Angiotensin Receptor Antagonist

Comparative Effectiveness of Olmesartan and Other Angiotensin Receptor Blockers in Diabetes Mellitus
Retrospective Cohort Study

Raj Padwal, Mu Lin, Mahyar Etminan, Dean T. Eurich

Abstract—Olmesartan has been linked with increased risk of cardiovascular mortality and sprue-like enteropathy. We compared outcomes between olmesartan and other angiotensin receptor blockers in a large clinical registry of patients with diabetes mellitus. A retrospective cohort analysis using nationwide US-integrated insurance and laboratory claims was performed in 45185 incident diabetic angiotensin receptor blocker users, including 10370 (23%) olmesartan users. Hazard ratios were computed using time-dependent Cox models adjusted for sociodemographic characteristics, comorbidities, laboratory data, drug use, healthcare utilization, and the propensity to receive olmesartan. Blood pressure data were unavailable. Subjects were followed up for 116721 patient-years. The primary end point was all-cause hospitalization or all-cause mortality and occurred in 10915 (24%) patients. Average age was 54.3±9.6 years, 52% were men, 17% had cardiovascular disease, and 10% chronic kidney disease. Compared with other angiotensin receptor blockers, the adjusted hazard for olmesartan was 0.99 (95% confidence interval, 0.94–1.05) for all-cause hospitalization and mortality; 0.90 (0.62–1.30) for all-cause mortality; 0.99 (0.94–1.05) for all-cause hospital admission; 0.88 (0.78–1.00) for cardiovascular disease–related admission, and 1.09 (0.98–1.20) for gastrointestinal disease–related hospitalization in the overall cohort. Olmesartan use was associated with an adjusted hazard for the primary outcome of 1.11 (0.99–1.24) in subjects with history of cardiovascular disease and 1.21 (1.04–1.41) in subjects with chronic kidney disease. In conclusion, there is no robust signal for harm with olmesartan use. Risk may be increased in kidney disease; thus, given the widespread availability of alternate agents, olmesartan should be used with caution in this subgroup pending further study. (Hypertension. 2014;63:977-983.) ● Online Data Supplement

Key Words: angiotensin receptor antagonists • cardiovascular diseases • comparative effectiveness research • hospitalization • mortality • olmesartan

Olmesartan, an angiotensin II type 1 receptor antagonist (ARB) first approved in 2002, is commonly used for the treatment of hypertension.1 Despite being the seventh ARB approved by the Food and Drug Administration and despite a lack of hard outcome trial data supporting its use, olmesartan is widely prescribed, with estimated worldwide sales of 2 billion US dollars in 2009.2 Two placebo-controlled randomized controlled trials examining the efficacy of olmesartan in delaying onset/progression of renal disease in patients with diabetes mellitus, Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) and Olmesartan Reducing Incidence of End Stage Renal Disease in Diabetic Nephropathy (ORIENT), have been recently published.3,4 In both trials, cardiovascular mortality was increased in subjects randomized to olmesartan treatment. In ROADMAP, cardiovascular deaths occurred in 15 (0.7%) olmesartan-treated subjects and 3 (0.1%) placebo-treated subjects (P=0.01). In subjects with pre-existing cardiovascular disease taking olmesartan, 11 cardiovascular deaths occurred compared with 1 in subjects assigned to placebo. In ORIENT, 10 (3.5%) subjects receiving olmesartan died of cardiovascular causes compared with 3 (1.1%) placebo-treated subjects (P>0.05). Although these data raise concerns, they do not definitively prove harm because cardiovascular death was not a primary end point, the absolute number of cardiovascular events was low in both studies, and nonfatal cardiovascular events were not significantly different between study arms in ROADMAP (81 [3.6%] for olmesartan versus 91 [4.1%] for placebo; P=0.31).

After undertaking a safety review of olmesartan in 2011, the US Food and Drug Administration determined that the benefits of the drug outweighed its potential risks in patients with hypertension but advised against use of olmesartan for...
delaying or preventing renal disease and underscored the need for more postmarketing surveillance. In 2013, following case reports describing a potential association between olmesartan and sprue-like enteropathy, the Food and Drug Administration issued a second warning and announced plans to conduct further safety reviews.

The objective of this study was to provide further postmarketing assessment of the comparative effectiveness and safety of olmesartan. Specifically, we assessed the effect of olmesartan therapy compared with other ARBs on overall mortality and cause-specific hospitalization and sought to quantify absolute event rates. Given prior evidence, we hypothesized that olmesartan use would increase the risk of mortality or hospitalization relative to other ARBs in patients with diabetes mellitus, and that this risk increase would be highest in patients with pre-existing cardiovascular disease and chronic kidney disease (CKD; ie, high-risk subgroups).

Methods

We performed a population-based retrospective cohort study using an anonymized large US claims and integrated laboratory database containing information on employed, commercially insured patients with dependants from all 50 states (Clinformatics Data Mart, Optum, Life Sciences). The database has been used in multiple previous studies, contains >13 million annual lives. We analyzed patient-level, clinically rich, deidentified longitudinal data, including administrative and demographic information (sex, age, type of insurance plan, eligibility date, and income); billable medical service inpatient, outpatient, and medical procedure claims (deidentified physician and facility identifier, date and place of service, cost of service, admission and discharge dates, procedure, and diagnosis codes); and laboratory test results and pharmacy claims data (deidentified prescribing physician, drug dispensed based on national drug codes, quantity and date dispensed, drug strength, days' supply, and cost of service). International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) clinical and procedure codes were used, and data were cleaned and analyzed using protocols compliant with the Health Insurance Portability and Accountability Act. Research ethics review board approval to conduct this study was obtained from the University of Alberta and the New England Institutional Review Board. The procedures followed were in accordance with institutional guidelines.

Cohort Selection

An inception cohort of 114010 new ARB users with diabetes mellitus aged ≥20 years and identified between January 1, 2004 and December 31, 2009 was created. The date of the first ARB prescription was designated as the index date. New users were individuals who did not have a prior prescription claim for any ARB for ≥1 year before their index date. We limited inclusion to subjects with ≥1 year of baseline data enrolled in a commercial medical insurance plan (Figure 1). Subjects were followed up until death, termination of medical insurance, or December 31, 2010 (study end) providing a maximum follow-up of 6 years. A priori, we decided to exclude users who crossed over from olmesartan to another ARB (or vice versa) during the follow-up period (n=3257). Mortality was ascertained by linking to the US national death index file. This is a highly valid and reliable method, with >98% sensitivity when social security number data are available.

The primary outcome was all-cause hospital admission or death. The composite outcome was analyzed using time-to-first event (eg, either admission date or date of death) as the dependent variable. Each component of this composite end point was also analyzed separately. Cause-specific mortality was not available. Other secondary end points included cardiovascular-related hospital admissions (ICD-9-CM codes 410, 411.1, 428, 430–438), the combined end point of cardiovascular-related hospital admission or all-cause mortality, gastrointestinal-related hospital admissions (ICD-9-CM codes 530–579), and admissions related to noninfec tious enteritis and colitis (ICD-9-CM codes 555–558). Patients were censored if they did not have an outcome of interest and reached study end (December 31, 2010) or their insurance was terminated.

Analyses

Time-varying Cox proportional hazards regression was used to estimate the effect of exposure to olmesartan (relative to all other ARBs) on each outcome. Time zero was set at index date. The days' supplied field in the prescription drug dispensations database was used as a proxy for the expected duration of each prescription and was used to compute time-varying drug exposure. We assumed that subjects were exposed to the drug of interest unless prescription refills were not obtained for 2 consecutive days' supplied periods. If drug discontinuation occurred, subjects were classified as unexposed from the end of the first consecutive days' supplied period to the end of the study or until they restarted the drug. In this time-varying primary analysis, outcome events were attributed to a given drug if the event occurred while the subject was exposed; no legacy or carryover effects from remote exposure were assumed.

Covariates

In addition to using time-varying exposure models to limit potential bias, additional potential confounders were included in the Cox regression models as time fixed baseline variables. These included age, sex, socioeconomic status (type of medical insurance and median household income according to the 2010 US census), cardiovascular comorbidities, clinical laboratory data (glycohemoglobin, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate [according to the Modified Diet in Renal Disease calculation: ≥90, 89.9–60, 59.9–30, <30 mL/min], albuminuria, and hemoglobin concentrations), and prescription drugs (eg, antidiabetic agents, antiplatelet drugs, anticoagulants, statins, calcium channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, renin inhibitors, diuretics, and nitrates). For patients who did not have specific clinical laboratory data measured, we used the missing indicator approach for all analyses.

To further control for baseline comorbidity and illness, we included an Adjusted Clinical Groups score in the model. This single comorbidity score is derived from the Johns Hopkins Adjusted Clinical Groups score system (Version 9) and is weighted by 32 adjusted diagnostic groups. It performs equally to or better than the Charlson and Elixhauser comorbidity scores. In addition, we adjusted for the total number of hospita l admissions in the year before the index date, the total number of chronic conditions at baseline, frailty (any occurrence of malnutrition, abnormal weight loss, morbidity, obesity, dementia, falls, and decubitus ulcer), and the time-varying propensity to receive olmesartan. For the latter, we computed the updated propensity or probability of receiving olmesartan every 3 months throughout the follow-up period. This propensity score was entered into the model as a continuous probability score that was based on ≥60 variables, including demographic variables (age, sex, age–sex interaction, state, and type of insurance), socioeconomic factors (income), comorbidities, health service use, laboratory data, markers of frailty, and drug treatments. A full list of model covariates and variables included in the propensity score is available on request.

Received Angiotensin Receptor Blockers (114 010)

Major Exclusions

no drug use after baseline, no state or income information (38)

less than 1 year of baseline data (65 530)

switches between olmesartan and other angiotensin receptor blockers during follow-up (13257)

Included in Analysis (45 185)

Figure 1. Inclusions and exclusions.
Subgroup and Sensitivity Analyses

Subgroup analyses were performed in subjects with a baseline history of cardiovascular disease and with CKD (defined as an estimated glomerular filtration rate <60 mL/min). A sensitivity analysis in which we repeated primary analysis comparing olmesartan with all other ARBs but censored subjects who switched from one ARB class to another (instead of excluding them) was also performed.

A dose–response analysis and an analysis comparing olmesartan with individual ARBs were also performed. Further methodological details are provided in the online-only Data Supplement.

Results

Of 114,010 ARB users, the final cohort comprised 45,185 subjects (Figure 1). Mean age was 54.3 (SD, 9.6) years, 52% were men, 17% had a history of cardiovascular disease, 13% had diabetes mellitus–related complications, and 10% had CKD (Table 1). We identified 10,370 (23%) olmesartan users and 34,815 (77%) who used other ARBs during the follow-up period. Additional baseline characteristics of the study population are summarized in Table 1. The prevalence of concomitant comorbidities was either equal between groups or lower in olmesartan users compared with users of other ARBs. One exception was hypertension, which was more common in olmesartan users. The average daily ARB doses prescribed during the follow-up period were olmesartan 22.1 mg, losartan 52.1 mg, valsartan 110.5 mg, telmisartan 41.9 mg, eprosartan 424.2 mg, irbesartan 145.9 mg, and candesartan 14.1 mg.

Subjects were followed up for 116,721 patient-years (median duration, 2.3 years [interquartile range, 1.1–3.8 years]). The primary composite end point occurred in 10,836 (24%) subjects; 10,315 (23%) olmesartan users and 34,815 (77%) who used other ARBs. The aHR for the primary outcome was increased in olmesartan users with other ARBs (aHR, 1.21 [1.04–1.41]).

Subgroup Analyses

Results in high-risk subjects are summarized in Table 3. In subjects with pre-existing cardiovascular disease, the aHR for the primary outcome was 1.11 (0.99–1.24) in olmesartan users. The aHR for the primary outcome was increased in olmesartan users with CKD (aHR, 1.21 [1.04–1.41]).

Sensitivity Analysis Censoring Rather Than Excluding ARB Switchers

In this analysis (n=48,475), the aHRs comparing olmesartan with all other ARBs for the primary outcome were 1.02 (95% confidence interval, 0.97–1.08) in the overall cohort,
In aggregate, our results do not demonstrate a robust signal for harm with olmesartan use in patients with diabetes mellitus, with the possible exception of diabetes mellitus with CKD. However, in the higher-risk subjects (those with pre-existing cardiovascular disease or CKD), the aHRs for this primary end point were increased, and this risk increase was statistically significant in subjects with CKD (however, this finding was not robust to sensitivity analysis). The increased risk was primarily driven by an increase in the relative hazard of all-cause hospitalization. When we examined cause-specific hospitalization, we found no statistically significantly increased risk for cardiovascular disease–related and gastrointestinal disease–related hospitalization. A dose–response analysis of olmesartan found an increased risk for the primary end point in the overall cohort and in subjects with cardiovascular disease. However, similar findings were observed in a dose–response analysis for valsartan (but not losartan). This suggests that higher doses might have been a marker of increased risk rather than a causative factor. Finally, in the agent-specific analysis, olmesartan was not consistently associated with the highest risk of harm. Few statistically significant differences were found between agents. Exceptions were that losartan was associated with a borderline statistically significant increase in the primary end point in subjects with cardiovascular disease, and the other ARBs (candesartan, eprosartan, and irbesartan) were associated with a lower risk for the primary end point in the CKD subgroup only (Table S2). In both cases, this result was driven by significant reductions in hospitalizations but not mortality (data not shown).

### Discussion

In this analysis of a clinically rich data set encompassing >45,000 patients with diabetes mellitus, after extensive multivariable adjustment, we found that olmesartan use compared with other ARB use was not associated with an increased risk of hospitalization or all-cause mortality in the overall cohort. In fact, there was a trend toward a lower relative hazard for cardiovascular hospitalizations. However, in the higher-risk subjects (those with pre-existing cardiovascular disease or CKD), the aHRs for this primary end point were increased, and this risk increase was statistically significant in subjects with CKD (however, this finding was not robust to sensitivity analysis). The increased risk was primarily driven by an increase in the relative hazard of all-cause hospitalization. When we examined cause-specific hospitalization, we found no statistically significantly increased risk for cardiovascular disease–related and gastrointestinal disease–related hospitalization. A dose–response analysis of olmesartan found an increased risk for the primary end point in the overall cohort and in subjects with cardiovascular disease. However, similar findings were observed in a dose–response analysis for valsartan (but not losartan). This suggests that higher doses might have been a marker of increased risk rather than a causative factor. Finally, in the agent-specific analysis, olmesartan was not consistently associated with the highest risk, and few statistically significant differences were found between agents. Exceptions were that losartan was associated with a borderline statistically significant increase in the primary end point in subjects with cardiovascular disease, and the other ARBs (candesartan, eprosartan, and irbesartan) were associated with a lower risk for the primary end point in the CKD subgroup only (Table S2). In both cases, this result was driven by significant reductions in hospitalizations but not mortality (data not shown).
ibesartan, and losartan. A limitation of this analysis was that olmesartan was prescribed to lower risk individuals, and no propensity score adjustment was used. In addition, the study population was broad and not limited to subjects with type 2 diabetes mellitus and no high-risk subgroup analyses were performed. Thus, although these findings are broadly consistent with the results of our study, they are not directly comparable because of differences in study populations and methodologic approaches.

Olmesartan is a third-generation high-affinity ARB with a 12- to 15-hour half-life that is prescribed once daily. It is available as a dual combination product with hydrochlorothiazide or amlodipine and as a triple combination preparation is available as a dual combination product with hydrochlorothiazide or amlodipine and as a triple combination preparation. No clinical trials demonstrating reductions in cardiovascular morbidity and mortality outcomes have been published. The ongoing 1147 patient Supplemental Benefit of an Angiotensin Receptor Blocker in Hypertensive Patients with Stable Heart Failure Using Olmesartan (SUPPORT) trial is evaluating the efficacy of olmesartan compared with non-ARB antihypertensives in reducing a composite of all-cause mortality, nonfatal acute myocardial infarction, nonfatal stroke, and hospital admissions for heart failure. Results are expected in 2013 to 2014.

Potential mechanisms to explain the association between olmesartan use and increased hospitalizations are not known. A J-curve mechanism resulting from excessive diastolic blood pressure lowering has been proposed to explain increased cardiovascular risk with olmesartan use in placebo-controlled studies. Notably, previous studies comparing olmesartan with either placebo or atenolol therapy have reported that olmesartan leads to comparatively favorable improvements in such surrogate cardiovascular end points as vascular remodeling, endothelial dysfunction, inflammatory biomarkers, and atherosclerotic plaque volume. In addition, olmesartan has been proposed to possess potential cardiovascular benefits compared with other ARBs because it is an inverse agonist at the angiotensin II type 1 receptor and because it reduces plasma angiotensin II levels. Thus, overall, published data support the hypothesis that olmesartan should reduce rather than increase cardiovascular events. It is possible that mechanistic studies to assess potential harm have yet to be performed given that signals for potential harm have only been recently reported.

Similarly, no mechanisms to definitively explain the putative association between olmesartan and sprue-like enteropathy are known. Case reports indicate that symptoms appear months to years after olmesartan initiation. Intestinal biopsies have revealed villous atrophy with mucosal inflammation and symptoms improve after drug discontinuation but not a gluten-free diet. IgA transglutaminase antibodies are notably absent. A cell-mediated or delayed hypersensitivity reaction, potentially associated with the human leukocyte antigen-DQ cell surface receptor type 2, has been proposed.

Strengths of this study include the availability of a nationally representative, clinically rich data set; a relatively large sample size and long follow-up duration; a comparative effectiveness design in which olmesartan was compared directly against other ARBs; the use of advanced statistical techniques to adjust for potential confounders (including propensity score analysis); and conduction of extensive sensitivity analyses. Limitations include the retrospective, observational nature of the study design, the relatively short follow-up period (median 2.3 years was shorter than ROADMAP [median 3.2] and ORIENT [mean 3.2]), and the inability to adjust for additional potential confounders. The most important missing confounder was blood pressure, and we acknowledge that the observed differences in outcomes could have resulted from differences in blood pressure control. For example, in the overall cohort, subjects with losartan notably had less comorbidity at baseline, and the inability to adjust.

Table 3. Subgroup Analyses in High-Risk Subjects Comparing Olmesartan Users With Users of All Other Angiotensin Receptor Blockers

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted HR (95% CI)</th>
<th>P Value</th>
<th>Time at Risk (Person-Years)</th>
<th>Events, n (%)</th>
<th>Adjusted HR (95% CI)</th>
<th>P Value</th>
<th>Time at Risk (Person-Years)</th>
<th>Events, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause hospitalization or mortality</td>
<td>1.11 (0.99–1.24)</td>
<td>0.08</td>
<td>2008</td>
<td>363 (4)</td>
<td>1.21 (1.04–1.41)</td>
<td>0.02</td>
<td>1131</td>
<td>208 (5)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.09 (0.95–2.03)</td>
<td>0.78</td>
<td>2462</td>
<td>12 (0)</td>
<td>0.88 (0.40–1.97)</td>
<td>0.76</td>
<td>1364</td>
<td>7 (0)</td>
</tr>
<tr>
<td>All-cause hospitalization</td>
<td>1.12 (0.99–1.25)</td>
<td>0.06</td>
<td>2008</td>
<td>362 (4)</td>
<td>1.23 (1.05–1.43)</td>
<td>0.09</td>
<td>1311</td>
<td>52 (1)</td>
</tr>
<tr>
<td>CV disease–related hospitalization</td>
<td>1.19 (0.98–1.46)</td>
<td>0.09</td>
<td>2335</td>
<td>115 (1)</td>
<td>1.30 (0.96–1.76)</td>
<td>0.09</td>
<td>1322</td>
<td>58 (1)</td>
</tr>
<tr>
<td>GI disease–related hospitalization</td>
<td>1.10 (0.87–1.37)</td>
<td>0.46</td>
<td>2348</td>
<td>91 (1)</td>
<td>1.27 (0.94–1.70)</td>
<td>0.12</td>
<td>1303</td>
<td>58 (1)</td>
</tr>
<tr>
<td>Noninfective enteritis and colitis-related admissions</td>
<td>1.13 (0.69–1.85)</td>
<td>0.62</td>
<td>2451</td>
<td>7 (0)</td>
<td>1.38 (0.79–2.42)</td>
<td>0.26</td>
<td>1351</td>
<td>9 (0)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; CV, cardiovascular; CKD, chronic kidney disease; GI, gastrointestinal; GFR, glomerular filtration rate; and HR, hazard regression.
for residual confounding may explain why there was a trend toward a lower hazard for the primary end point in olmesartan users in the overall group, yet risk was increased in the high-risk subgroups. Thus, it is important to emphasize that this type of study design provides associative and not causal evidence. In addition, all included subjects were middle aged Americans with commercial health insurance, which should be borne in mind when generalizing the results beyond this population. In particular, despite having cardiovascular risk factors or pre-existing disease, our study population had a crude death rate of only 392 per 100,000, which is lower than the 2010 crude death rate for all US adults aged 50 to 54 years (491.7 per 100,000) and indicates that the study population was relatively healthy and well treated. Finally, we did not have information on cause-specific mortality and could not directly evaluate the association between olmesartan use and cardiovascular mortality.

Perspectives

Olmesartan is a commonly prescribed antihypertensive drug, and recent evidence linking this agent to an increased risk of cardiovascular mortality and sprue-like enteropathy mandates the need for further study. Analyses of large-scale clinical registry data serve as a useful and important complement to randomized controlled trial data in terms of assessing drug-related harm. In the present analysis, although there was a suggestion that patients with CKD may be at higher risk of all-cause mortality or hospitalization, findings that would be consistent with the results of the ROADMAP study, our findings are not sufficiently robust or consistent to support the conclusion that olmesartan increases risk in patients with diabetes mellitus. About the subgroup of patients with CKD, given the results of ROADMAP and ORIENT and given our findings, we recommend that olmesartan use be used with caution in this patient population until further mechanistic, epidemiological, and interventional studies to clarify the effect of this drug on clinically important end points have been performed. We also recommend that further postmarketing surveillance of this agent be performed to assess risk in a more comprehensive fashion in different study samples and populations. This should take the form of additional analyses of clinical registries as well as a meta-analysis of individual patient-level data from previously published and soon-to-be-published randomized controlled trials.

Acknowledgments

R. Padwal originated the study idea and all authors contributed to the conception and design, the analysis, and interpretation of data. D.T. Eurich and M. Lin had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. R. Padwal and D.T. Eurich wrote the initial manuscript draft, all authors revised it critically for important intellectual content, and all authors provided final approval of the version to be published. We would also like to acknowledge Betsey Jackson at Health Data Services Corporation (www.hdscorp.biz), PO Box 53, Carlisle, MA 01741 for providing independent database acquisition services.

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Disclosures

R. Padwal has received research funding from Novo Nordisk and remuneration for speaking from Merck, Servier, and Abbott. The other authors report no conflicts.

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What Is New?

• Olmesartan has been linked to an increased risk of cardiovascular mortality in patients with diabetes mellitus.
• We conducted a retrospective analysis of >45,000 subjects using a nationwide US-integrated insurance and laboratory claims database.
• In a risk-adjusted analysis that included propensity scores, no increased risk of all-cause mortality or hospitalization was found in our overall cohort although risk may be increased in patients with chronic kidney disease.

What Is Relevant?

• Olmesartan is commonly prescribed.
• To our knowledge, this is the first large comparative effectiveness study involving olmesartan in patients with diabetes mellitus.

Summary

We found no robust signal for harm and no compelling reason to avoid the drug except, perhaps, in patients with chronic kidney disease. Further study is required, especially in diabetics with chronic kidney disease.
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http://hyper.ahajournals.org/content/63/5/977

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2014/02/17/HYPERTENSIONAHA.113.02855.DC1

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Comparative Effectiveness of Olmesartan and Other Angiotensin Receptor Blockers in Diabetes: Retrospective Cohort Study

Online Supplement

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Supplementary Methods

Dose-Response Sensitivity Analysis

A dose-response sensitivity analysis was also performed in which we used a standard (i.e., non-time dependent) Cox model to examine the association between tertiles of the average daily dose prescribed (low/medium/high) and the primary outcome in olmesartan users only. Subjects with the lowest level of exposure served as the reference group. Model covariates were identical to those used in the primary analysis except the propensity score adjusted for the propensity to receive a medium or high dose of olmesartan (compared to a low dose). To account for changes in dose over time, average daily dose was calculated by dividing the total dose prescribed over the follow-up period by the total drug exposure time. To calculate follow-up time, each subject was considered exposed to the drug until an event occurred (death or hospitalization), their insurance coverage was terminated or they discontinued therapy. If insurance coverage was terminated or treatment was discontinued, subjects were censored, with a censoring date of 60 days after the date on which their last prescription had ended. We also performed the same dose-response analysis for losartan and valsartan as a further sensitivity analysis. We did this to determine whether or not findings of the olmesartan dose-response analysis were similar for another ARB or specific to olmesartan alone.

Individual ARB Analysis

As a further sensitivity analysis, we performed an individual ARB analysis by dividing the primary cohort into separate ARB groups [olmesartan, losartan, valsartan, telmisartan and all others (candesartan, eprosartan and irbesartan)] and repeated the primary endpoint analysis (models adjusted as described above) to determine if olmesartan was associated with the highest risk of all-cause hospital admission or death. Olmesartan was used as the base comparator in this analysis, which was performed in the overall cohort and in the subgroups with pre-existing cardiovascular disease and chronic kidney disease. Subjects switching ARB agents were censored at the time the switch occurred.
Table S1. Sensitivity analysis examining the dose-response relationship within users of olmesartan, losartan and valsartan.

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose Tertiles</th>
<th>Medium Dose vs. Low Dose aHR (95% CI)</th>
<th>High Dose vs. Low Dose aHR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Olmesartan (n=10370)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall cohort</td>
<td>Low: &lt;18.7 mg</td>
<td>1.18 (1.04-1.34)</td>
<td>1.20 (1.05-1.37)</td>
</tr>
<tr>
<td></td>
<td>Medium: 18.7-29.8 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High: ≥29.9 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low: &lt;18.6 mg</td>
<td>1.62 (1.21-2.17)</td>
<td>1.40 (1.03-1.90)</td>
</tr>
<tr>
<td></td>
<td>Medium: 18.6-30.1 mg</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>High: ≥30.2 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low: &lt;19.9 mg</td>
<td>0.77 (0.51-1.14)</td>
<td>1.44 (0.99-2.10)</td>
</tr>
<tr>
<td></td>
<td>Medium: 19.9-32.3 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High: ≥32.4 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Losartan Sensitivity Analysis (n=8656)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall cohort</td>
<td>Low: &lt;37.4 mg</td>
<td>1.06 (0.96-1.19)</td>
<td>0.86 (0.77-0.97)</td>
</tr>
<tr>
<td></td>
<td>Medium: 37.4-60.8 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High: ≥60.8 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>Low:</td>
<td>Medium:</td>
<td>High:</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------</td>
<td>---------</td>
<td>--------</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>&lt;35.1</td>
<td>35.1-56.2</td>
<td>≥56.3</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>&lt;36.6</td>
<td>36.7-60.7</td>
<td>≥60.8</td>
</tr>
<tr>
<td><strong>Valsartan Sensitivity Analysis (n=16004)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall cohort</td>
<td>&lt;79.7</td>
<td>79.8-143.1</td>
<td>≥143.1</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>&lt;78.33</td>
<td>78.34-139.94</td>
<td>≥140.0</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>&lt;80.55</td>
<td>80.57-147.42</td>
<td>≥147.51</td>
</tr>
</tbody>
</table>

aHR=adjusted hazard ratio; CI=confidence interval
Table S2. Sensitivity analysis comparing all-cause hospitalization or mortality in olmesartan users versus different ARBs

<table>
<thead>
<tr>
<th>Agent (compared to olmesartan)</th>
<th>Overall Cohort (n=45185) HR (95% CI)</th>
<th>Cardiovascular Disease Subgroup (n=8755) HR (95% CI)</th>
<th>Chronic Kidney Disease Subgroup (n=4575) HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan (n=8656)</td>
<td>1.01 (0.94-1.08)</td>
<td>1.22 (1.07-1.40)</td>
<td>1.08 (0.90-1.30)</td>
</tr>
<tr>
<td>Valsartan (n=16004)</td>
<td>1.02 (0.96-1.09)</td>
<td>1.13 (0.99-1.28)</td>
<td>1.02 (0.86-1.20)</td>
</tr>
<tr>
<td>Telmesartan (n=3656)</td>
<td>0.94 (0.85-1.03)</td>
<td>1.09 (0.90-1.31)</td>
<td>0.87 (0.66-1.14)</td>
</tr>
<tr>
<td>All other ARBs (eprosartan, irbesartan, candesartan; n=6499)</td>
<td>1.00 (0.93-1.08)</td>
<td>1.03 (0.89-1.19)</td>
<td>0.79 (0.64-0.98)</td>
</tr>
</tbody>
</table>

Hazard ratios (HR) are relative to olmesartan (n=10370).