治療抵抗性高血圧にはスピロノラクトンが最適である (ESC2015 Presentation # 4137)

PATHWAY-2：利尿薬スピロノラクトンは治療抵抗性高血圧患者の血圧を有効に低下させる

PATHWAY-2: Diuretic spironolactone effectively lowers blood pressure in resistant hypertension

治療抵抗性高血圧患者において、利尿薬スピロノラクトン追加は他の降圧薬を追加するより効果的であるとのPATHWAY-2トライアルの結果が、2015年ESC Congressホットラインセッションで発表された。3剤（ACE阻害薬またはアンジオテンシン受容体拮抗薬；カルシウム拮抗薬；およびサイアザイド系利尿薬）の最大耐用量をすでに併用投与されている治療抵抗性高血圧患者を対象とした。ベースライン時の治療に加え、患者らはスピロノラクトン（25～50mg）、ビソプロロール（5～10mg）、ドキサゾシン（4～8mg徐放剤）およびプラセボのいずれかを引き続き12週間投与される群にランダムに割り付けられた。314人の患者において、スピロノラクトンはプラセボ（8.70mmHg低下、p<0.001）；ドキサゾシン（4.03mmHg低下、p<0.001）；およびビソプロロール（4.48mmHg低下、p<0.001）、さらにドキサゾシンとビソプロロールの平均（4.26mmHg低下、p<0.001）に比べ、血圧コントロールに優れていた。全体で、スピロノラクトンを追加された患者のほぼ4分の3で血圧が大きく改善し、ほぼ60%の患者においては厳格な血圧コントロールに合致した（p<0.001）。60% の患者においてスピロノラクトンが最良の降圧薬であったが、ビソプロロールやドキサゾシンが最良であったのはそれぞれ17%および18%のみであった。

Full Text

In patients with resistant hypertension, addition of the diuretic spironolactone was significantly more effective than adding other blood pressure lowering drugs according to results of the PATHWAY-2 trial presented during a Hot Line session at ESC Congress 2015.

The study's findings suggest spironolactone "was a clear winner and should be first choice for the additional treatment of resistant hypertension," said investigator Bryan Williams, M.D..

"These results have broad international relevance and applicability," noted Professor Williams, who is from University College London, and the British Hypertension Society Research Network.

"The PATHWAY-2 study showed that spironolactone was overwhelmingly the most effective blood pressure-lowering therapy compared to bisoprolol or doxazosin and suggest that the predominant underlying cause of resistant hypertension is sodium retention - even among patients with baseline diuretic therapy. This establishes, for the first time, a clear hierarchy for drug treatment of resistant hypertension which should influence future treatment guidelines and clinical practice globally."

Resistant hypertension is defined as uncontrolled blood pressure (BP) despite treatment with at least 3 BP-lowering medications. Prior to PATHWAY-2 there was no strong evidence supporting recommendations for the most appropriate additional drug to control blood pressure, and "there has been a growing perception that controlling BP in resistant hypertension is beyond the reach of existing drug therapies," explained Professor Williams. "But PATHWAY-2 shows that control is possible in the majority of patients, using a drug that has been available for many decades."

While the pathogenesis of resistant hypertension is poorly understood, one hypothesis is that it could be related to sodium retention – a result of reduced diuretic doses in recent years, he said.

PATHWAY 2 examined whether additional diuretic therapy with spironolactone would be the most effective at reducing BP compared to treatment with two other antihypertensives that have different mechanisms of action: doxazosin which acts to reduce arterial resistance, and bisoprolol which acts to reduce cardiac output.

The study included patients with resistant hypertension who were already treated with maximally tolerated doses of a combination of three drugs: an ACE-inhibitor or angiotensin receptor blocker (ARB); a calcium channel blocker (CCB); and a thiazide type diuretic. "The key question was, which drug should be added to get blood pressure controlled," said Professor Williams.

Uncontrolled BP was defined as seated clinic systolic BP of 140 mmHg or more for non-diabetic patients, or 135 mmHg or more for patients with diabetes, and a home systolic BP (HSBP) 130mmHg for all patients. In addition to their baseline BP therapy, patients were randomized to sequentially receive 12 weeks of spironolactone (25-50mg), bisoprolol (5-10mg), doxazosin (4-8mg modified release) and placebo in random order.

Blood pressure was measured with an automated BP monitor and recorded both in the clinic as well as at home over 4 consecutive days at baseline as well as at 6 and 12 weeks of each treatment cycle.

The primary end-point was average home systolic blood pressure (HSBP) for each of the treatments, with clinic systolic BP being a secondary endpoint.

In 314 patients, spironolactone had superior HSBP control compared to placebo (a reduction of 8.70 mmHg, p<.001); doxazosin (a reduction of 4.03 mmHg, p<0.001), and bisoprolol (a reduction of 4.48 mmHg, p<0.001); as well as the mean of doxazosin and bisoprolol (a reduction of 4.26 mmHg, p<0.001).

Overall, almost three quarters of patients with uncontrolled blood pressure saw a major improvement in their blood pressure on spironolactone, with almost 60% meeting a stringent measure of blood pressure control (p<0.001). Spironolactone was the best drug at lowering blood pressure in 60%, whereas bisoprolol and doxazosin where the best drug in only 17% and 18% respectively.

Clinic measurements mirrored the HSBP measurements except there was a large placebo effect in the clinic that was not seen at home.

"This is the first study to use home BP rather than clinic BP as a primary outcome in these patients," noted Professor Williams. "Not only did this reduce the placebo effect but it also eliminated patients with 'white coat hypertension' whose BP may have been spuriously elevated due to clinic anxiety."

The findings "challenge the concept that that resistant hypertension cannot be treated adequately with drug therapies, and suggest that treatments which have a natriuretic action, in that they promote sodium excretion, are likely to be the most effective," he concluded.

This trial and PATHWAY-3 are part of the PATHWAY program of trials in Hypertension undertaken by academic investigators within the British Hypertension Society, led by Professor Morris Brown of the University of Cambridge, Professor Williams, and Professor Tom MacDonald of the University of Dundee.

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