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The IDEAL Study: Towards Personalized Drug Treatment of Hypertension

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Abstract – Objective. To identify markers (phenotypic, genetic, or environmental) of blood pressure (BP) response profiles to angiotensin converting enzyme inhibitors (ACEIs) and diuretics. **Methods.** IDEAL was a crossover (two active and two wash out phases), double-blind, placebo-controlled trial. Eligible patients were untreated hypertensive, aged 25 to 70. After two visits, patients were randomized to one of four sequences. The main outcome was BP differences between the active treatment and placebo. **Results.** One hundred and twenty-four patients were randomised: mean age 53, men 65%, family history of hypertension 60%. Average BP fall at each visit before randomisation was about 2% of the initial level reflecting both a regression to the mean and a placebo effect. **Conclusion.** The results are expected to improve knowledge in drug's mechanisms of action and pathophysiology of hypertension, and to help in personalizing treatment. The estimation of BP responses to each drug in standardized conditions provided a benefit to each participant.

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Résumé – Étude IDEAL : vers la personnalisation du traitement médicamenteux de l'hypertension. Objectif. Identifier les marqueurs (phénotypiques, génétiques, environnementaux) des profils de réponse pressionnelle à un inhibiteur de l'enzyme de conversion de l'angiotensine et un diurétique. **Méthodes.** IDEAL est un essai en plan croisé (2 phases actives et 2 phases de désimprégnation) en double-insu *versus* placebo. Les patients étaient des hypertendus non traités de 25 à 70 ans. Deux visites précédaient la randomisation des patients. Le critère principal était la différence de PA traitement actif *versus* placebo. **Résultats.** Cent vingt-quatre patients ont été randomisés d'âge moyen 53, hommes 65 %, histoire familiale d'hypertension 60 %. La baisse moyenne de PA à chaque visite pré-randomisation était d'environ 2 % du niveau initial traduisant une régression vers la moyenne et un effet placebo. **Conclusion.** IDEAL permettra d'améliorer les connaissances sur les mécanismes d'action des médicaments dans l'hypertension, étape indispensable vers la personnalisation du traitement. L'estimation de la réponse pressionnelle dans des conditions standardisées a représenté un bénéfice réel pour chaque participant.

List of abbreviations: see end of article.

1. Background

Several classes of blood pressure (BP) lowering drugs have been shown to reduce cardiovascular morbidity and mortality for the primary and secondary prevention of hypertension as well as in high-risk patients.[1,2] Most randomised controlled trials (RCTs) used an adaptive intensification strategy based on BP response in order to achieve a predefined arbitrary BP target.[3] However, some large RCTs demonstrated the benefit of a fixed-dose strategy in primary prevention,[4,5] in secondary post-stroke prevention,[6,7] and in high-risk patients.[8,9]

The clinical benefit of the usual adaptive strategy has not been evaluated nor quantified when compared with the fixed-dose strategy or to an alternative adaptive strategy based on patients' pre-therapeutic characteristics such as BP level or medium-term risk. Several RCTs have suggested that the benefit associated with intensified BP-lowering treatment was either lower than the benefit of basic treatment[10] or absent in low-risk individuals.[11] In older or oldest individuals the intensification of BP-lowering treatment was also debatable.[12,13] The proportion of risk reduction explained by BP reduction varies between 20% to 70% depending on the criteria and methods used.[14–16] Yet efforts used to control BP ignore other potential mechanisms involved in drug effects.

The average BP reduction under treatment is about 5 to 6 mmHg for diastolic BP (DBP) and 12 to 15 mmHg for systolic BP (SBP),[17] which is about 6 to 10% of initial BP. The magnitude of this BP reduction is just as important as the standard deviation of the within-individual BP distribution during 24-hour ambulatory measurements.[18] It is easy to demonstrate BP reduction in therapeutic trials of tens or hundreds of participants with standardised procedures. However, it is impossible to show this in standard clinical practice. It is therefore an illusion to adjust drug treatment based on a patient's BP response, because BP varies considerably without any treatment administration. This has been recently illustrated in a meta-analysis of angiotensin-converting enzyme inhibitors (ACEIs) based on individual patient data.[19] The consequences of BP measurement errors have also been shown in simulation studies, with a 75% misclassification rate after four years.[20]

Several trials assessed the individual markers of BP response, through parallel groups or crossover designs. Materson *et al.* compared 6 drugs and a placebo in parallel groups in 1,292 patients.[21] Their trial showed that diltiazem, a calcium antagonist, was the most efficient at reducing BP. Diltiazem response was correlated to Afro-American ethnic origin, while the response to ACEIs and beta-blockers was correlated to age. The existence of BP response profiles to various drug classes was confirmed in a crossover, double-blinded trial.[22] Fifty-six participants received sequentially each of the four main drug groups, ACEIs (A), beta-blockers (B), calcium-channel antagonists (C), and diuretics (D). The authors observed a correlation of the specific response following the AB/CD rule. There were significant correlations between the BP responses to A and B, and between C and D, but not between the other four pairings of treatments. Attwood and his team applied a similar experimental design to a population of 72 participants (68 completed the study) with three drugs (a calcium-channel antagonist, a beta-blocker, and an ACEI).[23] They observed a stronger correlation of BP response between the beta-blocker and the ACEI. The response to the calcium-channel antagonist and to the beta-blocker was also significantly correlated. The activation level of the renin-angiotensin-aldosterone system offered an explanation to the AB/CD rule because beta-blockers and ACEIs depress the system, whereas diuretics and calcium-channel antagonists activate it. This was recently illustrated in a parallel group study evaluating atenolol and hydrochlorothiazide.[24,25]

The determinants of BP response patterns are not completely understood. In the above mentioned studies, Attwood and Dikerson sought to identify factors explaining the different BP responses between drugs. Active renin and initial BP levels were some of the factors that explained BP differences. The failure of both studies to determine whether age, body mass index, and

