one participant from the apocritentan 25 mg arm in part 1 and one participant from part 2, both associated with acute hypertensive crisis that likely precipitated the condition. Overall, seven participants (3%) discontinued apocritentan due to edema.

During the whole trial, eleven participants required hospitalizations for heart failure. In part 1, two cases occurred in the apocritentan 25 mg arm: one case involved pulmonary

edema that resolved with treatment and with completing parts 2 and 3 in the apocritentan 25 mg, while the other represented worsening of pre-existing chronic heart failure. Part 2 recorded six events, including one participant previously on apocritentan 25 mg and five placebo-switched participants. Three of them occurred within 3 weeks of apocritentan initiation. Part 3 featured three additional hospitalizations, with two occurring in the apocritentan 25 mg arm and one in the placebo arm.

In addition, a total of 11 treatment-emergent deaths (1.3% of participants) were reported but were not regarded by investigators to be study treatment-related. One death occurred in part 1, nine in part 2, and one in part 3. Causes included COVID-19 (5 participants), procedural colon perforation (1 participant), and cardiovascular deaths (5 participants). Adverse events leading to permanent treatment discontinuation were rare in part 1 but occurred slightly more often with apocritentan (3% at 12.5 mg, 2% at 25 mg) than with placebo (1%). In part 2, 3.8% of subjects discontinued due to adverse events, with higher rates in those who switched from placebo (5.1%) compared to those continuing 12.5 mg (2.6%) or 25 mg (3.8%).

OVERVIEW OF SPIRONOLACTONE

Spironolactone is a drug with the brand name Aldactone approved by the U.S. FDA on 21 January 1960, and it can be used as an add-on treatment for hypertension unresponsive to other therapies^(17,18). Spironolactone is also available as Qaialdo for use in the European Union, although currently it is mainly prescribed for managing refractory edema associated with diseases (e.g. heart failure, hepatic cirrhosis, nephrotic syndrome, and essential hypertension) and primary aldosteronism, but not resistant hypertension, in the European member states⁽¹⁹⁾. Other therapeutic uses of spironolactone include moderate to severe acne vulgaris and hirsutism in female gender. In Hong Kong, spironolactone is a registered pharmaceutical product with its date of registration that can be traced back to 1983⁽²⁰⁾. It is marketed as oral tablet dosage form in dosage strength of 25 mg, but the drug can also be prepared extemporaneously for oral suspension of different dosage strengths⁽¹⁸⁾. For treatment of hypertension, the dose is commonly initiated at 25 mg daily and titrated as needed after 2 to 4 weeks based on response and tolerability up to 100 mg daily^(2, 18).

Pharmacology

Spironolactone is an aldosterone antagonist that has a steroidal structure and also commonly known as mineralocorticoid receptor antagonist. It acts by competitive binding of aldosterone receptors at the principal cells in the collecting ducts of the kidney. This inhibition leads to two effects: inhibition of epithelial sodium channels (ENaCs) expression and inhibition of sodium-potassium ATPase (Na/K ATPase) expression. The inhibition of ENaC expression will decrease the ENaC concentration at the collecting duct, which leads to a decrease in sodium reabsorption. The inhibition of Na/K ATPase expression also decreases sodium reabsorption and potassium secretion. The above effects increase the excretion of water and lowers the effective circulating volume, which exhibits the diuretic and antihypertensive effect of spironolactone⁽²¹⁾. Of note, mineralocorticoid receptor antagonists are the only diuretics that do not require access to the tubular lumen for inducing diuresis, and it would be best for patients to take the diuretic drug earlier during a day to avoid urination in the late evening⁽²²⁾. In view of the effect of aldosterone antagonist on serum potassium level, the risk of hyperkalemia can magnify in patients with renal impairment and/or with concurrent use of potassium supplementation, food or drink that are rich in potassium, and drugs such as ACEI, ARB, and direct renin inhibitor. Aldosterone antagonist should be avoided in patients with hyperkalemia⁽¹⁷⁾.

Patients are advised to establish a routine pattern and be consistent to take spironolactone with regards to food on a daily basis, as food can increase the bioavailability of the drug by approximately 95%. Although spironolactone has a short half-life of about 1.4 hours, it is metabolized to multiple active metabolites including canrenone which has a long half-life of about 16.5 hours⁽²³⁾.

Spironolactone, notably, exhibits non-selective binding to progesterone and androgen receptors as well, and has the potential to cause progestational and anti-androgenic effects (collectively known as endocrine effects) including gynecomastia, impotence, and menstrual irregularities. Another aldosterone antagonist, eplerenone (Inspra), has very low affinity for the two sex hormone receptors owing to its 9,11-epoxide group, therefore it can largely avoid the

endocrine effects associated with spironolactone. However, eplerenone is less potent and often requires twice-daily dosing for adequate BP lowering effect, and previous randomized controlled trials did not show BP lowering in daily dosage range of 25 to 100 mg when compared with placebo, suggesting higher dosages are required for effective BP management^(24, 25, 26). Eplerenone, but not spironolactone, is also subject to CYP3A4-mediated drug interactions.

Efficacy

The role of spironolactone in treatment of resistant hypertension was first described by Ramsay et al. in medical literature back in 1980⁽²⁷⁾. In recent years, a number of randomized clinical trials aimed to validate and determine the efficacy of spironolactone in resistant hypertension, and many found that spironolactone was more effective than placebo or other antihypertensive drugs^(28, 29). Among all clinical trials, PATHWAY-2 offered the most compelling data about the efficacy of spironolactone.

PATHWAY-2 was a 12-month double-blinded, placebo-controlled, crossover phase 4 clinical trial with a sample size of 314 patients which compared the efficacy of spironolactone, doxazosin, and bisoprolol in treatment of resistant hypertension in the U.K.⁽³⁰⁾. Only patients aged 18 to 79 years with seated clinic systolic blood pressure (SBP) above 140 mmHg or home SBP above 130 mmHg despite on treatment for at least three months of maximally tolerated dose of an ACEI or an ARB, a CCB, and a diuretic were eligible for this trial. Patients rotated, in a randomized manner, through 12 weeks of once daily treatment with each of spironolactone, bisoprolol, doxazosin, and placebo, in addition to their baseline BP medications.

In PATHWAY-2, the average home SBP recorded in the morning and evening on 4 consecutive days before study visits served as the primary endpoint. Among the 314 patients, 219 (68.9%) of them achieved a home SBP of less than 135 mmHg, and 58% patients had their BP controlled, which resolved the resistant hypertension condition. The average reduction in home SBP by spironolactone was superior to placebo (8.7 mm Hg; $p < 0.0001$), superior to doxazosin (4.03 mm Hg; $p < 0.0001$), and superior to bisoprolol (4.48 mm Hg; $p < 0.0001$). The trial results supported that spironolactone was more effective than an alpha-1 blocker and beta-1 blocker as an add-on drug for the treatment of resistant hypertension.

ASPIRANT was another a prospective, double-blind, placebo-controlled, parallel-group trial addressing the concern about the drug that should be used in lowering BP in resistant hypertension⁽³¹⁾. Patients with office SBP ≥ 140 mm Hg or diastolic BP (DBP) ≥ 90 mm Hg despite treatment with at least 3 antihypertensive drugs, including a diuretic, were enrolled. A total of 117 patients were assigned using simple randomization method to receive either spironolactone or a placebo as an add-on drug to their antihypertensive regimen.

The primary endpoints in ASPIRANT were difference between fall of average daytime SBP and DBP between spironolactone and placebo groups after 8 weeks of treatment. Results showed that spironolactone led to an average decrease of 9.3 mm Hg in daytime SBP while the placebo resulted in an average decrease in 3.9 mmHg (between-group difference: 5.4 mm Hg; $p = 0.024$). However, spironolactone (- 4.2 mm Hg) did not significantly influence daytime DBP mm Hg compared to the placebo (-3.2 mm Hg) with a p -value of 0.358. In summary, the trial showed that spironolactone was an effective drug for lowering SBP in resistant hypertension patients using an average of 4.5 antihypertensive drugs after 8 weeks of treatment.

Safety

The safety results in PATHWAY-2 and ASPIRANT trials were illustrated below^(30, 31).

Spironolactone patients had the occurrence of similar adverse events such as fatigue, diarrhea, and exertional dyspnea in both trials. In PATHWAY-2 trial, 58 (19%) of the spironolactone participants experienced adverse events including diarrhea, fatigue, dizziness, and exertional dyspnea; whereas 67 (23%) of the doxazosin participants and 68 (23%) of the bisoprolol participants had experienced adverse events during the trial. These results showed that spironolactone patients had the lowest percentage of adverse events among patients of the three drugs. In ASPIRANT trial, 24 adverse events occurred in the spironolactone group ($n = 55$) while 26 occurred in the placebo group ($n = 55$), and the adverse events that were probably and possibly related to the study medication in the spironolactone group included diarrhea, fatigue, vertigo, and exertional dyspnea.

On the other hand, there were varying patterns of serious adverse events with only rare occurrence in both trials. In PATHWAY-2 trial, 7 (2%) spironolactone patients experienced serious adverse event such as atrial fibrillation, hypertension, neoplasm recurrence, skin graft, skin ulcer, transitional cell carcinoma, and type 2 diabetes mellitus. For other comparison groups, 5 (2%) doxazosin patients, 8 (3%) bisoprolol patients, and 5 (2%) placebo patients experienced serious adverse events, and the difference was not statistically significant among the four groups ($p = 0.82$). In ASPIRANT trial, only 2 serious adverse events occurred among 55 spironolactone patients: one patient with acute gastroenteritis and symptomatic hypotension, and one patient with diarrhea and dyspepsia.

Discontinuation of treatment due to intolerability of adverse events was also rare in both PATHWAY-2 and ASPIRANT trials. In PATHWAY-2 trial, there were only 4 (1%) withdrawals for adverse events in both the spironolactone group and bisoprolol group, and the withdrawals percentage was the same for the placebo group (1%). Doxazosin group had the highest number of withdrawals (9; 3%). Further analysis, however, showed that there was no statistically significant difference in the withdrawals for adverse events among the four groups ($p = 0.28$). In ASPIRANT trial, discontinuation of study medication due to adverse events occurred in 2 (3.6%) patients using spironolactone and in 1 (1.8%) patient using the placebo ($p = 0.618$).

In addition to the abovementioned adverse events, in PATHWAY-2 trial 6 out of 285 patients (2.1%) exposed to spironolactone developed hyperkalemia with serum potassium greater than 6.0 mmol/L, but discontinuation due to hyperkalemia as well as renal impairment and gynecomastia were not increased with spironolactone comparing with other antihypertensives and placebo. In ASPIRANT trial, there was an increase in serum potassium in the spironolactone group (0.3 mmol/L) while no change in the placebo group (0 mmol/L) and this between-group difference was statistical significant ($p < 0.001$); similarly, there was an increase in serum creatinine in the spironolactone group (7 μ mol/L) while no change in the placebo group (0 μ mol/L) and this between-group difference was also statistical significant ($p < 0.001$). No patient was excluded in ASPIRANT trial because of severe hyperkalemia or progression of renal impairment.

DISCUSSION

Both aprocitentan and spironolactone were proven to be well-tolerated and effective in the treatment of resistant hypertension. PRECISION and PATHWAY-2 trials showed the efficacy of aprocitentan and spironolactone, respectively, in reducing BP. However, as neither study concurrently evaluated both drugs in the same trial, a direct comparison of their efficacy cannot be made. To compare the efficacy of two drugs, a head-to-head

randomized controlled trial would be necessary to show their comparative efficacy. Overall, both drugs resulted in a very low discontinuation rate due to adverse effects. For the adverse effect profile of the two drugs, dose-dependent fluid retention and anemia were the major adverse side effects observed in aprocitentan treatment while hyperkalemia and fatigue are the major adverse effects associated with spironolactone treatment. The summary of PRECISION and PATHWAY-2 trials are presented in Table 1 and 2.

Table 1: Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial⁽¹⁶⁾

Journal	Lancet
Publication Year	2022
Study Year	June 2018 to April 2022
Locations	Europe, North America, Asia, and Australia
Settings	Hospitals and research centres
Settings	730 were randomized • 704 completed Part 1 • 613 completed Part 2 • 577 completed Part 3
Baseline patient characteristics	More than half were between age of 18 to 65 years, more than half were men, more than half were recruited in Europe, majority (>80 %) were White, and majority (>60%) used at least 4 antihypertensives at screening
Interventions / Comparison groups	Part 1: Aprocitentan 12.5 mg vs. Aprocitentan 25 mg vs. Placebo Part 2: Aprocitentan 25 mg Part 3: Aprocitentan 25 mg vs. placebo
Outcome(s) / endpoint(s)	Changes in mean trough sitting office SBP from baseline to week 4 (part 1) and from withdrawal baseline (week 36) to week 40 (part 3) Changes at week 4 and week 40 in mean trough sitting office DBP and in 24-hour SBP and DBP measured by ambulatory BP monitoring
Efficacy data	The least square mean change in office SBP at 4 weeks: • Aprocitentan 12.5 mg: -15.3 mm Hg • Aprocitentan 25 mg: -15.2 mm Hg • Placebo: -11.5 mm Hg Office DBP also decreased with both aprocitentan doses compared with placebo: • Aprocitentan 12.5 mg: -3.9 mm Hg • Aprocitentan 25 mg: -4.5 mm Hg Office SBP after 4 weeks of withdrawal increased with placebo compared with aprocitentan (5.8 mm Hg) Office DBP after 4 weeks increased with placebo compared with aprocitentan (5.2 mm Hg) The results from ambulatory BP monitoring confirmed those derived from office measurements
Safety data	Most frequent adverse event was mild-to-moderate edema or fluid retention: • Aprocitentan 12.5 mg: 9% patients • Aprocitentan 25 mg: 18% patients • Placebo: 2% patients Edema or fluid retention also led to discontinuation in 7 patients treated with aprocitentan No signs of hepatotoxicity were observed Hemoglobin levels decreased with both aprocitentan doses: • Aprocitentan 12.5 mg: -8.0 g/L • Aprocitentan 25 mg: -8.5 g/L • Placebo: -0.4 g/L

Table 2: Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial⁽³⁰⁾

Journal	Lancet
Publication Year	2015
Study Year	May 2009 to July 2014
Locations	United Kingdom
Settings	Primary and secondary care sites
Number of patients	335 were randomly assigned and 21 were excluded due to no follow-up for any drug; 230 patients completed all treatment cycles
Baseline patient characteristics	Mean age of 61.4 years, 69% were male gender, mean home SBP of 147.6 mm Hg and mean DBP of 90.0 mm Hg, serum potassium level of 4.1 mmol/L, and eGFR of 91.1 mL/min
Interventions / Comparison groups	Spironolactone group vs. doxazosin group vs. bisoprolol group vs. placebo group
Outcome(s) / endpoint(s)	1. Difference in the home SBP change from baseline between spironolactone and placebo 2. Difference in home SBP change from baseline between spironolactone and the average of the other two active drugs (doxazosin and bisoprolol) 3. Difference in home SBP change from baseline between spironolactone and each of the other two active drugs (doxazosin and bisoprolol)
Efficacy data	Mean difference in home SBP change from baseline (all p-values < 0.0001): • Spironolactone vs placebo: 8.7 mm Hg • Spironolactone vs mean bisoprolol and doxazosin: -4.26 mm Hg • Spironolactone vs doxazosin: -4.03 mm Hg • Spironolactone vs bisoprolol: -4.48 mmHg
Safety data	Participants with serious adverse events: • Spironolactone (7; 2%) vs. doxazosin (5; 2%) vs. bisoprolol (8; 3%) vs. placebo (5; 2%) (p = 0.82) Participants with any adverse events: • Spironolactone (58; 19%) vs. doxazosin (67; 23%) vs. bisoprolol (68; 23%) vs. placebo (42; 15%) (p = 0.036) Participants with withdrawal for adverse events: • Spironolactone (4; 1%) vs. doxazosin (9; 3%) vs. bisoprolol (4; 1%) vs. placebo (3; 1%) (p = 0.28) Discontinuations due to renal impairment, hyperkalaemia, and gynaecomastia were not increased with spironolactone relative to other active drugs and placebo

Due to the risk of hyperkalemia, renal dose adjustment is required in spironolactone and it should not be used in patients with an elevated baseline potassium level, while renal dosing adjustment is not required in the treatment of aprocitentan. While aprocitentan provides a promising therapeutic option for resistant hypertension, it has a significantly higher cost than spironolactone. Its availability to patients is also a concern in other countries. For example, currently in the U.S., Tryvio is only available to patients through a specialty pharmacy. Aprocitentan also carries the boxed warnings about fetal harm based on animal data and therefore should be avoided in

pregnancy⁽¹¹⁾. Unlike spironolactone which had a long history of usage and clinical data, aprocitentan is a very novel drug newly approved for use in the U.S. and European Union last year, and its current place in therapy for resistant hypertension is yet to be defined clearly in different treatment guidelines. The latest 2025 American hypertension guideline is the first major clinical guideline that clearly defined the role of aprocitentan in the treatment algorithm for resistant hypertension⁽²⁾. Table 3 summarizes the pharmacological treatment recommendations for resistant hypertension with a focus on the use of spironolactone and aprocitentan in different clinical guidelines.

Table 3: Pharmacological treatment recommendations for resistant hypertension in international clinical guidelines

	Spironolactone	Aprocitan
2025 AHA/ACC guideline for hypertension ⁽²⁾	Addition of a MRA for uncontrolled BP cases with an eGFR of ≥ 45 mL/min/1.73 m ² , despite use with the first-line antihypertensives (combination of ACEI/ARB, CCB, thiazide-like diuretics)	For uncontrolled BP cases who cannot tolerate or have contraindications to MRA, the addition of one of the following drugs is reasonable: amiloride, beta-blocker, alpha-blocker, central sympatholytic, dual endothelin receptor antagonists, or direct vasodilators
2024 ESC guideline for hypertension ⁽³⁾	In uncontrolled BP cases despite use of first-line antihypertensives, the addition of spironolactone should be considered. If BP is not controlled with a 3-drug combination and in whom spironolactone is not effective or tolerated, the following should be considered: • Use of eplerenone instead of spironolactone • Addition of a beta-blocker if not already indicated • Addition of a centrally-acting drug, an alpha-blocker, hydralazine, or a potassium-sparing diuretic	New medication that awaits supportive evidence from cardiovascular outcomes trials prior to guideline endorsement
2023 ESH guideline for hypertension ⁽³²⁾	For uncontrolled BP cases with eGFR ≥ 30 mL/min/1.73 m ² despite use of ACEI/ARB, CCB, and thiazide diuretic, the following should be considered: • Addition of spironolactone (preferred) or other MRA • Addition of beta-blocker or alpha-1 blocker • Addition of centrally acting drug	May also be used depending on approval and availability
2023 updated NICE guideline for hypertension ⁽³³⁾	Use of further diuretic therapy with low-dose spironolactone should be considered for cases who have a blood potassium level of 4.5 mmol/L or less Use of an alpha-blocker or beta-blocker should be considered for cases who have a blood potassium level of more than 4.5 mmol/L	<i>Not mentioned</i>

CONCLUSION

At present, few studies examining the long-term adverse effects of aprocitan had been conducted, and more follow-up research has to be conducted to investigate its long-term safety profile and evaluate the possibility of registration of aprocitan in Hong Kong.

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Questions for Pharmacy Continuing Education Program

1. Which of the following option(s) best describes the definition of resistant hypertension?

- Blood pressure above goal despite treatment with any two antihypertensive drugs.
- Blood pressure above goal despite treatment with three antihypertensive drugs with different mechanisms of action, including a diuretic, at maximally tolerated doses.
- Blood Pressure is controlled only when four or more antihypertensive drugs are used.

- I only
- II only
- I & III
- II & III

2. Which of the following statements about resistant hypertension is correct?

- Resistant hypertension is very rare around the world.
- Chronic kidney disease, obesity, and diabetes are the risk factors for resistant hypertension.
- Spironolactone is the only add-on drug for treating resistant hypertension.
- There is no local data on the prevalence of resistant hypertension in Hong Kong.

3. Which statement is correct for aprocitentan?

- High-fat meals greatly reduce its absorption.
- It is administered once daily due to its long half life.
- Dose adjustment is required in different ethnic groups.
- It must be taken on an empty stomach to avoid toxicity.

4. Which of the following is NOT an effect due to the pharmacology of spironolactone?

- It increases the secretion of potassium.
- It increases the excretion of water.
- It decreases sodium reabsorption.
- It increases the risk of hyperkalemia.

5. Compared with other add-on agents, which is NOT a key statistical finding that supports the use of spironolactone for resistant hypertension?

- Spironolactone produced a significantly greater reduction in home systolic blood pressure than placebo.
- Spironolactone produced a significantly greater reduction in home systolic blood pressure than both doxazosin and bisoprolol.
- Spironolactone significantly reduced both diastolic blood pressure and systolic blood pressure.
- Spironolactone showed no association with hyperkalemia and renal impairment.



2 CE Units

Use of Aprocitentan and Spironolactone in Resistant Hypertension Management

6. Based on PATHWAY-2 and ASPIRANT, which clinical strategy best applies the trials' safety and efficacy findings to routine care for resistant hypertension?

- Start low-dose spironolactone in every patient with resistant hypertension, irrespective of their serum potassium or creatinine levels.
- Avoid spironolactone entirely in resistant hypertension because of hyperkalemia risk.
- Use spironolactone only after all other antihypertensives have failed and dialysis is imminent.
- Start spironolactone at a moderate dose in suitable patients, check potassium and creatinine within a few weeks and titrate while monitoring.

7. Which of the following regions has aprocitentan been approved in?

- United States
 - European Union
 - Hong Kong
- I and II
 - II and III
 - I and III
 - I, II and III

8. Which of the following statements is true about the PATHWAY-2 trial?

- The trial took place in Japan.
 - Spironolactone was found to be more effective as an add-on drug for the treatment of resistant hypertension than both an alpha-1 blocker and a beta-1 blocker.
 - It was a phase 4 clinical trial.
- I only
 - II only
 - I & II
 - II & III

9. In a patient with resistant hypertension, when is spironolactone generally considered an appropriate fourth-line agent regarding baseline serum potassium and kidney function?

- Potassium ≤ 3.5 mmol/L with eGFR > 20 mL/min/1.73 m²
- Potassium ≤ 4.5 mmol/L with eGFR > 45 mL/min/1.73 m²
- Potassium 4.5–5.0 mmol/L with eGFR > 45 mL/min/1.73 m²
- Potassium ≤ 5.5 mmol/L with eGFR > 30 mL/min/1.73 m²

10. Which of the following is correct about the PATHWAY-2, ASPIRANT, and PRECISION trials?

- All were parallel-group trials.
- PATHWAY-2 was a crossover trial; ASPIRANT and PRECISION were parallel-group trials.
- No placebo arms were used in any of the trials.
- All trials had a 12-month duration.

Answers will be released in the next issue of HKPJ.

CE Questions Answer for HKPJ Vol 323(D&T)

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1. D 2. B 3. C 4. D 5. A 6. B 7. D 8. C 9. D 10. D