Supplementary Online Content

Toh S, Reichman ME, Houstoun M. Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. *Arch Intern Med.* Published online October 15, 2012. doi:10.1001/2013.jamainternmed.34

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Number of Patients Censored by Reason by Drug Class

Reason	ACEIs	ARBs	Aliskiren	ß-blockers
Death	6,195 (0.3%)	1,000 (0.2%)	4 (0.1%)	10,187 (0.6%)
End of health plan enrollment	267,365 (14.5%)	68,375 (14.6%)	820 (16.8%)	178,214 (11.2%)
End of first treatment episode	1,064,534 (57.7%)	291,248 (62.3%)	2,945 (60.5%)	1,046,812 (65.7%)
Switching to another study drug of a different class	193,913 (10.5%)	39,645 (8.5%)	646 (13.3%)	143,998 (9.0%)
End of 365 days of follow-up	309,830 (16.8%)	66,757 (14.3%)	445 (9.1%)	212,152 (13.3%)

Abbreviations: ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

eTable 2. Comparison of Results Obtained From the Case-Centered Logistic Regression Approach and Meta-analysis Over a Maximal Follow-up Period of 365 Days, 2001-2010

Drug	Site-adjusted HR (95% CI)		Propensity score-adjusted HR (95% CI)	
	Case-centered Approach	**Inverse Variance-Weighted Meta-analysis**	**Case-centered Approach**	**Inverse Variance-Weighted Meta-analysis**
Angioedema				
ACEIs	2.77 (2.57, 2.98)	2.70 (2.50, 2.90)	3.04 (2.81, 3.27)	2.98 (2.76, 3.21)
ARBs	1.11 (0.97, 1.28)	1.15 (1.00, 1.32)	1.16 (1.00, 1.34)	1.15 (1.00, 1.33)
Candesartan	0.91 (0.34, 2.43)	1.03 (0.39, 2.77)	0.95 (0.35, 2.55)	1.08 (0.40, 2.89)
Eprosartan	--	--	--	--
Irbesartan	1.05 (0.70, 1.58)	1.17 (0.77, 1.75)	1.11 (0.73, 1.67)	1.18 (0.78, 1.78)
Losartan	1.48 (1.20, 1.84)	1.56 (1.26, 1.93)	1.53 (1.23, 1.90)	1.52 (1.22, 1.89)
Olmesartan	0.84 (0.60, 1.16)	0.82 (0.59, 1.14)	0.88 (0.63, 1.22)	0.86 (0.62, 1.19)
Telmisartan	0.83 (0.45, 1.50)	0.99 (0.54, 1.80)	0.86 (0.47, 1.56)	0.98 (0.54, 1.79)
Valsartan	1.04 (0.85, 1.28)	1.07 (0.87, 1.32)	1.08 (0.88, 1.34)	1.09 (0.89, 1.35)
Aliskiren	2.75 (1.30, 5.81)	2.83 (1.34, 5.98)	2.85 (1.34, 6.04)	2.86 (1.35, 6.04)
Serious angioedema				
ACEIs	4.42 (3.29, 5.96)	4.04 (2.99, 5.46)	4.91 (3.62, 6.65)	4.20 (3.08, 5.71)
ARBs	0.52 (0.26, 1.05)	0.56 (0.28, 1.14)	0.56 (0.28, 1.14)	0.59 (0.28, 1.22)
Candesartan	--	--	--	--
Eprosartan	--	--	--	--
Irbesartan	--	--	--	--
Losartan	0.97 (0.30, 3.18)	1.08 (0.33, 3.54)	1.01 (0.31, 3.34)	0.94 (0.28, 3.16)
Olmesartan	0.80 (0.10, 6.20)	0.67 (0.09, 5.13)	0.83 (0.11, 6.57)	0.80 (0.10, 6.36)
Telmisartan	--	--	--	--
Valsartan	1.05 (0.43, 2.56)	1.23 (0.50, 3.03)	1.14 (0.46, 2.82)	1.31 (0.52, 3.31)
Aliskiren	8.67 (1.11, 67.62)	7.04 (0.92, 54.20)	8.84 (1.13, 69.41)	8.53 (1.08, 67.41)

Abbreviations: ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CI, confidence interval; HR, hazard ratio.

eTable 3. Results by Study Drug Over a Maximal Follow-up Period of 365 Days, Using a 365-Day Look-Back Period, 2001-2010

Drug	Number of Events	Persons	Person-years	Cumulative Incidence Per 1,000 Persons (95% CI)	Incidence rate per 1,000 Person-years (95% CI)	Site-Adjusted HR (95% CI)*	Propensity Score-Adjusted HR (95% CI)*
Angioedema							
ACEIs	2,623	1,392,602	584,873	1.88 (1.81, 1.96)	4.49 (4.32, 4.66)	3.04 (2.79, 3.31)	3.36 (3.07, 3.67)
ARBs	181	312,826	119,234	0.58 (0.50, 0.67)	1.52 (1.31, 1.76)	1.12 (0.94, 1.34)	1.21 (1.01, 1.45)
Candesartan	2	7,754	2,683	0.26 (0.03, 0.93)	0.75 (0.09, 2.69)	0.79 (0.20, 3.20)	0.87 (0.22, 3.50)
Eprosartan	0	609	211	--	--	--	--
Irbesartan	12	27,845	10,261	0.43 (0.22, 0.75)	1.17 (0.60, 2.04)	0.96 (0.54, 1.71)	1.04 (0.58, 1.86)
Losartan	62	73,600	29,432	0.84 (0.65, 1.08)	2.11 (1.62, 2.70)	1.49 (1.14, 1.94)	1.57 (1.20, 2.05)
Olmesartan	22	61,936	20,468	0.36 (0.22, 0.54)	1.08 (0.67, 1.63)	0.79 (0.51, 1.23)	0.85 (0.55, 1.31)
Telmisartan	6	17,743	5,612	0.34 (0.12, 0.74)	1.07 (0.39, 2.33)	0.80 (0.36, 1.79)	0.86 (0.38, 1.93)
Valsartan	73	123,339	47,883	0.59 (0.46, 0.74)	1.53 (1.20, 1.92)	1.12 (0.86, 1.44)	1.18 (0.91, 1.53)
Aliskiren	3	3,260	1,034	0.92 (0.19, 2.69)	2.90 (0.60, 8.48)	3.68 (1.18, 11.51)	4.01 (1.28, 12.57)
β-blockers	655	1,185,727	419,639	0.55 (0.51, 0.60)	1.56 (1.44, 1.69)	Referent	Referent
Serious Angioedema							
ACEIs	246	1,392,602	585,257	0.18 (0.16, 0.20)	0.42 (0.37, 0.48)	5.05 (3.50, 7.29)	5.56 (3.83, 8.09)
ARBs	9	312,826	119,280	0.03 (0.01, 0.06)	0.08 (0.04, 0.14)	0.81 (0.37, 1.78)	0.87 (0.39, 1.91)
Candesartan	0	7,754	2,683	--	--	--	--
Eprosartan	0	609	211	--	--	--	--
Irbesartan	0	27,845	10,264	--	--	--	--
Losartan	2	73,600	29,449	0.03 (0.00, 0.10)	0.07 (0.01, 0.25)	1.20 (0.28, 5.25)	1.23 (0.28, 5.45)
Olmesartan	1	61,936	20,473	0.02 (0.00, 0.09)	0.05 (0.00, 0.27)	1.47 (0.17, 12.84)	1.47 (0.17, 12.87)
Telmisartan	0	17,743	5,613	--	--	--	--
Valsartan	6	123,339	47,900	0.05 (0.02, 0.11)	0.13 (0.05, 0.27)	1.75 (0.69, 4.44)	1.94 (0.75, 5.02)
Aliskiren	0	3,260	1,035	--	--	--	--
β-blockers	33	1,185,727	419,837	0.03 (0.02, 0.04)	0.08 (0.05, 0.11)	Referent	Referent

Abbreviations: ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CI, confidence interval; HR, hazard ratio.
*From the case-centered logistic regression approach.

eTable 4. Results by Study Drug Over a Maximal Follow-up Period of 365 Days, Restricting to Angioedema Events Observed During an Inpatient or Emergency Department Encounter, 2001-2010

Drug	Number of events	Exposed persons	Exposed person-years	Cumulative incidence per 1,000 persons (95% CI)	Incidence rate per 1,000 person-years (95% CI)	Site-adjusted HR (95% CI)*	Propensity score-adjusted HR (95% CI)*
ACEIs	1,782	1,845,138	753,386	0.97 (0.92, 1.01)	2.37 (2.26, 2.48)	4.87 (4.29, 5.52)	5.34 (4.69, 6.07)
ARBs	83	467,313	173,496	0.18 (0.14, 0.22)	0.48 (0.38, 0.59)	0.99 (0.76, 1.29)	1.09 (0.83, 1.42)
Candesartan	0	12,286	4,178	--	--	--	--
Eprosartan	0	1,165	392	--	--	--	--
Irbesartan	7	44,094	16,001	0.16 (0.06, 0.33)	0.44 (0.18, 0.90)	1.00 (0.47, 2.14)	1.13 (0.53, 2.44)
Losartan	26	106,522	41,250	0.24 (0.16, 0.36)	0.63 (0.41, 0.92)	1.43 (0.95, 2.16)	1.54 (1.02, 2.33)
Olmesartan	8	92,973	30,179	0.09 (0.04, 0.17)	0.27 (0.11, 0.52)	0.52 (0.25, 1.05)	0.57 (0.28, 1.17)
Telmisartan	4	26,530	8,180	0.15 (0.04, 0.39)	0.49 (0.13, 1.25)	0.97 (0.36, 2.62)	1.10 (0.41, 2.99)
Valsartan	38	183,743	69,417	0.21 (0.15, 0.28)	0.55 (0.39, 0.75)	1.05 (0.74, 1.49)	1.16 (0.81, 1.67)
Aliskiren	2	4,867	1,499	0.41 (0.05, 1.48)	1.33 (0.16, 4.82)	2.49 (0.61, 10.09)	2.72 (0.67, 11.07)
β-blockers	282	1,592,278	548,885	0.18 (0.16, 0.20)	0.51 (0.46, 0.58)	Referent	Referent

Abbreviations: ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CI, confidence interval; HR, hazard ratio.
*From the case-centered logistic regression approach.

eTable 5. Results by Study Drug Over a Maximal Follow-up Period of 365 Days, Restricting to the Study Period Following FDA Approval of Aliskiren (3/5/2007–12/31/2010)

Drug	Number of events	Persons	Person-years	Cumulative incidence per 1,000 persons (95% CI)	Incidence rate per 1,000 person-years (95% CI)	Site-adjusted HR (95% CI)*	Propensity score-adjusted HR (95% CI)*
Angioedema							
ACEIs	1,951	1,083,869	406,278	1.80 (1.72, 1.88)	4.80 (4.59, 5.02)	2.70 (2.44, 2.98)	2.94 (2.65, 3.27)
ARBs	175	269,549	91,542	0.65 (0.56, 0.75)	1.91 (1.64, 2.23)	1.09 (0.91, 1.31)	1.17 (0.97, 1.41)
Candesartan	2	5,178	1,693	0.39 (0.05, 1.40)	1.18 (0.14, 4.27)	1.14 (0.28, 4.60)	1.24 (0.31, 4.99)
Eprosartan	0	135	48	--	--	--	--
Irbesartan	11	22,228	7,446	0.50 (0.25, 0.89)	1.48 (0.74, 2.64)	0.92 (0.50, 1.67)	0.97 (0.53, 1.78)
Losartan	61	57,130	19,761	1.07 (0.82, 1.37)	3.09 (2.36, 3.97)	1.66 (1.27, 2.18)	1.76 (1.33, 2.32)
Olmesartan	28	63,351	19,420	0.44 (0.29, 0.64)	1.44 (0.96, 2.08)	0.82 (0.56, 1.20)	0.87 (0.59, 1.29)
Telmisartan	6	17,643	5,180	0.34 (0.13, 0.74)	1.16 (0.43, 2.52)	0.64 (0.29, 1.44)	0.68 (0.30, 1.52)
Valsartan	65	103,884	36,442	0.63 (0.48, 0.80)	1.78 (1.38, 2.27)	1.00 (0.76, 1.31)	1.07 (0.81, 1.41)
Aliskiren	7	4,867	1,498	1.44 (0.58, 2.96)	4.67 (1.88, 9.63)	2.68 (1.26, 5.68)	2.83 (1.33, 6.00)
β-blockers	467	811,257	245,174	0.58 (0.53, 0.63)	1.91 (1.74, 2.09)	Referent	Referent
Serious Angioedema							
ACEIs	224	1,083,869	406,539	0.21 (0.18, 0.24)	0.55 (0.48, 0.63)	3.93 (2.74, 5.63)	4.40 (2.74, 5.63)
ARBs	7	269,549	91,584	0.03 (0.01, 0.05)	0.08 (0.03, 0.16)	0.55 (0.24, 1.28)	0.58 (0.25, 1.35)
Candesartan	0	5,178	1,694	--	--	--	--
Eprosartan	0	135	48	--	--	--	--
Irbesartan	0	22,228	7,448	--	--	--	--
Losartan	3	57,130	19,776	0.05 (0.01, 0.15)	0.15 (0.03, 0.44)	1.37 (0.41, 4.55)	1.34 (0.40, 4.49)
Olmesartan	1	63,351	19,427	0.03 (0.00, 0.09)	0.05 (0.00, 0.29)	0.80 (0.10, 6.20)	0.83 (0.11, 6.57)
Telmisartan	0	17,643	5,181	--	--	--	--
Valsartan	3	103,884	36,457	0.03 (0.01, 0.08)	0.08 (0.03, 0.24)	1.15 (0.33, 4.00)	1.21 (0.34, 4.27)
Aliskiren	1	4,867	1,499	0.21 (0.01, 1.14)	0.67 (0.03, 3.72)	8.67 (1.11, 67.62)	8.84 (1.13, 69.41)
β-blockers	35	811,257	245,297	0.04 (0.03, 0.06)	0.14 (0.20, 0.20)	Referent	Referent

Abbreviations: ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CI, confidence interval; HR, hazard ratio.
*From the case-centered logistic regression approach.

eTable 6. Relative Risk of Angioedema Comparing ACEIs and ß-Blockers With Additional Adjustment for Race

Observed Adjusted Relative Risk in the Current Study	Relative Risk Between African American Race and Angioedema	Prevalence of African American Race Among ACEI Initiators	Prevalence of African American Race Among β-Blocker Initiators*	Relative Risk With Additional Adjustment for African American Race
3.04	1.00	0.00	0.13	3.04
3.04	1.50	0.00	0.13	3.23
3.04	2.00	0.00	0.13	3.42
3.04	2.50	0.00	0.13	3.61
3.04	3.00	0.00	0.13	3.81
3.04	3.50	0.00	0.13	4.00
3.04	4.00	0.00	0.13	4.19
3.04	4.50	0.00	0.13	4.38
3.04	5.00	0.00	0.13	4.57
3.04	5.50	0.00	0.13	4.76
3.04	1.00	0.03	0.13	3.04
3.04	1.50	0.03	0.13	3.18
3.04	2.00	0.03	0.13	3.32
3.04	2.50	0.03	0.13	3.46
3.04	3.00	0.03	0.13	3.59
3.04	3.50	0.03	0.13	3.72
3.04	4.00	0.03	0.13	3.84
3.04	4.50	0.03	0.13	3.96
3.04	5.00	0.03	0.13	4.08
3.04	5.50	0.03	0.13	4.20
3.04	1.00	0.06	0.13	3.04
3.04	1.50	0.06	0.13	3.14
3.04	2.00	0.06	0.13	3.23
3.04	2.50	0.06	0.13	3.32
3.04	3.00	0.06	0.13	3.40
3.04	3.50	0.06	0.13	3.48
3.04	4.00	0.06	0.13	3.55
3.04	4.50	0.06	0.13	3.62
3.04	5.00	0.06	0.13	3.69
3.04	5.50	0.06	0.13	3.75
3.04	1.00	0.09	0.13	3.04

3.04	1.50	0.09	0.13	3.09
3.04	2.00	0.09	0.13	3.14
3.04	2.50	0.09	0.13	3.18
3.04	3.00	0.09	0.13	3.23
3.04	3.50	0.09	0.13	3.26
3.04	4.00	0.09	0.13	3.30
3.04	4.50	0.09	0.13	3.33
3.04	5.00	0.09	0.13	3.36
3.04	5.50	0.09	0.13	3.39
3.04	1.00	0.00	0.13	3.04
3.04	1.50	0.00	0.13	3.23
3.04	1.00	0.13	0.13	3.04
3.04	1.50	0.13	0.13	3.04
3.04	2.00	0.13	0.13	3.04
3.04	2.50	0.13	0.13	3.04
3.04	3.00	0.13	0.13	3.04
3.04	3.50	0.13	0.13	3.04
3.04	4.00	0.13	0.13	3.04
3.04	4.50	0.13	0.13	3.04
3.04	5.00	0.13	0.13	3.04

Reference: Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Saf.* 2006;15(5):291-303.

*Assuming the prevalence of African American race among ß-blocker initiators is the same as the prevalence of the U.S. general population based on 2010 U.S. Census data (http://www.census.gov/prod/cen2010/briefs/c2010br-02.pdf).