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Usage of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in diabetic hypertensive patients-A Review

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Review article

Usage of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in diabetic hypertensive patients-A Review

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Abstract

Abstract: Diabetes and Hypertension are diseases that can be debilitating and life-threatening if not well-controlled respectively and the risk of complication further increases when both diseases co-exist in a patient. They can lead to various cardiovascular complications such as heart failure, coronary artery disease, myocardial infarction and stroke as well as nephropathy and neuropathy. According to CPG guideline Malaysia, there are two groups of drugs which are strongly recommended for treatment of diabetic hypertension, namely angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). Through this review, we hope to compare superiority of ACEI and ARB usage in diabetic patients with hypertension. The criteria for eligible studies were as follows: (i) RCT comparing the efficacy of ACEI or ARB with various classes of antihypertensive agents, ACEI versus ARB, different ARBs and combination use of ACEI and ARB in hypertensive patients with diabetes and (ii) primary outcome data was available including P-values and hazard ratios comparing the active and control treatment with corresponding confidence interval (CI). Following this search, 53 articles were selected. Both ACEI and ARB are beneficial in lowering blood pressure and are preferred hypertension medications for patients with hypertension comorbid with diabetes. They also help in preventing progression of diabetic nephropathy from microalbuminuria to macroalbuminuria.

Keywords: Angiotensin Converting Enzyme inhibitors, Angiotensin Receptor Blockers, Diabetes Mellitus, Hypertension

Backgroud

Hypertension and diabetes are some of the most commonly seen diseases in individuals across the world. What used to be known as the "elderly disease" is gradually becoming more prominent among the younger generation due to various external factors especially lifestyle. According to a study in 2011, Malaysia contributed 12.1% of the total number of diabetic patients in the world population and it was predicted that this number will increase to 13.7% by 2030. Apart from that, out of 100 Malaysians, there are approximately 12 people suffering from diabetes and this is expected to increase to 14 out of 100 people [2]. As for hypertension, according to Ministry of Health Malaysia (MOH), in 2011, 32.7% of Malaysians who are 18 years and above are hypertensive and when the age range increased to 30 and above, the total population diagnosed with hypertension was 43.5%[3].These two diseases can be debilitating and life-threatening if not well-controlled respectively and the risk of complication further increases when both diseases co-exist in a patient. Hypertension is a risk factor of diabetes and vice versa. According to an article from the Diabetes Research and Clinical Practice published in 2008, it was estimated that the prevalence of diabetes among adults in the age group of 20-79 will be 6.4% of the world population and is estimated to

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increase to 1.1% by 2030. Hence, once an individual is diagnosed with either one of the diseases, the chances of getting the other will be much higher than a normal healthy individual. The comorbidities of hypertension and diabetes can lead to various cardiovascular complications such as heart failure, coronary artery disease, myocardial infarction and stroke as well as nephropathy and neuropathy[1]. According to Clinical Practice Guidelines (CPG) guideline Malaysia, there are two groups of drugs which are highly recommended for the treatment of diabetic hypertension, which are angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)[3].

However, the best choice between these two groups of drugs is still under debate due to conflicting results in various randomized controlled trials. Therefore, in this article, we are going to review articles related to the use of ACEIs and ARBs in diabetic hypertensive patients. Through this systematic review, we hope to compare superiority of ACEI and ARB use in diabetic patients with hypertension.

Method

A systematic search was carried out using various online databases such as PubMed, ProQuest, Science Direct and Springer through January 1997 to December 2014 for relevant studies performed on hypertensive patients with diabetes. The subject heading and keywords used during the literature search included: (i) diabetes, (ii) hypertension, (iii) angiotensin converting enzyme inhibitor (ACEI), (iv) angiotensin II receptor blocker (ARB), Randomized Control Trial (RCT) and human studies. The titles, abstract and full text of articles was reviewed by 7 reviewers. The criteria for eligible studies were as follows: (i) RCT comparing the efficacy of ACEI or ARB with various classes of antihypertensive agents, ACEI versus ARB, different ARBs and combination use of ACEI and ARB in hypertensive patients with diabetes and (ii) primary outcome data was available including P-values and hazard ratios comparing the active and control treatment with corresponding confidence interval (CI). Following this search, 53 articles were selected.

Results

Table 1: Renal Effects

Author	Year of publication	Study Design	Treatment	No. of patients	Follow up period (weeks)	Outcomes					
						Diabetic nephropathy	End stage renal failure	Albuminuria	Proteinuria	GFR	Creatinine doubling
Heather M. Campbell [4]	2013	Retrospective cohort study	ACEI vs. ARB	5166	-	N/A	↓	N/A	N/A	N/A	N/A
E. Jennifer Weil [5]	2013	RCT	ARB vs placebo	280	72	↔#	N/A	↑#	N/A	N/A	N/A
						↓##	N/A	↓##	N/A	N/A	N/A
Michael Mauer [6]	2009	RCT	ARB vs placebo	1065	60	N/A	N/A	↔	N/A	↔	N/A
			ACEI vs placebo			N/A	N/A		N/A		N/A
NasreenA. Al-Sayed [7]	2013	Retrospective observational study	ACEI vs ARB	16,489	96	N/A	N/A	↓	N/A	N/A	↓
E Imai [8]	2011	RCT	ARB vs placebo	566	166	N/A	N/A	N/A	↓	N/A	N/A
Sheldon W. Tobe et al [9]	2011	Post hoc analysis	ONTARGET: ARB + ACEI vs ARB/ACEI	25,620	208	↑	N/A	↔	N/A	↔	N/A
			TRANSCEND: ARB vs placebo	5,926	260	N/A	N/A	N/A	N/A	N/A	↓##
						N/A	N/A	N/A	N/A	N/A	↑#
						N/A	N/A	N/A	N/A	N/A	↓###
Linda F. Fried[10]	2013	RCT	ARB+ACEI vs ACEI+placebo	1448	42	N/A	↓	N/A	N/A	N/A	N/A
Sadreddin Rasi Hashemi[11]	2012	RCT	ACEI + N-acetylcysteine vs ACEI	70	2	N/A	N/A	N/A	↔	N/A	N/A
Hermann Haller [12]	2014	RCT	ACEI vs placebo	4447	166	N/A	N/A	↓	N/A	N/A	N/A

Author	Year of publication	Study Design	Treatment	No. of patients	Follow up period (weeks)	Outcomes					
						Diabetic nephropathy	End stage renal failure	Albuminuria	Proteinuria	GFR	Creatinine doubling
Anthony H. Barnett [13]	2004	RCT	ARB vs ACEI	250	260	N/A	N/A	N/A	N/A	↓	N/A
Hans-Henrik Parving [14]	2001	RCT	ACEI vs placebo	590	104	N/A	N/A	↓	N/A	N/A	N/A
Piero Ruggenenti et al. [15]	2011	RCT	CCB + ACEI vs Placebo + ACEI	380	156	N/A	N/A	N/A	↔	N/A	N/A
Enyu Imai et al. [16]	2013	RCT	ARB+ACEI vs placebo	563	166	N/A	N/A	N/A	↓	N/A	N/A
Marc Evans et al.[17]	2011	RCT	ARB vs CCB/ placebo	1715	151	↓	N/A	N/A	N/A	N/A	N/A
Peter Rossing[18]	1997	RCT	ARB vs ACEI	49	52	N/A	N/A	↓	N/A	N/A	N/A
Jan Menne [19]	2014	RCT	ARB vs placebo	1758	172	N/A	N/A	↓	N/A	N/A	N/A
Alireza Esteghamati [20]	2013	Open label RCT	Spironolactone + ARB vs ACEI + ARB	136	78	N/A	N/A	N/A	↓	N/A	N/A

#: Patients initially were normoalbuminuric. ##: Patients initially were microalbuminuria. ###: Patients initially were macrolbuminuric.

Table 2: Cardiovascular effects

Author	Year of publication	Study design	Treatment	No. of patients	Follow up period (weeks)	Outcomes		
						BP	Non-fatal CV events	Fatal CV events
Enrico Agabati-Rosei [21]	2014	RCT	ACEI+HCTZ vs ARB+HCTZ	361	18	↔	N/A	N/A
NasreenA.Al-Sayed et al [7]	2013	Retrospective observational study	ACEI vs ARB	16,489	624	N/A	↔	↔
John J McMurray et al [22]	2010	RCT	ARB vs Placebo	9306	60	↓	N/A	↔
Hala H Zreikat [23]	2014	Prospective cohort study	ACEI/ARB vs Non ACEI/ ARB	777	572	↔	↓*/↔**	↔
Tony Antoniou [24]	2013	Retrospective cohort study	Telmisartan (ARB) vs Irbesartan/ Candesartan/ Losartan/ Valsartan (ARB)	54186	-	N/A	↓	↓
Toshihide Kawai [25]	2011	Prospective cohort study	Olmesartan (ARB) vs Non-Olmesartan	90	-	N/A	↓	N/A
Arya M. Sharma [26]	2012	RCT	ARB+CCB vs CCB	706	8	↓	N/A	N/A
Susan van Dieren [27]	2012	RCT	ACEI+CCB vs Placebo	11140	224	↓	N/A	↔
Caroline A. Daly [28]	2005	RCT	ACEI vs Placebo	1502	224	↓	N/A	↔
Takashi Muramatsu et al [29]	2011	Open-labelled prospective	ARB vs CCB	1150	166	↔	↓	↔
N Racine [30]	2010	Open-labelled prospective	ARB+ diuretics vs ARB	1714	52	↓	N/A	N/A
Anthony H. Barnett [13]	2004	RCT	ARB vs ACEI	250	260	↔	N/A	N/A
Peter Rossing [18]	1997	RCT	ACEI vs CCB	49	52	↓	N/A	N/A
PieroRuggenenti et al [15]	2011	RCT	CCB+ACEI vs ACEI vs Placebo	380	156	↓	N/A	↓

* Angioplasty events ** Cerebrovascular events

Table 3: Endocrine Effects

Author	Year of publication	Study design	Treatment	No. of patients	Follow up period (weeks)	Outcomes						
						FBG	HbA1C	New onset of diabetes	Fasting serum insulin	TC	HDL	LDL
Shinji Makita [31]	2008	Prospective	ACEI+HCTZ vs ARB+HCTZ	361	18	↓	N/A	N/A	N/A	N/A	N/A	N/A
Christo V Rizos [32]	2010	Open-labelled prospective	ACEI vs ARB	16,489	624	↔	↔	N/A	↓	↓	↔	↓
N Racine [30]	2011	Open-labelled prospective cohort study	ARB vs Placebo	9306	60	↔	↔	N/A	N/A	N/A	N/A	N/A
OrlyVardeny [33]	2011	RCT	ACEI /ARB vs Non ACEI / ARB	777	572	↔	N/A	↓	N/A	N/A	N/A	N/A
Walter Zidek [34]	2012	Prospective	Telmisartan (ARB) vs Irbesartan/Candesartan/ Losartan/ Valsartan	54186	-	↔	↔	↓	N/A	N/A	N/A	N/A
John J. McMurray [22]	2010	RCT	Olmesartan (ARB) vs Non-Olmesartan	90	-	↔	N/A	↓	N/A	N/A	N/A	N/A

Table 4: Mortality Events

Author	Year of Publication	Study Design	Treatment	No. of patients	Follow up period (weeks)	Outcomes	
						Composite of death from CV diseases	All-cause mortality
M Z Molnar [35]	2014	Retrospective cohort study	any ACEI/ARB vs Placebo	40494	Most patients received 90-day supplies of ACEI/ARB and almost all received at least a 30-day supply	↓	↓
Heather M. Campbell [4]	2013	Retrospective cohort study	any ACEI vs any ARB	5166	156 weeks	N/A	↓
NasreenA.Al-Sayed [7]	2013	Retrospective observational study	ACEI vs ARB	16489	96 weeks	↔	N/A
John J McMurray [22]	2010	RCT	ARB vs. Placebo	9306	260 weeks (338 weeks for vital status)	↔	N/A
Hala H Zreikat [23]	2014	Prospective cohort study	ACEI/ARB vs non ACEI/ARB	777	572 weeks	N/A	Univariate: ↔ Multivariate: ↔
Linda F Fried [10]	2013	RCT	ARB+ACEI vs. ARB+placebo	1448	114.4 weeks	↔	N/A
Caroline A Daly [28]	2005	RCT	ACEI vs. placebo	1502	338 weeks	↔	N/A
Enyu Imai et al [16]	2013	RCT	ARB vs placebo	563	166 weeks	↓	N/A
Anthony H Barnett [13]	2004	RCT	ARB vs. ACEI	250	260 weeks	↔	N/A

Discussion

Renal Outcome

Out of 53 articles studied, 17 articles were related to renal outcomes including diabetic nephropathy, end stage renal failure, glomerular filtration rate, creatinine doubling, albuminuria and proteinuria.

Supported by the articles studied, it was found that ARB was able to decrease the incidence of diabetic nephropathy, level of albuminuria, proteinuria and creatinine doubling. A study which was conducted to compare the effect of ARB versus placebo showed that ARB was able to decrease the risk of diabetic

nephropathy in microalbuminuria patients whereas in another study which was conducted using the same comparison also showed the same effect regardless of albumin level in test subjects [5,19].
When comparing two studies regarding the outcome of albuminuria, it was seen that ARB was able to reduce the incidence of albuminuria particularly in microalbuminuria patients compared to normoalbuminuric patients [5,19].

However, levels of albuminuria in the subjects were allowed to influence the outcome of the test drug. According to a study conducted by Sheldon W. Tobe et al. where three categories of albuminuric patients were assessed, ARB was able to decrease creatinine doubling, microalbuminuria (HR=0.60; CI [0.25-1.46]; P=0.01) and macroalbuminuria (HR= 0.71; CI [0.21 to 2.44]; P=0.01) but it increased the creatinine doubling in patients who had normoalbuminuria (HR= 2.35; CI [1.33- 4.15]; P=0.01) [9].

When comparing the effects of ACEI against ARB, it was found that ACEI was superior in decreasing the risk of end stage renal failure (OR, 0.33; 95% CI [0.13–0.82]) and creatinine doubling (HR= 1.207; 95% CI [0.921-1.583]; P =0.173) [4,7]. However, the results for creatinine doubling do not show significant difference. Superiority of ACEI and ARB on albuminuria remains controversial as one study showed that ACEI was more superior to ARB in decreasing the incidence of albuminuria whereas another study showed that ARB was more superior[7,18].

The combination of ACEI and ARB in diabetic patients also remained controversial as one study showed that the combination increased the risk of diabetic nephropathy (RR= 21%; 95% CI[0.00-0.46) whereas another study showed that this combination was able to decrease the risk of end stage renal failure (HR= 0.88; 95% CI[0.70 to 1.12]; P=0.30)[9,10]. Hence, more studies are required for determining reno-protective effect of this combination.

Cardiovascular events

A total of 15 articles are linked to cardiovascular events. The outcomes include a reduction in blood pressure, non- fatal cardiovascular events, and fatal cardiovascular events. The non-fatal cardiovascular events include congestive heart failure, myocardial infarction, stroke, CABG, angioplasty, transient ischemic attack, and coronary artery disease.

Angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are commonly used antihypertensives that may correct insulin sensitivity. In a study conducted by Zreikat HH et al, the follow-up period showed that the blood pressure control was not significantly different between those who used ACEI/ARB and the control group except for the third year. There is a significant reduction in risk of coronary events (MI, silent MI, coronary heart disease death, CABG, angioplasty, or angina) with the use of ACEI/ARB (adjusted HR = 0.530, 95% CI [0.321–0.875], P=0.013]). However, there were no effects on cerebrovascular events (HR = 1.173, 95% CI [0.621–2.217], P=0.6228).The use of ACEI/ARB did not have a significant effect on the mortality rate in both univariate (HR = 1.068, 95% C.I. [0.713–1.600], P=0.7494) and multivariate models (HR=1.078, 95% C.I. [0.714–1.629], P = 0.7198) [23].

Another study has concluded that there was no significant difference between ACEI and ARB in systolic blood pressure at 75% of the subjects had a systolic pressure of less than 160 mm Hg and 42% had a systolic pressure of less than 140 mm Hg. In the ARB group, there were nine incidences of congestive heart failure and myocardial infarctions respectively. On the other hand, the ACEI has a lower incidence of congestive heart failure myocardial infarction [13].

The comparison of ARB and ACEI in two clinical trials revealed that, ARB and ACEI did not significantly reduce the incidence of cardiovascular events such as death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure, arterial revascularization, or hospitalization for unstable angina (ARB extended cardiovascular outcomes: P=0.43; ARB core cardiovascular outcome P=0.85; ACEI: P= 0.131). The effects of blood pressure levels are significant in both ARB and ACEI treatment groups whereby the overall mean reduction in systolic and diastolic pressure was (P<0.001) for both treatment groups [22,29].

Hence, both ARB and ACEI did not have significant effects on cardiovascular events such as death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure, arterial revascularization, or hospitalization for unstable angina but it decreased the blood pressure level.

Mortality rate

In this review, out of 52 trials, nine discussed mortality outcomes: composite outcomes from cardiovascular diseases and all cause mortality. A total of 75995 patients taking an ACEI, ARB, placebo and non-treatment were studied for their mortality outcomes. In a trial (40,494 patients) comparing any ACEI/ARB versus no treatment, there was a major increase in survival rate with the administration of ACEI/ARB [35]. Lower odds of all-cause mortality associated with the administration of ACEI was observed in another trial (5166 patients) in the comparison of any ACEI vs any ARB (OR, 0.10 [95% CI, 0.04–0.21])[4]. However, no significant difference in all cause mortality was demonstrated in a trial (777 patients) on both univariate (HR=1.068, 95% CI [0.713, 1.600], P=0.7494] and multivariate models ((HR=1.078, 95% CI [0.714, 1.629], P=0.7198)[23].

No significant difference between ACEI and ARB in terms of a composite of death from cardiovascular diseases was observed in a retrospective observational study (16,489 patients) (P = .81) [4]. Another trial (1448 patients) showed a similar result in the comparison between ACEI vs ARB (hazard ratio - 1.04, 95% CI - 0.73-1.49, P=0.75)[10]. Telmisartan vs Enalapril (250 patients) showed no significant reduction in mortality rate(13).Valsartan (ARB) has no significant effect in reducing the incidence of death from composite of cardiovascular diseases as compared with the placebo (8.1% vs. 8.1%; hazard ratio, 0.99; 95% CI, 0.86 to 1.14; P = 0.85) [22]. Perindopril (1502 patients) also demonstrated no significant difference in mortality rate from cardiovascular disease when compared to placebo regimen (relative risk reduction 19% [(95% CI, 27 to 38%), P=0.13]) [28]. However, a trial (563 patients) comparing ACEI/ARB vs non ACEI/ARB showed a reduction in incidence of the composite of death from cardiovascular diseases[9-16].

Although it has been demonstrated in two trials that comparison of any ACEI/ARB vs placebo and Olmesartan (ARB) vs placebo was associated with a reduced risk of composite death of cardiovascular diseases, they could not convincingly conclude that ACEI/ARB have beneficial effect on improving mortality outcome. Meanwhile, two direct comparison trials between ACEI and ARB in large sample trials (16739 patients) identified no significant difference in terms of preventing death. Thus, there is no strong evidence that ACEI or ARB are superior to one another in terms of lowering the incidence of composite death from cardiovascular illnesses.

On the other hand, in terms of all cause mortality, it is controversial to conclude that the effect of ACEI and ARB as two trials identified a reduction in all cause mortality incidence while one trial showed no difference in risk reduction when comparing ACEI/ARB vs non ACEI/ARB. Although there is a direct comparison trial between ACEI vs ARB (5166 patients) identified a lower risk of death in all-cause, there is insufficient evidence that ACEI is superior to ARB in reducing mortality rates.

Endocrine outcome

We have selected six studies to analyze the endocrine outcomes when comparing the use of angiotensin converting enzyme inhibitor (ACEI) with angiotensin receptor blocker (ARB). The endocrine outcomes include the fasting blood glucose (FBG), glycated hemoglobin (HbA1C), fasting serum insulin and the new-onset of diabetes. Out of the 6 studies, only one study has shown that ARBs do decrease the level of FBG of hypertensive patients with glucose intolerance. In the study (Shinji Makita et al 2008), Telmisartan (TEL) was compared with Candesartan (CAN) and placebo and has shown to reduce the FBG level by -1.7 % from the baseline (p=0.045), whereas the other two treatments showed significant increased levels from the baseline. On the other hand, only one study (Rizos et al, 2010) compares the effect of combination therapies, which comprise different ARBs (Telmisartan, Irbesartan and Olmesartan) when in use with Rosuvastatin in treating patients with impaired fasting glucose, stage 1 hypertension and mixed hyperlipidemia [32]. Among the 3 treatments analyzed, the combination

of Rosuvastatin and Telmisartan is the most effective in decreasing fasting serum insulin ($p<0.01$)[32]. However, all three combination therapies showed insignificant change in FBG and HbA1C unlike the reported results of the study mentioned above (Shinji Makita et al 2008)[31]. On another note, the Rosuvastatin and Telmisartan combinatory therapy was able to reduce the levels of Total Cholesterol (TC), Triglycerides (TG), High Density Lipoprotein (HDL) and Low Density Lipoprotein (LDL) ($p=0.001$)[31].

From the data of various studies we have selected, we have also noticed that ACEIs and ARBs delay the development of diabetes mellitus. In a study (Vardeny et al, 2011) which compares Trandolapril and an equivalent placebo when in use with a -blocker, the Trandolapril combination treatment shows reduced new-onset of diabetes ($p<0.001$)[33]. Similarly, another study (Zidek et al, 2012) matches the effectiveness of combination therapies Ramipril and Felodipine /Other Calcium Channel Blocker (CCB) with the use of diuretics and ß-blockers[34]. The data of the study displays that the Ramipril combination therapy reduces the recent onset of diabetes ($p<0.05$)[34]. From these two studies, we can see that ACEIs play an important role in decreasing the new onset of diabetes but the two studies share a common limitation, which is the absence of FBG data. Nevertheless, another study (Murray et al, 2010) compares the combination therapies of Valsartan and Nateglinide with a matching placebo and Nateglinide and have shown that like the two ACE inhibitors mentioned above, ARBs may also reduce the new-onset of diabetes as the study data reports that Valsartan have a lower incidence of diabetes (33.1%) than the placebo treatment (36.8%) ($p<0.001$)[22].

The final study (Racine et al, 2011) that we analyzed has shown that Losartan, when used with or without Hydrochlorothiazide is an effective antihypertensive therapy, however no significant values on the levels of FBG and incidence of diabetes were found. The incidence of new onset diabetes during the 52-week follow-up of the study was 2.2% (n=37). This incidence was 2.4% for patients with grade-I hypertension and 1.5% for those with grade-II or III hypertension ($P=0.16$) [30].

Conclusion

Based on the discussions above, we can clearly conclude that both ACEI and ARB are beneficial in lowering blood pressure and are preferred hypertension medications for patients with hypertension comorbid with diabetes. They also help in preventing progression of diabetic nephropathy from microalbuminuria to macroalbuminuria [36]. However, superiority between ACEI and ARB remains controversial as different studies showed superior results for ACEI and ARB respectively. Therefore, more studies comparing the pros and cons of ACEI and ARB should be conducted to obtain more conclusive results of whether ACEI or ARB will provide better therapeutic effects to patients suffering from diabetes with comorbid hypertension. Numerous aspects should be analyzed during the studies to get a better picture of the overall effect of the drugs on patients. These results are essential to health-care professionals when deciding the choice of medication to be prescribed so that the most appropriate medication regimen can be provided to the patient to ensure that the hypertension and diabetes are well-controlled.

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