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Practical Diabetes

Angiotensin-Converting Enzyme Inhibitors vs. Angiotensin Receptor Blockers for the Treatment of Hypertension in Adults With Type 2 Diabetes: Why We Favour Angiotensin Receptor Blockers

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Key Messages

- Angiotensin receptor blockers (ARBs) have efficacy similar to that of angiotensin-converting enzyme inhibitors (ACEIs) with respect to cardiovascular and renal outcomes in patients with diabetes.
- The combination of an ACEI or ARB with a mineralocorticoid receptor blocker in patients with diabetic nephropathy has shown promising results.
- Sodium-glucose cotransporter type 2 inhibitors constitute a useful adjunct to ARBs for the prevention of cardiovascular and renal events in patients with diabetes.

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ABSTRACT

Cardiovascular disease is the principal cause of morbidity and mortality in patients with diabetes mellitus. The incidence or progression of kidney disease is also common in these patients. Several clinical trials have established the efficacy of angiotensin receptor blockers for the prevention of adverse cardiovascular and renal outcomes in this population and are summarized in this review article. Head-to-head comparison of angiotensin receptor blockers with angiotensin-converting enzyme inhibitors has shown similar cardioprotective and renoprotective properties of both medication classes. However, angiotensin receptor blockers have an improved safety profile with fewer episodes of cough and angioedema and may be the agent of choice in patients with diabetes and hypertension. Novel therapeutic strategies, such as those that include a mineralocorticoid receptor blocker or a selective sodium-glucose cotransporter type 2 inhibitor, may further protect patients with diabetes from cardiovascular and renal complications.

Mots clés :
événements cardiovasculaires indésirables
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RÉSUMÉ

Les maladies cardiovasculaires sont la principale cause de morbidité et de mortalité chez les patients atteints de diabète sucré. L'incidence ou la progression de la maladie rénale est également fréquente chez ces patients. Dans le présent article de revue, nous résumons de nombreux essais cliniques qui ont permis d'établir l'efficacité des bloqueurs des récepteurs de l'angiotensine dans la prévention des événements cardiovasculaires et rénaux indésirables dans cette population. La comparaison directe des bloqueurs des récepteurs de l'angiotensine aux inhibiteurs de conversion de l'angiotensine a démontré des propriétés cardioprotectrices et rénoprotectrices similaires des deux classes de médicaments. Toutefois, puisque les bloqueurs des récepteurs de l'angiotensine ont un meilleur profil d'innocuité et entraînent moins d'épisodes de toux et d'angioœdème, ils constituent le médicament de choix chez les patients diabétiques et hypertendus. De nouvelles stratégies telles que celles qui utilisent un bloqueur du récepteur minéralocorticoïde ou un inhibiteur du cotransporteur sodium-glucose de type 2 peuvent davantage protéger les patients diabétiques des complications cardiovasculaires et rénales.

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Introduction

Cardiovascular disease is the principal cause of morbidity and mortality in patients with diabetes mellitus (1). Comprehensive management of these patients includes not only adequate glycemic control but also attention to additional recognized risk factors. Hypertension is a cardiovascular risk factor with very high prevalence in people with diabetes, and several clinical trials have demonstrated improved cardiovascular or renal outcomes with blood pressure (BP) control in patients with diabetes (2).

The hallmark trial demonstrating improved clinical outcomes with BP reduction was the United Kingdom Prospective Diabetes Study, which enrolled 1,148 patients who had hypertension with diabetes and randomized them to achieve a BP target of below 150/85 mmHg (intensive arm) or below 180/105 mmHg (control arm) by using captopril or atenolol. The primary outcome, a composite of any diabetes-related complication, was reduced by 24% in the intensive arm over a mean follow-up period of 8.4 years (3). Microvascular and macrovascular complications were reduced by 37% and 34%, respectively.

Several trials were conducted thereafter using various antihypertensive agents and various BP targets and assessing cardiovascular or renal outcomes. Blockade of the renin angiotensin aldosterone system with either angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) was demonstrated to be highly effective for cardiovascular and renal protection. This review article focuses on current evidence of ARBs in patients with type 2 diabetes and explores novel strategies that may enhance the cardioprotective and renoprotective properties of ARBs.

Cardiovascular Outcomes with ARBs in Patients with Diabetes

When ARBs became available, several trials evaluated their efficacy in cardiovascular outcomes in the general population and in various patient subgroups. The Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) program was the first to assess efficacy of an ARB in patients with heart failure and included 3 independent randomized controlled trials (4). A total of 28% of patients in the CHARM program had diabetes. The primary endpoint for each of the 3 CHARM trials was time to cardiovascular death or hospital admission for heart failure. It occurred in 30% of patients in the candesartan arm and in 35% of patients in the placebo arm; adjusted hazard ratio (HR) 0.84, 95% confidence interval (CI) 0.77 to 0.91. Candesartan was also associated with reduction in all-cause mortality (adjusted HR 0.90, 95% CI 0.82 to 0.99), driven by reduction of cardiovascular mortality, particularly in patients with heart failure involving reduced left ventricular ejection fraction (<40%).

The Losartan Intervention For Endpoint reduction study enrolled patients with hypertension and left ventricular hypertrophy on electrocardiogram and randomized them to receive either a losartan-based or an atenolol-based antihypertensive regimen. A prespecified subgroup analysis included the 1,195 patients who had diabetes at the beginning of the study (5). The primary composite endpoint of cardiovascular mortality, stroke or myocardial infarction occurred in 18% of patients in the losartan group vs. 23% of patients in the atenolol group (adjusted HR, 0.76, 95% CI 0.58 to 0.98). Patients in the losartan group also had lower incidences of all cause-mortality and heart failure compared with patients in the atenolol group. These results were obtained despite a similar BP decrease in both arms throughout the follow-up period.

The Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Trials evaluated the efficacy of telmisartan vs. placebo in patients with established cardiovascular disease or diabetes with end-organ damage who were intolerant to ACEIs (6). More than 35% of the 5,926 patients enrolled had diabetes. The primary outcome, a composite of cardiovascular death, myocardial infarction, stroke or hospitalization for heart failure, occurred in 15.7% of patients in the telmisartan group vs. 17.0% of patients in the placebo group (HR 0.92, 95% CI 0.81 to 1.05). The secondary outcome of cardiovascular death, myocardial infarction or stroke occurred in 13.0% of patients in the telmisartan group vs. 14.8% of patients in the placebo group (HR 0.87, 95% CI 0.76 to 1.00). These important outcomes trended in favour of a benefit from telmisartan but did not reach statistical significance due to an event rate that was too low for the power of the study and that could be attributed to improved standard-of-care baseline treatment (55% of patients were taking statins, 58% were taking beta blockers and 85% were taking antiplatelet agents). Despite these limitations, another secondary outcome, hospitalizations for any cardiovascular cause, was statistically significantly lower (p=0.025) in favour of the telmisartan group (30.3%) vs. the placebo group (33.0%). Importantly, the proportion of patients who discontinued telmisartan for the same reason they were intolerant to ACEIs was low and was similar to that of the placebo group.

The Irbesartan Diabetic Nephropathy Trial enrolled patients with type 2 diabetes, proteinuria of at least 0.9 g/24 h, BP >135/85 mmHg and moderate kidney impairment (creatinine 88 to 265 μmol/L in women or 106 to 265 μmol/L in men). Patients were randomized to receive irbesartan (titrated from 75 to 300 mg daily), amlodipine (titrated from 2.5 to 10 mg daily) or placebo (7). Cardiovascular endpoints were monitored as secondary outcomes in this study and were reported separately (8). The composite cardiovascular endpoint included death from cardiovascular causes, nonfatal myocardial infarction, hospitalization for heart failure, cerebrovascular event with permanent neurologic deficit, or above-the-ankle lower-limb amputation. No significant difference was detected among the 3 treatment groups for this outcome. However, the study was not adequately powered for the cardiovascular endpoint. Irbesartan was superior to amlodipine for the heart failure component of the cardiovascular outcome (p=0.002).

The reduction of endpoints in the Noninsulin-Dependent Diabetes Mellitus trial with the Angiotensin II Antagonist Losartan trial included patients with type 2 diabetes, albuminuria (albumin to creatinine ratio ≥ 300 mg/g or 24 h proteinuria of at least 0.5 g) and moderate kidney impairment (creatinine 115 to 265 μmol/L). They were randomized to receive losartan (titrated up to 100 mg daily) or placebo on the top of conventional antihypertensive medication. The BP target was <140/90 mmHg (9). The secondary outcome of the study was a composite of death from cardiovascular causes, myocardial infarction, stroke, first hospitalization for heart failure or unstable angina, and coronary or peripheral revascularization. It occurred in 32.9% of patients in the losartan group vs. 35.2% in the placebo group (p=0.26). However, the study was not adequately powered for the cardiovascular endpoint. Furthermore, a first hospitalization for heart failure was less commonly observed in the losartan group (11.9%) compared with the placebo group (16.7%; p<0.01).

The Candesartan Antihypertensive Survival Evaluation in Japan trial enrolled hypertensive Japanese patients with 1 additional risk factor and randomized them to receive either candesartan at 4 to 8 mg daily (increasing up to 12 mg per day) or amlodipine at 2.5 to 5 mg per day (up to 10 mg daily). The primary outcome of the study was a composite of cardiovascular and renal events (sudden cardiac death; stroke or transient ischemic attack; heart failure, angina pectoris or acute myocardial infarction; dissecting aortic aneurysm or occlusion of a peripheral artery; creatinine ≥4 mg/dL; doubling creatinine; or end-stage renal disease). A posthoc analysis including 2,018 patients with diabetes at baseline was published separately (10). Although diabetes was an independent predictor of cardiovascular events, no difference was detected between patients