http://www.kidney-international.org

Adherence to antihypertensive agents improves risk reduction of end-stage renal disease

Louise Roy[1], Brian White-Guay[2], Marc Dorais[2], Alice Dragomir[3], Myriam Lessard[1] and Sylvie Perreault[2]

[1]Faculté de Médecine, Université de Montréal, Montréal, Québec, Canada; [2]Faculté de Pharmacie, Université de Montréal, Montréal, Québec, Canada and [3]Faculté de Médecine, Université McGill, Montréal, Québec, Canada

Uncontrolled hypertension is associated with an increased risk of end-stage renal disease (ESRD). Intensified blood pressure control may slow progression of chronic kidney disease; however, the impact of antihypertensive agent adherence on the prevention of ESRD has never been evaluated. Here we assessed the impact of antihypertensive agent adherence on the risk of ESRD in 185,476 patients in the RAMQ databases age 45 to 85 and newly diagnosed/treated for hypertension between 1999 and 2007. A case cohort study design was used to assess the risk of and multivariate Cox proportional models were used to estimate the adjusted hazard ratio of ESRD. Adherence level was reported as a medication possession ratio. Mean patient age was 63 years, 42.2% male, 14.0% diabetic, 30.3% dyslipidemic, and mean follow-up was 5.1 years. A high adherence level of 80% or more to antihypertensive agent(s) compared to a lower one was related to a risk reduction of ESRD (hazard ratio 0.67; 95% confidence intervals 0.54–0.83). Sensitivity analysis revealed that the effect is mainly in those without chronic kidney disease. Risk factors for ESRD were male, diabetes, peripheral artery disease, chronic heart failure, gout, previous chronic kidney disease, and use of more than one agent. Thus, our study suggests that a better adherence to antihypertensive agents is related to a risk reduction of ESRD and this adherence needs to be improved to optimize benefits.

Kidney International (2013) **84,** 570–577; doi:10.1038/ki.2013.103; published online 22 May 2013

KEYWORDS: adherence to treatment; antihypertensive drugs; chronic renal insufficiency

Correspondence: *Sylvie Perreault, Chercheure Nationale du FRSQ, Chaire sanofi-aventis sur l'utilisation des médicaments, Faculté de Pharmacie, Université de Montréal, Case Postale 6128, Succursale Centre-Ville, Montréal, Québec H3C 3J7, Canada. E-mail: sylvie.perreault@umontreal.ca*

Received 21 September 2011; revised 15 January 2013; accepted 17 January 2013; published online 22 May 2013

Hypertension is the most common chronic disease in industrialized countries.[1] It is a major cause of target organ damage and untreated hypertension increases the risk of stroke, ischemic heart disease, congestive heart failure, and renal disease.[2,3] With diabetes, it accounts for most cases of chronic kidney disease worldwide.[1] It is well recognized that poor control of blood pressure is an independent risk factor and results in accelerated progression to end-stage renal disease (ESRD).[4,5] Even relatively modest elevation or normal high blood pressure is a risk factor for ESRD.[4–6] There is also a clear correlation between the severity of hypertension and the risk of ESRD.[2,4,5] ESRD significantly increases cardiovascular morbidity and mortality; it is therefore associated with substantial health and economic costs.[7–9]

Intensified blood pressure control is a key treatment strategy to slow chronic kidney disease progression. Although we have significantly improved our awareness and treatment of hypertension during the past 20 years,[10,11] there are still 30–60% of patients who have uncontrolled hypertension.[11,12] There are many reasons for poorly controlled blood pressure, including nonadherence to antihypertensive (AH) agents.[13] In fact, nonadherence is more common in chronic and asymptomatic conditions, such as hypertension.[13,14] Some authors estimate that at least 50% of hypertensive patients do not adhere to the prescribed medications.[13,15] Moreover, persistence to AH therapy declines after 6 months and is much lower among patients with newly diagnosed hypertension.[16] Good blood pressure control is more likely achieved in those with good medication-taking behavior.[15,17]

Nonadherence to AH treatment is likely an important source of preventable cardiovascular morbidity and mortality. Some studies have examined the impact of a better adherence to AH agents on cardiovascular and cerebrovascular outcome in primary prevention.[18–20] However, to our knowledge, no study has assessed the relationship between adherence levels to AH medication and outcome for primary prevention of ESRD. This study was designed to evaluate the impact of better adherence to AH therapy on ESRD among patients newly treated for hypertension.

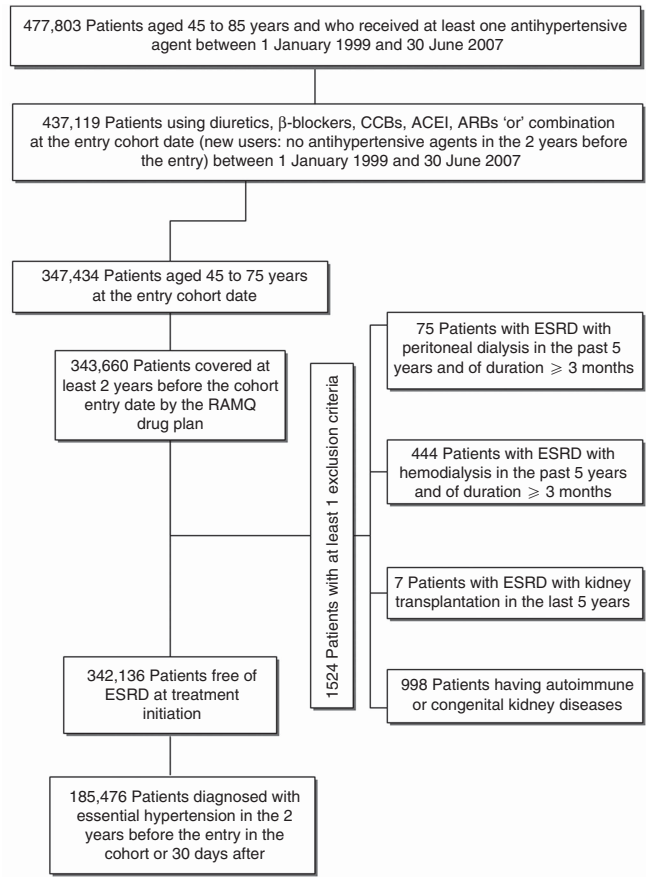

Figure 1 | Flowchart of inclusion and exclusion criteria. Exclusion criteria were applied in the 5 years preceding the cohort entry date for diagnoses and medical procedures and 2 years before the cohort entry date for medication. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; ESRD, end-stage renal disease.

RESULTS

Patient characteristics

After applying the inclusion and exclusion criteria (Figure 1), the resulting cohort consisted of 185,476 patients with a mean age at entry of 63 years, 42.2% of whom were male, 14.0% were diabetic, and 30.3% had a dyslipidemia (Table 1). As a first AH monotherapy treatment, angiotensin-converting enzyme inhibitors (22.6%) were used most often, followed by diuretics (19.6%), angiotensin II receptor blockers (17.5%), calcium channel blockers (12.0%), and β-blockers (10.8%). Table 1 shows the demographic and clinical characteristics at the time of initiating the first prescription of AH agents. Table 2 provides baseline demographic and clinical characteristics of the whole cohort of patients according to the adherence level of AH agents during follow-up. We did not observe any clinically significant difference between low and high adherence groups, except for the use of AH agents, in the whole cohort (Table 2) and among patients with prior chronic kidney disease (Table 3); however, these latter patients had more associated comorbidities.

The mean follow-up time was 5.1 years. During this follow-up, we identified 424 cases of ESRD (0.23% of cohort or 0.04 per 100 persons-year). The death rate in the whole cohort during the follow-up was 5.2% (9690 cases or 1.02 per 100 persons-year). As shown in Table 4, the cases were more likely to be male, have more diabetes, cardiovascular diseases, more urologic interventions, gout and chronic kidney disease, and being users of more than one AH agents compared with noncases.

Impact of the adherence level of AH agents on ESRD, and the risk factors of ESRD

Figure 2 shows the cumulative incidence rate of ESRD among high and low adherence levels of AH agents; we observed a significant effect of high-adherence level to AH treatment after 5 years. On the other hand, as shown in Figure 3, the cumulative incidence rate of ESRD among patients with high versus low adherence level of AH agents is significantly different only in patients without prior chronic kidney disease.

The overall mean adherence level to AH agents was 83.9% ($\pm$27.1%). The adjusted hazard ratio (HR) of ESRD was significantly lower in the high adherence group compared with the lower one (HR: 0.67; 0.53–0.83; Table 5). Furthermore, many other risk factors for ESRD onset were identified such as male gender, diabetes, peripheral vascular diseases, chronic heart failure, gout, urologic intervention, chronic kidney disease male, and the number of drugs used for antihypertensive treatment (Table 5).

Validity of the methodological approach

High adherence level to proton pump inhibitors (HR: 0.97; 0.73–1.29) or benzodiazepines (HR: 1.17; 0.94–1.47) had no impact on ESRD onset. High adherence to AH agent specifically was associated with a reduction of ESRD, but this effect was not present with non-antihypertensive drugs.

DISCUSSION

Our study reveals that adherence to AH treatment of $\geqslant$80% in this newly diagnosed hypertensive population is associated with a significant 33% decreased risk of ESRD onset. This association was not significant among patients followed up for $<$5 years, suggesting that the efficacy of AH agents in ESRD prevention may take several years before becoming apparent. This is in accord with literature[4] and supports the fact that ESRD develops over a longer period than cardiovascular events that appear earlier.[20,21]

Our sensitivity analyses reveal that the effect is significant only among patients without chronic kidney disease. This reflects the fact that chronic kidney disease is a very strong predictive factor of ESRD. Moreover, chronic kidney disease patients have more comorbidities that are associated with ESRD.

In addition, results indicate that male gender, diabetes, peripheral vascular diseases, chronic heart failure, gout, urologic intervention, chronic kidney disease, and the number of drugs used for AH treatment are associated with