HOT OFF THE PRESS

Emerging evidence to start antihypertensive medication with low dose drug combinations

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The detection and treatment of hypertension remains inadequate in many countries, and patients treated for hypertension often do not reach recommended target blood pressure values¹. Most of the effect on blood pressure reduction, and the lowest risk for side effects, occurs with low doses for most antihypertensive medications, suggesting that starting treatment with a combination of blood pressure lowering medicines at low doses may improve blood pressure control². This concept is further supported by a recent study by Chow et al³. This randomised controlled parallel group multicentre study in Australia included 591 hypertensive patients with an untreated standard office blood pressure of 140–179 mm Hg systolic and/or 90–109 mm Hg diastolic (or daytime average ambulatory blood pressure of 135 and/or 85 mm Hg or above), or receiving monotherapy with a treated standard office blood pressure of 130–179 mm Hg systolic and/or 85–109 mm Hg diastolic (or daytime average ambulatory blood pressure of 125 and/or 80 mm Hg or above). Mean age was 59 years, 40% were female, 82% were white, and 50% were previously untreated; baseline standard office blood pressure was 153/89 mm Hg.

The participants were randomised double blind to a single pill low dose combination (irbesartan 37.5 mg, amlodipine 1.25 mg, indapamide 0.625 mg, and bisoprolol 2.5 mg) or initial monotherapy (irbesartan 150 mg). Amlodipine 5 mg was added at 6 weeks, with additional further drugs if required, to achieve a standard office blood pressure below 140/90 mm Hg. Primary outcome was the change in unattended office systolic blood pressure (OMRON HEM907 device) at 12 weeks.

The results³ show a greater reduction in unattended office blood pressure by the single pill combination than by initial monotherapy (142/86 to 120/71 mm Hg vs 140/83 to 127/78 mm Hg), with a difference in unattended systolic blood pressure of -6.9 (95% confidence limits 4.9–8.9; $p < 0.001$) mm Hg. Additional therapy was more common in the initial monotherapy group (40 vs 15%). The results were consistent across subgroups, for ambulatory and standard office blood pressures, and for systolic and diastolic blood pressures. The findings were maintained in favour of the single pill combination (-7.7, 5.2–10.3 mm Hg; $p < 0.001$) during a 52 week follow up. There were no major differences in safety and tolerability between the two study groups.

Initiation of treatment with two or more medicines, as compared to monotherapy, improves drug and treatment adherence and persistence, reduce care provider inertia, improves blood pressure control, and reduces cardiovascular events; and single pill combinations appear to offer additional advantage⁴⁻⁸. The study by Chow et al³ extend these findings by showing that a single pill low dose combination will achieve target blood pressure quicker and maintain blood pressure control more effectively than the prevailing practice to start with a single medicine, without major impairment of safety or tolerability. However, studies to demonstrate how blood pressure reduction with single pill low dose combinations translates into a superior reduction in cardiovascular morbidity and mortality are important. Also, the optimal combination of antihypertensive agents (numbers, classes, and doses) to include in a single pill low dose combination for best performance warrant further study. Of note, a similar strategy in the

management of chronic heart failure with reduced left ventricular ejection fraction to start treatment with several medicines simultaneously (i.e. an angiotensin converting enzyme-inhibitor or angiotensin receptor-neprilysin inhibitor, mineralocorticoid receptor-antagonist, beta-blocker, and a sodium-glucose co-transporter 2-inhibitor) is recommended in recent guidelines ^[9], and there is emerging evidence for a polypill concept (two or more antihypertensive agents plus statin, with or without thrombocyte inhibitor) in the primary prevention of cardiovascular disease ^[10]. These results may eventually change our management of high risk cardiovascular patients.

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