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The differential effect of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers with respect to foot ulcer and limb amputation in those with diabetes

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Abstract

Foot ulcers (DFU) or lower extremity amputation (LEA) are complications of diabetes. In those with diabetes, angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are commonly used to prevent the progression of kidney disease. Recent studies have indicated that angiotensin may effect angiogenesis and wound repair. Our goal was to evaluate in those with diabetes the likelihood of developing a DFU or LEA among users of ACEi or ARB using a retrospective cohort design of general practices in the United Kingdom. We studied 40,342 individuals at least 35 years of age with diabetes who were first prescribed ACEi or ARB between 1995 and 2006. 35,153 individuals were treated with ACEi, 12,437 individuals with ARB, and 7,310 both. The hazard ratio for DFU was 0.50 (95% CI: 0.43, 0.59), showing an increased risk of DFU for those using ACEi versus ARB. The hazard ratio for LEA was 0.72 (0.48, 1.01). However, among those with lower extremity peripheral arterial disease the hazard ratio was 0.45 (0.22, 0.91) for the new onset of a LEA. In conclusion, among those with diabetes, exposure to ACEi as compared to ARB increases the risk of developing a DFU or LEA..

Key Terms

amputation; foot ulcer; diabetes; comparative effectiveness; epidemiology

INTRODUCTION

Diabetes mellitus is associated with several vascular complications. Among these are chronic kidney disease (CKD), foot ulcers (DFU), and lower extremity amputations (LEA). While angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are used to treat hypertension they also have an essential role in the prevention of CKD in those with diabetes^{1–4}. While both of these medications are recommended for the prevention of CKD in those with diabetes, their mechanisms of action differ. ACEi block the production of angiotensin II and ARB selectively block the action of this compound at the angiotensin II type 1 receptor but not the angiotensin II type 2 receptor⁵. ARB blockade results in an increase in circulating angiotensin II⁵. Potentially, this pharmacologic

difference could result in different safety profiles for these agents. A few studies and commentaries have opined about the potential for differential safety concerns with respect to angiogenesis resulting in myocardial infarction and alterations in tumor angiogenesis^{6–8}.

The lifetime prevalence of a DFU is between about 10 to 20%^{9, 10}. LEAs occur at a significantly higher rate in those with DM than those without and mainly occur in those with an active or previous history of a DFU. DFUs and LEAs are associated with shortened life expectancy, diminished quality of life, and increased cost of care^{9, 10}. Recently, we have shown an increased risk of DFU or LEA with worsening CKD¹¹.

The objective of this study was to evaluate whether the risk of developing a DFU or LEA in those with diabetes is different in users of ACEi versus ARB. In order to evaluate this hypothesis, we assessed individuals with diabetes who were exposed to ACEi or ARB in a large prospectively collected medical records database of general practices in the United Kingdom.

METHODS

This was a retrospective cohort study using the general medical practices of The Health Information Network (THIN). By agreement, patient data are recorded and stored in THIN as if it were an electronic medical record including all past and current medical diagnoses (acute and chronic) using Read codes and information on prescribed medications, using British National Formulary (BNF) codes. All laboratory values, aspects of the physical exam, hospitalizations, consultations, and prescription medications are electronically entered into THIN datasets. Subjects in THIN have been previously shown to be demographically comparable to the general UK population¹². The THIN database includes records for more than 4.7 million patients, with approximately 2.26 million active patients from 300 practices in England and Wales. The annual estimated number of subjects lost to follow-up is small (3%). Our study was reviewed and accepted by the Institutional Review Board of the University of Pennsylvania.

Study Population

To be included in our inception cohort, a subject had to have at least two separate medical records for diabetes noted between January 1995 and August 2006. We used this algorithm to assure that the subject truly had diabetes. In addition, the subject had to be at least age 35 at the time of diagnosis, could not have had a previous history of venous leg ulcer, DFU or LEA, and must have used an ARB and/or ACEi, which was first prescribed between 1995 and 2006.

Outcomes, exposures and confounders

The primary exposure variable was a BNF code for ARB or ACEi. Exposure-time was estimated from the first prescription until either an outcome occurred (LEA or DFU), the study subject died, the study subject left the practice, the last transaction date in the database, or the subject received a prescription for the other drug (i.e., ACEi switched to ARB or vice versa).

Outcomes were separately determined for each study subject for incident DFU and incident LEA based on computerized medical records in the THIN database during ACEi or ARB exposure. Our goal was for the DFU or LEA to be incident and, therefore, the subject could have had no report of a DFU or LEA for at least 6 months prior to entry into our dataset. The Read codes used for these outcomes have been previously evaluated¹¹. It is most likely that the DFUs that were coded by GPs were either chronic or severe enough to require a subject to seek medical care and may not represent all wounds on the feet of those with diabetes

(i.e., ones that required medical attention)¹¹. However, this is a novel study so there is no reason to believe that the diagnosis of DFU or LEA was more likely to be considered in users of ACEi or ARB (i.e., non-differential information bias) nor that one drug was more likely to be given to an individual more likely to develop a DFU or LEA.

For this study, confounding variables were variables that could be associated with our outcomes and our exposure. The following confounding variables were assessed: age; sex; cigarette use; duration of therapy; duration of diabetes disease; any diagnosis of cardiac ischemia; diagnosis of lower extremity peripheral arterial disease (PAD); a diagnosis of CKD (based on clinical diagnosis or eGFR when available); obesity (body mass index (BMI) of greater than 30), history of cigarette usage, and history of hypertension (HTN). In addition to these potential confounders, in a separate subset of newly diagnosed people with diabetes from January 2002 to August 2006 we also evaluated CKD as defined by an estimated glomerular filtration rate (eGFR) of less than 30, ankle brachial index, hemoglobin A1c (as a continuous variable as percent greater than 7%), and mean arterial pressure.

Statistical analysis

First, descriptive analyses were performed. Next, Cox proportional hazard models were used to assess the association (hazard ratio) between treatment and our two outcomes. The proportional hazard models allowed for ACEi or ARB exposure to be time-varying. All of our confounders were first evaluated as risk factors for outcomes, then as confounders to our exposures, and finally included in our multivariable models if either they changed the exposure effect estimate by more than 10% or because *a priori* they were deemed as potential important confounders (i.e., age, gender, PAD, CKD, HTN). Proportional hazards models and the hazard ratios are reported with 95% confidence intervals (CIs). We also explored PAD as an interaction term. All statistical analyses were performed using Stata 9.2 (College Station, TX). Within all time-frames studied, the proportional hazards assumption was met. The adequacy of our models was confirmed visually by analyzing log-log hazard function plots, Martingale residuals, and Schoenfeld residuals plots.

Several sensitivity analyzes were conducted including analysis of a sub-cohort comprised of those with diabetes newly diagnosed after 2002 [a date that approximates many National Health Services (NHS) guideline and laboratory recommendations] was studied. These guidelines were followed by more than 90% of THIN providers. We also studied a cohort of individuals who had diabetes and a diabetic foot ulcer prior to commencing therapy with an ACEi or ARB, compared ACEi or ARB users to non users, and compared just those who received ACEi and ARB in different time sequences.

RESULTS

Based on our selection criteria, we identified 78,178 individuals with diabetes. ACEi or ARB were used by 40,342 individuals (51%). From this group 35,153 individuals were treated with ACEi, 12,437 individuals with ARB, and 7,248 were exposed to both drugs. The total number of evaluable exposures was 47,590. 107 individuals were excluded from our analysis because they were treated with both agents at the same time. The mean age of our subjects was 64.4 (95% CI: 64.2, 64.5) years with a median of 64.4 years. Females represented 45% (18,281) of the cohort. The mean total duration of diabetes was 6.3 years (median 5.98) and total person-time of 216,070 years. There were some statistical differences in covariates based on whether they received ACEi or ARB (Table 1). As expected, many of the health conditions that we measured were associated with the onset of DFU and LEA (Table 2).

The total number of individuals with DFUs during our eligibility period was 1,450 (3.6% of subjects). The number of DFUs during ACEi exposure was 1,181 (3.4% of all ACEi users). The total number of individuals who developed a DFU during ARB exposure was 269 (2.2% of ARB users). Mean time of exposure for ACEi users was 4.5 years (SD 3.7) and median time was 3.6 years. On average ACEi users received 28.7 prescriptions (SD 31.7), a median of 19 prescriptions (6, 40) or 10.2 prescriptions per year. For ARB users, the mean time of follow-up was 3.9 years (SD 2.4) and the median time was 3.5 years. On average ARB users received 24.8 prescriptions (SD 23.4), a median of 18 prescriptions (8, 35), or 10.2 prescriptions per year. In our cohort, the overall hazard ratio for DFU was 0.50 (95% CI: 0.43, 0.59), showing an increased risk of DFU for those using ACEi versus ARB (Table 3). Fully adjusted values were not significantly different [HR=0.51, (0.43, 0.59)]. A small increased risk with ACEi exposure was noted in those with a history of PAD [HR=0.44, (0.29, 0.65)] as compared to those who did not have clinically significant PAD [0.53 (0.45, 0.63)]. Intriguingly, the hazard ratio for DFU changed over time and differed between treatments. In the first year of exposure, patients using ACEi were less likely to develop DFU than ARB. However, this effect was reversed at all subsequent time points. Specifically, the hazard ratio comparing ACEi to ARB exposure was 1.51 (1.11, 2.06) for less than one year of exposure, 0.65 (0.47, 0.92) for one year to less than two years of exposure, 0.47 (0.35, 0.63) for two years to less than 3 years of exposure, and 0.37 (0.27, 0.51) for more than or equal to three years of exposure (Table 3).

There were 173 new LEAs in our cohort. Among those exposed to ACEi, there were 135 (0.4%) LEAs and 38 LEAs (0.3%) among those exposed to ARB. The overall hazard ratio comparing ACEi versus ARB exposure for LEA was 0.72 (0.48, 1.01, Table 2). Fully adjusted values were not significantly different [0.71 (0.47, 1.06)]. An analysis for interaction between the drug exposure and PAD revealed a significant ($p<0.001$) and clinically important increased risk of LEA in those exposed to ACEi as compared to those exposed to ARB in association with a history of PAD [0.45 (0.22, 0.91)]. However, in patients without a PAD diagnosis ACEi or ARB did not increase the risk of LEA [0.94 (0.57, 1.56)] (Table 3). In contrast to the DFU analysis, no interactions associated with the duration of exposure to ACEi or ARB was identified.

To confirm our findings, several sensitivity analyses were conducted including two additional sub-cohort analyses. First, to place our results in perspective we separately compared ACEi and ARB users to the 37,836 individuals who did not use these medications. The non-users did not appear to have a clinically important elevated risk of DFU or LEA as compared to ACEi users [1.12 (.05, 1.18) and 1.09 (0.87, 1.37), respectively] but did appear to have an increase risk as compared to ARB users [0.84 (0.78, 0.91) and 0.70 (0.55, 0.90), respectively]. While this may not be a fair comparison in that the decision to use an agent that interferes with the rennin-angiotensin-aldosterone system could be associated with the severity of diabetes, the similarity of the effect is supportive of our main results. Second, there were 7,403 individuals exposed to both drugs. Modeling the order of exposure or excluding these individuals from our analysis did not significantly alter our results and the effect estimate was nearly the same if only those who received both drugs were evaluated. Third, a sub-cohort of individuals ($N=13,401$) newly diagnosed with diabetes and treated in years 2002–2006 was also evaluated. During this time frame, the NHS mandated that hemoglobin A1c, eGFR, MAP, and lower extremity pulse examination be obtained in those with diabetes. As in our main analysis, the overall hazard ratio comparing exposures to ACEi versus ARB with respect to the onset of DFU was 0.68 (0.48, 0.96) (Table 3). As anticipated, our additional confounders (MAP, lower extremity pulse examination, A1c, eGFR) were important predictors of these outcomes but, importantly, did not confound our results with respect to ACEi and ARB exposure. Due to the size of this sample very few LEA occurred resulting in an estimated hazard ratio for LEA that was not

precise, but included our full cohort risk estimate [1.00 (0.29, 3.80)] (Table 3). Fourth, we had a small group of subjects who entered our dataset with a DFU prior to exposure to either ACEi or ARB. For these individuals (N=1,378), the risk of subsequent LEA was also increased among those exposed to ACEi as compared to ARB exposure [0.43 (0.18, 1.04)]. Finally, as would be expected for a chronic therapy, using the number of prescriptions and a surrogate for months of exposure in our models yielded nearly identical results.

DISCUSSION

In order to prevent the onset and progression of CKD in those with diabetes, several interventions are recommended. One such intervention is the chronic long-term use of agents that interfere with the renin-angiotensin-aldosterone system (<http://www.renal.org/CKDguide/full/UKCKDfull.pdf>). The most commonly used pharmacologic agents that interfere with the renin-angiotensin-aldosterone system are categorized as ACEi, which block the production of angiotensin II, and ARB, which block the binding of angiotensin II to the angiotensin II type I receptor⁵. Large clinical studies, however, have not consistently shown a clinical advantage of one class of these agents over the other and, as a result, neither agent is preferred as first line therapy.^{1, 2, 13} In our dataset, we were able to document that these agents are frequently used and used long-term. The rate of use in our population was similar to that recently reported in a large longitudinal study¹⁴. These agents are associated with different rates of onset of DFU [0.50 (0.43, 0.59)] and LEA [0.72 (0.48, 1.01)]. Specifically, individuals who received ARB for at least one year as compared to those who received an ACEi were less likely to develop a DFU and at all time points they were less likely to have an LEA. The risk of LEA was most dramatic for those individuals who also had clinically diagnosed PAD [0.45 (0.22, 0.91)]. DFU or LEA are infrequently reported as outcomes in clinical trials and we are not aware of any previous studies that have evaluated DFU or LEA as potential adverse events associated with different blockades of the renin-angiotensin-aldosterone system.^{15–17} Our findings were robust and supported by several sensitivity analyzes.

In those with diabetes, the renin-angiotensin-aldosterone system has been implicated in the progression of renal disease via the angiotensin II type 1 (ATR1) receptor⁵. This system is altered by ACEi inhibiting the activity of angiotensin-converting enzyme (ACE) thereby preventing the synthesis of angiotensin II or by ARB blocking the interaction of angiotensin II AT1 receptor. Interestingly, ARB does not block the effect of angiotensin II on the angiotensin II type 2 (AT2) receptor⁵.

Extra-renal effects of angiotensin include a role in the synthesis of growth factors such as hypoxia-inducible factor-1 α , platelet-derived growth factor, fibroblast growth factor, and transforming growth factor- β 1 as well as a suspected role in vasculogenesis^{8, 18–20}. The AT1 receptor in particular plays a role in angiogenesis and wound healing by stimulating type 1 collagen mRNA and protein synthesis and activating the epidermal growth factor receptor (EGFR) to increase angiopoietin 2 and VEGF synthesis²¹. In contrast, activation of the AT2 receptor has an anti-angiogenic effect by blocking EGFR phosphorylation²¹. These events might be expected to favor wound healing in those with ACEi inhibitors because about 40% of angiotensin I is converted to angiotensin II by non-ACE-dependent pathways²².

However, ARB blocks the AT1 receptor, so ultimately angiotensin II is increased by a feedback mechanism. This will increase activation of NOS with release of NO from the endothelium, and AT2 receptor activation also augments NOS protein synthesis^{23, 24}. Whereas angiotensin-mediated AT2 receptor activation induces NOS synthesis, AT1 receptor activation will inhibit this pathway^{24, 25}. NO plays important roles in endothelial

cell functions and in growth factor-mediated angiogenesis. All elements of the renin-angiotensin-aldosterone axis are present in bone marrow cells and NO production in the bone marrow enhances EPC mobilization and circulation^{26, 27}. Therefore, the activation of the AT2 receptor (e.g., vasodilation, liberation of EPC and growth factors) could have the potential to improve the likelihood that a wound will heal thereby preventing a DFU from becoming chronic as well as preventing the need for an LEA especially in an individual with PAD. Elevated levels of angiotensin II have also been shown to increase levels of hypoxia-inducible factor-1 α , which in turn cause an increased synthesis of vascular endothelial growth factor and neo-angiogenesis^{19, 20}. Finally, it has been postulated that ACEi may have a role as an anti-angiogenic agent with respect to tumor angiogenesis⁸.

The notion that angiotensin II and the activation of the angiotensin II type 2 receptor have multiple effects may help to explain why we noted effect modification with respect to DFU and the duration of administration and effect modification with respect to PAD and the onset of LEA. The differential effects that we note may also help to explain some of the controversy associated with ARB and myocardial infarction. There has been concern that ARB may increase the risk of MI and cardiovascular morbidity^{6, 28, 29}. However, this concern may have at least partially been based on studies of varying length⁶. Based on larger meta-analyses it is very unlikely that ARB use is associated with an increased risk of MI⁶.

There are a number of important potential limitations to our study. We do not know why the GP placed their patient on an agent that modifies the renin-angiotensin-aldosterone system. Based on guideline recommendation it was likely to prevent the progression or onset of CKD. They are also used to treat hypertension. Further, we do not know why the GP selected an ACEi or ARB. Both agents are currently recommended for the population that we studied². In the UK, the cost of these agents is mostly covered by the NHS. Selection bias could have occurred if the subjects were preferentially selected in such a fashion that the selection to use one agent or another could impact our outcome. It is not obvious how the major clinical reasons for selection of ARB over ACEi – cough or allergy – could alter DFU or LEA risk. There may be other benefits to using one agent or the other but these are not evident. Perhaps selection bias could still have impacted our study if the likelihood of compliance, better hygiene/foot care, better glycemic control or any other factor associated with the onset of DFU or LEA influenced or was associated with the physician's choice of the ACEi or ARB. This is highly unlikely in that we noted this effect in our full cohort as well as a cohort of more recent-onset diabetics, and a cohort that received these agents after the onset of a foot ulcer. Furthermore, it would be very difficult to explain the interactions that we noticed in the setting of preferential use of one agent versus the other (i.e., treatment selection bias). Finally, our sensitivity analysis comparing ACEi or ARB versus no use largely confirmed our findings.

In conclusion, we have shown that long-term use of ACEi and ARB has differential effects on important complications associated with diabetes, DFU, and LEA. We did not study any other risks or benefits inherent to using one compound or the other. In general, those exposed to ACEi are more likely to develop a DFU or LEA than those exposed to ARB. Those using ACEi are about 50% more likely to have a DFU and specifically among those with PAD about 50% increase risk of an LEA. This effect is more pronounced as the time of exposure increases. With respect to LEA this effect is most pronounced in those with PAD, the group most at risk for an LEA. The purpose of this study was not to dispute the necessity for using these agents for the prevention of CKD. In conjunction with recent findings calling into question the beneficial effect of angiotensin blockade in early diabetic nephropathy, our findings of differential DFU risk in early diabetes raise the specter of previously unrecognized risk that should be considered in guideline development: Angiotensin axis blockade for the purpose of nephropathy prevention in the absence of either hypertension or

early nephropathy may not be as risk-free as has been widely assumed^{4, 5, 30, 31}. Our observational study design can not be used to prove causation. However, with respect to the lower extremity complications, DFU and LEA, it appears that these complications are less likely in those using ARB. This finding needs to be considered with respect to other differences that may exist between these two compounds and ultimately needs to be replicated in additional studies.

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ABBREVIATIONS

ACEi	Angiotensin converting enzyme inhibitors
ARB	Angiotensin receptor blockers
BMI	Body mass index
BNF	British National Formulary
CKD	Chronic kidney disease
CI	Confidence interval
eGFR	Estimated glomerular filtration rate
DFU	Foot ulcer
HTN	Hypertension
LEA	Lower extremity amputation
NHS	National health service
PAD	Peripheral arterial disease
THIN	The Health Information Network

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Table 1

Distribution of important covariates between users of ACEi or ARB. Percentages are based on the number who had the covariate divided by the number of exposures to either ACEi or ARB.

	ACEi (35, 153)	ARB (12,437)	<i>p</i> -value
Age			
mean	64.4 (SD 11.7)	64.4 (SD 11.1)	0.77
median	64.4 (56,73)	64.4 (57,73)	
Sex			
F	15,633 (44.5%)	6,865 (55.2%)	<0.0001
M	19,510 (51.5%)	5,572 (48.5%)	
Renal disease	9,140(26.0%)	3,482(28.0%)	0.04
Obese	18,385 (52.3%)	7,052 (56.7%)	0.004
MAP (median)	89.0 (SD 36.5) 101.3 (93.2,107.6)	93.5 (SD 33.2) 103.0 (96.2, 109.1)	<0.0001
Hemoglobin A1C (>7%) *	7648 (66.7%)	2,999 (65.2%)	0.06
PAD	1722 (4.9%)	568 (4.5%)	0.10

* Hemoglobin A1c based on laboratory values are from the smaller dataset (2002–2006).

Table 2

Relationship between important covariates and the onset of DFU or LEA. Percentages are based on the number who have the covariate divided by the number of exposures.

Outcome	DFU		Overall HR of variable unadjusted (CI)	LEA		Overall HR of variable unadjusted	
Variable	Yes	No		Yes	No		
Age by category (years)							
	35 to 40	29	955	Ref	1	983	
	>40 to 50	83	4,714	0.59 (0.43, 0.81)	10	4,787	
	>50 to 60	237	10,528	0.62 (0.46, 0.82)	26	10,739	
	>60 to 70	402	14,315	0.75 (0.57, 0.99)	35	1,468	
> 70	699	15,628	1.16 (0.88, 1.53)	94	16,233	3.71 (0.51, 26.68)	
Gender							
	F	661	21,365	Ref	56	21,970	Ref
M	787	21,749	1.1 (0.98, 1.22)	108	25,428	1.97 (1.40,2.78)	
History of Hypertension							
	Y	430	31,918	0.83 (0.74, 0.93)	123	32,813	1.07 (0.75,1.53)
N	1,018	14,220		39	14,611		
Obese							
	Y	774	24,651	1.00(0.82, 1.21)	78	25,347	1.0 (0.22, 4.51)
N	676	21,489		88	22,077		
History of Chronic Renal Disease							
	Y	160	2,074	2.63 (2.22, 3.12)	14	2,220	3.62 (1.59, 8.24)
N	1,290	2,074		150	45,204		
History of PAD							
		253	2,000	4.06 (3.54, 4.65)	70	2,183	14.29 (10.49,19.46)
	1,197	44,138		94	45,241		
Duration years of diabetes (mean, c.i.)		7.33 (7.17, 7.49)	6.25 (6.22, 6.28)	1.07 (1.05, 1.10)	7.82 (7.31,8.32)	6.29 (6.25,6.32)	1.13 (1.07, 1.20)
Rxtime years (mean, c.i.)		7.14 (6.92, 7.35)	5.23 (5.19, 5.26)	0.97 (0.96, 0.99)	4.18 (3.64,4.72)	5.30 (5.26,5.34)	0.62 (0.58, 0.66)

Table 3

Hazard ratios for DFU (a) and LEA (b) comparing ACEi exposure to ARB exposure in the full cohort of individuals with diabetes and our two sub-cohorts. All values adjusted for the covariates listed in table 1.

a. DFU	
	HR DFU
Full cohort 1995–2006	0.50 (0.43, 0.59)
< 1 year of exposure	1.51 (1.11, 2.06)
1 to < 2 years of exposure	0.65 (0.47, 0.92)
2 to < 3 years of exposure	0.47 (0.35, 0.63)
≥ 3 years of exposure	0.37 (0.27, 0.51)
Sub cohort: New Diabetics 2002–2006	0.68(0.48, 0.96)
b. LEA	
	HR LEA
Full cohort 1995–2006	0.72 (0.48, 1.01)
h.o. PAD	0.45 (0.22, 0.91)
No h.o. PAD	0.94 (0.57, 1.56)
Sub cohort: New Diabetics 2002–2006	1.00 (0.26, 3.80)
Sub cohort: Individuals had a DFU and where then treated with ACEi or ARB	0.43(0.18, 1.04)