# Safety of the neprilysin/renin-angiotensin system inhibitor LCZ696

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#### **ABSTRACT**

Objectives: The combined neprilysin/rennin-angiotensin system inhibitor sacubitril/valsartan (LCZ696) has shown its superiority over ACEI/ARB therapy. In view of the existing concern of its adverse effects, we aimed to provide evidence of the safety of the new drug.

Results: A total of 6 randomized trials with 11,821 subjects were included in this analysis. No significant differences were found in any adverse effects between LCZ696 and ACEI/ARB or placebo groups. LCZ696 significantly decreased the risks of serious adverse events and death compared with ACEI/ARB. LCZ696 also significantly decrease the risk of discontinuation of treatment for any adverse event no matter compared with ACEI/ARB or a placebo. LCZ696 significantly increased the risk of angioedema and dizziness, while it decreased the risk of renal dysfunction and bronchitis. There was no difference for hypotension, hyperkalemia, cough, upper respiratory tract inflammation, diarrhoea, back pain, nasopharyngitis, headache and influenza between the LCZ696 group and the ACEI/ARB group.

Materials and Methods: A meta-analysis of eligible studies that used LCZ696 in heart failure and hypertension was performed. Embase, PubMed and the Cochrane Library were searched for randomized controlled trials (RCTs) with data on any adverse effects, serious adverse events, discontinuation of treatment for any adverse event, death, angioedema, hypotension, hyperkalemia, and other adverse effects to perform this meta-analysis.

Conclusions: In addition to the beneficial effect of LCZ696 on end point events, the available evidences showed that LCZ696 was associated with less drug-risks than a placebo and ACEI/ARB.

#### **INTRODUCTION**

Neprilysin, a neutral endopeptidase, has been seen as a potential therapeutic target in heart failure and hypertension because of its potent cardiorenal protective effects due to vasodilation, natriuresis, diuresis and attenuation of hypertrophy and fibrosis [1]. Inhibition of neprilysin can increase the level of NPs, and several drugs involved in inhibiting neprilysin were developed, such as ecadotril, racecadotril, and candoxatril. But these agents did not display efficient effects compared with traditional drugs [2–4]. The reason why neprilysin inhibition alone didn't exert a significant effect is because of the promotive effect of neprilysin inhibition

on plasma Ang II concentration and the restraining effect on metabolic clearance of Ang II in the medium [5]. Therefore, combined inhibition of both neprilysin and the renin–angiotensin system is seen as a plausible direction in the field. Omapatrilat, the first-in-class neprilysin and angiotensin-converting enzyme inhibitor, was developed. Although omapatrilat showed its promising potential, further development of omapatrilat was discontinued because of an increased incidence of angioedema [6].

LCZ696 (sacubitril/valsartan), which consists of the neprilysin inhibitor prodrug sacubitril (AHU377) and the ARB valsartan in a 1:1 molar ratio, provides simultaneous neprilysin inhibition and angiotensin-II receptor blockade. Different from omapatrilat, the design of LCZ696 mainly blocks ang-II, but not ACE, which lowers the risk of angioedema. And from the researches before, LCZ696 has shown greater blood pressure reduction in patients with hypertension [7, 8] and reduced all-cause mortality in heart failure patients compared with valsartan or enalapril [9, 10]. While results from individual clinical trials[7-10] and a meta-analysis [4] have confirmed the beneficial effects of LCZ696 and it was reported to be well tolerated in patients in individual clinical trials [11, 12], but the incidences of the side effects reported in each trial were still different. The purpose of this meta-analysis is to compare the safety of all published randomized controlled trials (RCTs) using LCZ696 inhibitors versus ACEI or ARB or a placebo for treating patients with heart failure and hypertension.

#### RESULTS

#### Any adverse events

We firstly compared the difference between LCZ696 and a placebo (Ruilope's study [7], Kario's study [8] and Ratio study [13] were included). The heterogeneity test result of these studies was calculated as  $I^2 = 0\%$ . Therefore, the fixed effect model was used for further analyses, and the results demonstrated that there was no difference between LCZ696 group and placebo group [RR = 0.97,95% CI (0.80, 1.17), Z = 0.32, P = 0.75] (Figure 1A). Then, we compared the difference between LCZ696 and ACEI/ARB (Ruilope's study [7], PARAMOUNT study [10], PARADIGM-HF study [9], Ratio study [13] and Parameter Study [14] were included). The heterogeneity test result of these studies was calculated as  $I^2 = 26\%$ . Therefore, the fixed effect model was used for further analyses, and the results demonstrated that there was no difference between the LCZ696 group and the ACEI/ ARB group [RR = 0.98, 95% CI (0.96, 1.00), Z = 1.71, P = 0.09] (Figure 1B).

#### Serious adverse events

For serious adverse events, we collected the data involving LCZ696 versus ACEI/ARB from the

PARAMOUNT study, PARADIGM-HF study and Parameter Study. The heterogeneity test result of these studies was calculated as  $I^2 = 0\%$ . Therefore, the fixed effect model was used for further analyses, and LCZ696 showed a significant decrease in serious adverse events compared with the ACEI/ARB group [RR = 0.91, 95% CI (0.87, 0.95), Z = 4.23, P < 0.0001] (Figure 1C).

# Discontinuation of treatment for any adverse event

We first compared the difference between LCZ696 and a placebo. The heterogeneity test result of the 2 studies (Ruilope's study and Kario's study) was calculated as  $I^2 = 0\%$ . Therefore, the fixed effect model was used for further analyses, and LCZ696 showed a significant decrease in discontinuation of treatment for any adverse event compared with the placebo group [RR = 0.33, 95%]CI (0.13, 0.87), Z = 2.24, P = 0.03] (Figure 2A). Then, we compared the difference of discontinuation of treatment for any adverse event between LCZ696 and ACEI/ARB. The heterogeneity test result of the 4 studies (Ruilope's study, PARAMOUNT study, PARADIGM-HF study and Parameter Study) was calculated as  $I^2 = 34\%$ . Fixed effect model was used and LCZ696 showed a significant decrease in discontinuation of treatment for any adverse event compared with ACEI/ARB group [RR = 0.71, 95%CI (0.56, 0.90), Z = 2.88, P = 0.004] (Figure 2B).

#### Death

In Ruilope's study and Kario's study, no case of death was reported. In PARAMOUNT study and Parameter study, 1 and 2 cases of death were reported respectively in the LCZ696 group and the valsartan/ olmesartan group, while in PARADIGM-HF study, 711 and 835 cases of death were reported respectively in LCZ696 group and enalapril group. The heterogeneity test result of the 3 studies was calculated as  $I^2 = 0\%$ . The fixed effect model was used and the results demonstrated that the LCZ696 group significantly decreased death from any cause compared with the ACEI/ARB group [RR = 0.85, 95% CI (0.78, 0.94), Z = 3.40, P = 0.0007] (Figure 2C).

#### Angioedema

From Ruilope's study, the PARAMOUNT study, the PARADIGM-HF study, the Ratio study and the Parameter Study, we collected and analyzed the data of the difference between LCZ696 and ACEI/ARB. The heterogeneity test result of these studies was calculated as  $I^2 = 0\%$ . The fixed effect model was used and the results demonstrated that there was no difference between the LCZ696 group and the ACEI/ARB group [RR = 1.93, 95% CI (1.02, 3.68), Z = 2.01, P = 0.04] (Figure 2D).

#### Hypotension

The data of the PARAMOUNT study, the PARADIGM-HF study and the Parameter Study were collected and analyzed for the difference of hypotension between LCZ696 and ACEI/ARB. The heterogeneity test result of these studies was calculated as  $I^2 = 57\%$ . Therefore, the random effect model was used and the results demonstrated that there was still no difference between the LCZ696 group and the ACEI/ARB group [RR = 1.23, 95% CI (0.80, 1.89), Z = 0.96, P = 0.34] (Figure 2E).

# Hyperkalemia

Only the PARAMOUNT study, the PARADIGM-HF study and the Parameter Study reported the occurrence of hyperkalemia. The heterogeneity test result of these studies was calculated as  $I^2 = 0\%$ . Therefore, the fixed effect model was used for further analyses, and the results demonstrated that there was no difference between the LCZ696 group and the ACEI/ARB group [RR = 0.95, 95% CI (0.86, 1.04), Z = 1.17, P = 0.24] (Figure 2F).

## **Renal dysfunction**

Only the PARAMOUNT study and the PARADIGM-HF study reported the occurrence of renal dysfunction. The heterogeneity test result of these studies was calculated as  $I^2 = 0\%$ . The fixed effect model results demonstrated that the LCZ696 group significantly decreased renal dysfunction compared with the ACEI/ ARB group [RR = 0.73, 95% CI (0.59, 0.91), Z = 2.87, P = 0.004] (Figure 2G).

A Forest plot of any adverse events comparison: LCZ696 group vs. placebo group.



#### B Forest plot of any adverse events comparison: LCZ696 group vs. ACEI/ARB group.

	LCZ69	-CZ696 ACEI/ARB			Risk Ratio			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Fixed, 95% C		IV, Fixed, 95% CI
Paradigm 2014#	3419	4203	3503	4229	95.9%	0.98 [0.96, 1.00]		
Parameter 2017	132	229	121	225	1.4%	1.07 [0.91, 1.26]		
Paramount 2012	96	149	111	152	1.6%	0.88 [0.76, 1.03]		
Ratio 2017	42	142	38	143	0.3%	1.11 [0.77, 1.62]		
Ruilope 2010	126	497	108	493	0.8%	1.16 [0.92, 1.45]		
Total (95% CI)		5220		5242	100.0%	0.98 [0.96, 1.00]		•
Total events	3815		3881					
Heterogeneity: Chi <sup>2</sup> = 5.43, df = 4 (P = 0.25); l <sup>2</sup> = 26%								
Test for overall effect: Z = 1.71 (P = 0.09)							0.5	Favours [LCZ696] Favours [ACEI/ARB]

C Forest plot of serious adverse events comparison: LCZ696 group vs. ACEI/ARB group.

Study or Subgroup	LCZ696 Events T	6 AC	CEI/ARE	tal We	aht	Risk Ratio M-H. Fixed, 95% CI		Risk M-H. Fix	Ratio	
				00 00		0.04 K0.07, 0.051				
Paradigm 2014 #	1937 4	4203 2	142 42	29 98	3.0%	0.91 [0.87, 0.95]				
Parameter 2017	16	229	13 2	25 0	0.6%	1.21 [0.60, 2.46]			· · · · ·	
Paramount 2012	22	149	30 1	50 1	1.4%	0.74 [0.45, 1.22]			<u> </u>	
Total (95% CI)	4	1581	46	04 100	0.0%	0.91 [0.87, 0.95]		•		
Total events	1975	2	185							
Heterogeneity: Chi <sup>2</sup> = 1			H							
The for every left of $T = 4.22 (P < 0.0001)$							0.2	0.5	1 2	5
1 = 51 + 101 + 000 = 1000 + 1000 = 1000 = 1000 = 1000 = 1000 = 1000 = 1000 = 100000 = 1000000 = 100000 = 100000 = 100000 = 100000 = 100000 = 100000 = 100000 = 100000 = 100000 = 100000 = 100000 = 1000000 = 100000 = 1000000 = 1000000 = 10000000 = 10000000 = 100000000								Favours [LCZ696]	Favours [ACE	I/ARB]

#: The data of Paradigm-HF study in this part was from Supplementary Appendix of their article.

Figure 1: Forest plots depicting the comparison of LCZ696 and a placebo or ACEI/ARB on any adverse events, serious adverse events and discontinuation of treatment for any adverse event.

A Forest plot of discontinuation of treatment for any adverse event comparison: LCZ696 group vs. placebo group.



Figure 2: Forest plots depicting the comparison of LCZ696 and a placebo or ACEI/ARB on death, angioedema, hypotension, hyperkalemia and renal dysfunction.

#### **Other adverse effects**

The PARAMOUNT study didn't explicitly provide the data involving other adverse effects, while the other 4 studies (Ruilope's study, PARADIGM-HF study, Ratio study and Parameter Study) mentioned the adverse effects of cough, dizziness, upper respiratory tract inflammation, diarrhoea, bronchitis, back pain, nasopharyngitis, headache and influenza. For cough and back pain, random effect model were used ( $I^2 = 69\%$  and  $I^2 = 56\%$ ) and the results showed no difference between the LCZ696 group and the ACEI/ARB group [RR = 1.29, 95% CI (0.44, 3.77), Z = 0.47, P = 0.64; RR = 0.88, 95% CI (0.42, 1.87), Z = 0.33, P = 0.74] (Figure 3A and 3D). For upper respiratory tract inflammation, diarrhoea, nasopharyngitis, headache and influenza, fixed effect model was used and the results also showed no difference between the LCZ696 group and the ACEI/ARB group [respectively: RR = 1.01, 95% CI (0.84, 1.21), Z = 0.05, P = 0.96; RR = 1.04, 95% CI (0.86, 1.26), Z = 0.41, P = 0.68; RR = 1.20, 95% CI (1.00, 1.45), Z = 1.92, P = 0.05; RR = 0.99, 95% CI(0.77, 1.26), Z = 0.10, P = 0.92; RR = 1.22, 95% CI (0.98, 1.53), Z = 1.75, P = 0.08 (Figure 3B, 3C, 3E, 3H, 3I). LCZ696 significantly decreased the occurrence risk of bronchitis compared with ACEI/ARB [fixed effect model, respectively: RR = 0.82, 95% CI (0.68, 0.98), Z = 2.14, P = 0.03] (Figure 3F). However, LCZ696 significantly increased the occurrence risk of dizziness compared with ACEI/ARB [RR = 1.28, 95% CI (1.08, 1.52), Z = 2.88, P = 0.004] (Figure 3G).

# DISCUSSION

The main findings were as follows: (1) individuals assigned LCZ696 showed a statistically decreased risk of death compared with those assigned ACEI/ARB; (2) treatment with LCZ696 significantly decreased the risk of serious adverse events, discontinuation of treatment for any adverse event, renal dysfunction and bronchitis compared with a placebo or ACEI/ARB treatment; (3) LCZ696 significantly increased the risk of angioedema and dizziness; (4) for any adverse event, hypotension, hyperkalemia, cough, upper respiratory tract inflammation, diarrhoea, back pain, nasopharyngitis, headache and influenza, there was no significant difference between groups.

Recently, both ACC/AHA/HFSA [15] and ESC [16] guidelines for treatment of heart failure gave LCZ696 a class I level B recommendation based on the evidence of the PARADIGM-HF study. The guidelines also explicitly states that ARNI should not be administered concomitantly with ACEI or within 36 hours of the last dose of an ACEI, and should not be administered to patients with a history of angioedema, which mainly based on the trials of omapatrilat which was associated with a higher frequency and unacceptable incidence of

angioedema [6]. In the PARADIGM-HF study, although they have excluded the participants who could not tolerate the therapy of LCZ696 or enalapril during an active runin phase of 5–9 weeks, the incidence of angioedema was still seemed higher in the LCZ696 group than the enalapril group although without statistical significance. In the present study, we only wanted to know whether LCZ696, rather than ARNI, could increase the risk of angioedema, so we didn't include the studies involving omapatrilat. The results suggested that LCZ696 statistically increased the risk of angioedema, but the P value was just 0.04. In the studies of Ruilope's study and Kario's study, no case of angioedema was found during the 8 weeks experimental period. The PARAMOUNT study reported only 1 case of angioedema in LCZ696 group during the 36 weeks and and Ratio Study also reported only 1 case of angioedema in valsartan group during the 8 weeks experimental period. Thus, the results of the present meta-analysis mainly from the PARADIGM-HF study and Parameter study. We thought that the reason why the cases reported in Ruilope's study, Kario's study, PARAMOUNT study and Ratio Study were much less than the other 2 studies was the shorter follow-up period, which might lead to an unreliable conclusion.

Despite the superiority of LCZ696 over enalapril, symptomatic hypotension has been seen as another important adverse effect that restricted the further application of LCZ696 in clinical practice. In the PARADIGM-HF study, symptomatic hypotension was more often present in the LCZ696 group compared with the enalapril group (14% vs 9.2%, P < 0.001). However, hypotension seems less occurred in LCZ696 group compared with olmesartan group in Parameter study (0.9%) vs 2.2%), and there was no difference between groups in PARAMOUNT study (19% vs 18%, P=0.88). Integrating the above data, we obtained the result that the incidence of hypotension in the LCZ696 group was not higher than the ACEI/ARB group (P = 0.34). We thought about the results above, and speculated the reason of the difference might because of the difference of the enrolled population. The PARAMOUNT study enrolled heart failure with a preserved ejection fraction, and the PARADIGM-HF study enrolled heart failure with a reduced ejection fraction, while the Parameter study enrolled patients with only hypertension.

Although Fiona Bodey's meta-analysis, which included 4 studies: the IMPRESS study [17], the OVERTURE study [18], the PARAMOUNT study and the PARADIGM-HF study, has demonstrated that ARNI decreased relative risk of renal dysfunction in heart failure compared to ACEI or ARB alone by 32%[19], the risk of renal insufficiency was still emphasized in the ACC/AHA/HFSA's update [15]. The reason why LCZ696 was connected with renal impairment might be the greater hypotensive effect. However, clinical increases in the serum creatinine level and discontinuation for

#### A Forest plot of cough comparison: LCZ696 group vs. ACEI/ARB group.

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$\begin{aligned} \begin{array}{cccccccccccccccccccccccccccccccccccc$	Total (PS-C)         Soft 1         Soft 23 (P + 6/2)         Total (PS-C)         Formation (CCIII)         Formation (CCIIII)         Formation (CCIIIII)         Formation (CCIIIII)         Formation (CCIIIII)         Formation (CCIIIII)         Formation (CCIIIII)         Formation (CCIIIII)         Formation (CCIIIIII)         Formation (CCIIIIII)         Formation (CCIIIIII)         Formation (CCIIIIIIII)         Formation (CCIIIIIII)         Formation (CCIIIIIIIII)         Formation (CCIIIIIIIIIIIII)         Formation (CCIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII		Ruilope 2010	7	497	3	493	24.3%	2.31 [0.60. 8 90]	
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Parameter 2014         203         423         201         422         55.4         1.02 (Del 1, 1.3)           Parameter 2017         5         2.0         4.2         1.43         0.5%         0.28 (D.2, 2.0.7)           Parameter 2017         3         4.2         1.43         0.5%         0.28 (D.2, 2.0.7)           Parameter 2017         3         4.2         1.43         0.5%         0.28 (D.2, 2.0.7)           Parameter 2017         3         4.2         1.7         4.3         0.5%         0.28 (D.2, 2.0.7)           Total events         2.15         1.10 (D.200)         1.0 (D.200)         1.0 (D.200)         1.0 (D.200)         1.0 (D.200)           Total events         2.15         1.0 (D.200)         1.0 (D.200)         1.0 (D.200)         1.0 (D.200)         1.0 (D.200)           Parameter 2017         1.2 (D.200)         7.67 (D.200)         1.20 (D.200)         1.20 (D.200)         1.0 (D.200)         Parameter 2010         7.67 (D.200)         1.20 (D.200)         1.20 (D.200)         1.20 (D.200)         Parameter 2010         7.67 (D.200)         1.20 (D.200)<	Parameter 2014 # 200 442 2016 42 2016 42 2016 44 200 444 100 20 44		Study or Subgroup	Events 1	Total F	vents	Total	Weight	M-H. Fixed, 95% C	M-H Fixed 95% Cl
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Ratiop 2017       3       442       1       443       0.5%       0.03 (0.2, 28.70)         Ratiop 2017       3       442       1       443       0.5%       0.03 (0.2, 28.70)         Teal (95% C)       5071       5000       100.0%       1.01 (0.8, 1.21)       0.1       10	Reline 2017       3       142       1       143       0.5%       3.02 (0.22, 28.70)         Reline 2010       201       201       0.30 (0.11, 1.80)       1.01 (0.84, 1.21)         Total (9%) (0)       207       1.03 (0.11, 0.20)       1.01 (0.84, 1.21)         Total (9%) (0)       C.2269       ACELARS       Risk Ratio       Risk Ratio         Parameter 2017       6       2.23       2.22       9.5%       1.18 (0.27, 3.01)         Parameter 2017       1.2       2.42       3.43       1.45       0.07 (0.11, 3.80)         Parameter 2017       2.42       3.43       1.45       0.07 (0.11, 3.80)         Parameter 2017       2.42       3.43       1.45 (0.87, 1.38)       0.16 (0.71, 1.38)         Parameter 2017       2.42       3.43       1.45 (0.87, 1.38)       0.16 (0.71, 1.38)         Total (9%) (C)       S071       5.00 (0.07, 1.42)       0.01 (0.11, 3.80)       0.01 (0.11, 3.80)         Total (9%) (C)       S071       5.00 (0.22, 0.22)       1.30 (0.44, 4.53)       0.01 (0.11, 3.80)         Total (9%) (C)       C2209       ACELARD       Risk Ratio       Risk Ratio       Risk Ratio         Parameter 2017       3.22 (0.21, 0.22)       1.30 (0.20, 0.44)       1.30 (0.20, 0.44)       1.30		Parameter 2017	6	229	6	225	2.8%	0.98 [0.32, 3.00]	— <del>—</del> —
Rulege 2010 3 407 7 403 3.3% 0.43 (0.1, 1.53) Total (#95/ C) 507 1 509 100.0% 1.01 (p.4.1.21) Total (#95/ C) 70 202 100 222 100 223 100 (p.0.1.41) Total (#95/ C) 70 202 100 223 100 (p.0.1.41) Total (#95/ C) 70 509 100.0% 1.20 (p.0.1.42) Total (#95/ C) 70 70 509 100.0% 1.20 (p.0.1.42) Total (#95/ C) 70 70 509 100.0% 1.20 (p.0.1.41) Total (#95/ C) 70 70 509 100.0% 1.20 (p.0.1.41) Total (#95/ C) 70 70 509 100.0% 1.20 (p.0.1.41) Total (#95/ C) 71 500 100.0% 2	Rulage 2010 3 407 7 403 33% 0.43 011.163 Total (95% C) 2071 7 407 5 409 125% 1.43 (2.4.1.21) Total (95% C) 2071 7 407 5 409 125% 1.53 (2.4.1.21) Total (95% C) 2071 7 407 5 409 125% 1.53 (2.4.1.21) Total (95% C) 2071 7 477 5 409 125% 1.53 (2.4.1.21) Total (95% C) 2071 7 477 5 409 125% 1.53 (2.4.1.21) Total (95% C) 2071 7 477 5 409 125% 1.53 (2.4.1.21) Total (95% C) 2071 7 477 5 409 125% 1.53 (2.4.1.21) Total (95% C) 2071 7 477 5 409 125% 1.53 (2.4.1.21) Total (95% C) 2071 7 477 15 409 125% 1.53 (2.4.1.21) Total (95% C) 2071 7 477 15 409 125% 1.53 (2.4.1.21) Total (95% C) 2071 7 477 15 409 125% 1.53 (2.4.1.21) Total (95% C) 2071 7 10 25% 2070 7 8.4.1.21 Total (95% C) 2071 7 10 22% 100 22% 1.53 (2.4.1.21) Total (95% C) 2071 7 10 22% 100 22% 1.53 (2.4.1.21) Total (95% C) 2071 7 10 22% 100 22% 1.53 (2.4.1.21) Total (95% C) 2071 7 10 22% 100 22% 1.53 (2.4.1.21) Total (95% C) 2071 7 10 22% 100 22% 1.53 (2.4.1.21) Total (95% C) 2071 7 10 22% 100 7		Ratio 2017	3	142	1	143	0.5%	3.02 [0.32, 28.70]	
1 voli events       201       201       1.51 (0.44, 1.21)       1.51 (0.44, 1.21)         1 voli events       201       0.11       0.1       0.1       1.51 (0.14, 1.21)         1 voli events       2.03 (0.14, 3.2)       0.01       0.1       1.51 (0.14, 1.21)       1.51 (0.14, 1.21)         1 voli events       1.62 (0.14, 0.21)       1.62 (0.14, 0.21)       1.62 (0.14, 0.21)       1.61 (0.14, 0.21)         1 voli events       1.62 (0.14, 0.21)       1.61 (0.14, 0.21)       1.61 (0.14, 0.21)       1.61 (0.14, 0.21)         1 voli events       1.62 (0.14, 0.21)       1.62 (0.14, 0.21)       1.62 (0.14, 0.21)       1.61 (0.14, 0.21)         1 voli events       1.62 (0.14, 0.21)       1.62 (0.14, 0.21)       1.62 (0.14, 0.21)       1.61 (0.14, 0.21)         1 voli events       1.62 (0.14, 0.21)       1.62 (0.14, 0.21)       1.61 (0.14, 0.21)       1.61 (0.14, 0.21)         1 voli events       1.62 (0.14, 0.21)       1.64 (0.14, 0.21)       1.61 (0.14, 0.21)       1.61 (0.14, 0.21)         1 voli events       1.62 (0.14, 0.21)       1.62 (0.14, 0.21)       1.64 (0.14, 0.21)       1.61 (0.14, 0.21)         1 voli events       1.62 (0.14, 0.21)       1.62 (0.14, 0.21)       1.64 (0.14, 0.21)       1.61 (0.14, 0.21)         1 voli events       1.62 (0.14, 0.21)       1.62 (0.14, 0.21)<	Total (9%) (c)       507       509       100, %       1.51 [0,44, 1.21]         Total events       215       215         Metoposenity, Chir = 2.5, 0, g = 3, 0 = 0.48, 1 = 0.5       Control (1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,		Ruilope 2010	3	497	7	493	3.3%	0.43 [0.11, 1.63]	
Total avents       21       Development       Development <thdevelopment< th="">       Development       <th< td=""><td>Trail events 0 = 2.5 M = 2.6 M = 2.6 M = 0.6 M</td><td></td><td>Total (95% CI)</td><td>,</td><td>5071</td><td></td><td>5090</td><td>100.0%</td><td>1 01 [0 84 1 21]</td><td>4</td></th<></thdevelopment<>	Trail events 0 = 2.5 M = 2.6 M = 2.6 M = 0.6 M		Total (95% CI)	,	5071		5090	100.0%	1 01 [0 84 1 21]	4
Homogeneity: Ch <sup>2</sup> = 20, dis 3 (P = 0.48); if = 90;         Loc 200         Loc 200         Loc 200         Loc 200         Favoura (Loc 2006);         Fav	Historgoning: Ch <sup>2</sup> 2.9. (a) <sup>2</sup> 3 (a) <sup>2</sup> a (b) <sup>2</sup> (b) (c) (c) (c) (c) (c) (c) (c) (c) (c) (c		Total events	215		215		1001070		
Test for overall effect 2 = 0.65 (P = 0.96)       Color 100       Fareware (LC2006)       Fareware (LC2067)       Fareware (LC2067	Test for overall field: 2 = 0.65 (P = 0.80)       Color       Color       Fanore (L, C2896)       Fanore (L, C2896) <td< td=""><td></td><td>Heterogeneity: Chi<sup>2</sup> = 3</td><td>2.50, df = 3</td><td>(P = 0.48</td><td>3); I<sup>2</sup> =</td><td>0%</td><td></td><td></td><td></td></td<>		Heterogeneity: Chi <sup>2</sup> = 3	2.50, df = 3	(P = 0.48	3); I <sup>2</sup> =	0%			
C Forest plot of diambers comparison: LC2696 group vs. ACEUARB group. Example 2010 F 427 5 403 2.55 1.301 Wash Mit Ended SS C Mit Ford 395 Cl Parameter 2017 6 4 220 5 225 2.55 1.18 [0.37, 3.81] Ratio 2017 2 14 (2 3 143 143 164) 1.09 (3 4.03) 1 0 0 10 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	C Forset plot of dambes comparison: LC2969 groups vs. ACEUARB group.  Extension 2000 199 423 9 53 C1  State or Subsystem 1 fold. Foreints 1 fold. Weight MH. Flored 955 C1  Paradiag 2017 2 14 42 3 143 154 154 0 456 154  Paradiag 2017 2 14 42 3 143 154 154 0 456 154  Paradiag 2017 2 14 42 3 143 154 154 0 456 0 154  Paradiag 2017 2 14 42 3 143 154 154 0 456 0 154  Paradiag 2017 2 14 42 3 143 154 154  Paradiag 2017 2 14 42 3 143 154 154  Paradiag 2017 2 14 42 3 143 154 154  Paradiag 2017 2 14 42 3 143 154 154  Paradiag 2017 2 14 42 3 143 154  Paradiag 2017 2 14 42 3 143 154  Paradiag 2017 2 14 42 3  Paradiag 2017 14 5 223 8 0 10  Paradiag 2017 14 5 228 9 0 00  Paradiag 2017 14 5 228 9 0 00  Paradiag 2017 14 2 225 0 127  Paradiag 2017 14 2 228 0 10  Paradiag 2017 14 10 220  Paradiag 2017		Test for overall effect:	Z = 0.05 (P	= 0.96)					Eavours [LCZ696] Eavours [ACEI/ARB]
Construct         Construction         Construction <td>C Note part is many part in the part of the</td> <td>С</td> <td>Forest plot of diarr</td> <td>hoea com</td> <td>parison.</td> <td>LC7</td> <td>696 g</td> <td>roup vs</td> <td>ACEI/ARB group</td> <td></td>	C Note part is many part in the part of the	С	Forest plot of diarr	hoea com	parison.	LC7	696 g	roup vs	ACEI/ARB group	
Bits Attain         CL2000         ALELARS         Weight Mit 100 455 (2)         Number 201         Number 201           Paradim 2017         6         229         5         255         255         255         1180 237, 251         1441 Fibra 2020 CL           Paradim 2017         2         442         3         143         155         0.67         1180 237, 251         1441 Fibra 2020 CL           Paradim 2017         2         920         100, 051         144 [0.86, 1.26]         0	Here Handling         Here Handling           Here Handling         Here Handling         Here Handling           Here Handling         Here Handling         Here Handling           Here Handling         Here Handling         Here Handling           Here Handling         Here Handling         Here Handling         Here Handling         Here Handling <th< td=""><td>0</td><td>Torest plot of uture</td><td>ioeu comp</td><td>-</td><td></td><td></td><td>roup vo.</td><td>nobinito gioup.</td><td></td></th<>	0	Torest plot of uture	ioeu comp	-			roup vo.	nobinito gioup.	
Image: 2017         6         223         5         255         103[0.61, 120]         mm.1, 120, 202, 204           Parameter 2017         2         142         3         143         1556         0.67 [0,11, 3.69]           Parameter 2017         2         142         3         143         1556         0.67 [0,11, 3.69]           Parameter 2017         2         142         3         143         1556         0.67 [0,11, 3.69]           Test of overall effect 2 = 0.41 [P = 0.55]         502         144         1556         0.67 [0,11, 3.69]           D         Forest plot of back print comparison: LC22696 group vs. ACEL/ARB group.         Factor and LC22684         Factor and LC22684         Factor and LC22684           Study or Subgroup         6.420         75         432.38         139 [0.23, 1.80]         Factor and LC22684         Factor and LC22684           Study or Subgroup         6.420         75         423.28         1.91 [0.23, 1.80]         Factor and LC22684         Factor and LC2268	Parameter 201         # 10         ACE / ARB group           Parameter 2017         6         4 20         95 / 1         100 / 1		Study or Subgroup	LCZ69t	5 /	ACEI	ARB	Woight	Risk Ratio	Risk Ratio
Parameter 2017       1       2       2       2       5       2       2       5       2       2       5       2       2       5       2       2       5       2       2       5       1       100       7       130       0.47       130       0.47       130       0.44       4.33         Trait (BYC, 0)       5071       5000       100.0%       1.44       0.44       0.44       0.1	Parameter 2017 1 2 14 23 143 155 156 075 01.13 19 0.47, 281 Rulo 2010 7 497 5 403 2.55 1.39 0.44, 4.35 Total (95% C) 507 1 509 100.0% 1.44 [0.46, 1.20] D Fortest plot of back phin comparison: LC2596 group vs. ACEL/ARB group: LC2596 ACEL/ARB Rule Rule Rule Rule Rule Rule Rule Rule	-	Paradiam 2014 #	10.4	4203	189	4220	03 5%	1 03 [0 85 1 26]	M+H, FIXed, 35% CI
Reline 2017       2       142       3       143       15%       0.67       113       0.67       0.67       113       0.67 <th0.67< th=""> <th< td=""><td>Particle 2017         2         142         3         135         0.07         0.15         <t< td=""><td></td><td>Parameter 2017</td><td>6</td><td>229</td><td>5</td><td>225</td><td>2.5%</td><td>1.18 [0.37, 3.81]</td><td>—<del>—</del>—</td></t<></td></th<></th0.67<>	Particle 2017         2         142         3         135         0.07         0.15 <t< td=""><td></td><td>Parameter 2017</td><td>6</td><td>229</td><td>5</td><td>225</td><td>2.5%</td><td>1.18 [0.37, 3.81]</td><td>—<del>—</del>—</td></t<>		Parameter 2017	6	229	5	225	2.5%	1.18 [0.37, 3.81]	— <del>—</del> —
Rulepe 2010       7       477       5       493       2.5%       1.39 (0.44, 4.35)         Total (6%) (2)       9571       5990       100,0%       1.34 (0.84, 1.26)         Test for overall effect 2 = 0.41 (P = 0.85)       7       0.40 (0.86, 1.26)         Test for overall effect 2 = 0.41 (P = 0.85)       7       0.40 (0.86, 1.26)         Paradigm 2010       6       6477       5       435       2.5%       0.40 (0.86, 1.26)         Paradigm 2014       6       422       447       100,0%       0.88 (0.42, 1.87)       100         Paradigm 2014       6       497       1.63       2.5%       0.896, 1.41       0.937, 3.871         Test for overall effect 2 = 0.12       1.13       1.55       1.13       0.82, 0.42, 1.871       1.15         Hoteoponenky: Tat = 0.24, 0.01 = 4.20       4.23       0.44, 0.35       0.896, 4.21, 1.871       1.15       1.15       1.16       1	Ruleps 2010       7       477       6       493       2.5%       1.39 (0.44, 4.35)         Test (957)C       299		Ratio 2017	2	142	3	143	1.5%	0.67 [0.11, 3.96]	
$ \begin{array}{c} \label{eq:spin} \\ \mbox{Test for overall effect 2 = 0.31 ($p^2 = 0.95$);} \\ \mbox{Test for overall effect 2 = 0.41 ($p^2 = 0.85$);} \\ \mbox{Test for overall effect 2 = 0.41 ($p^2 = 0.85$);} \\ \mbox{Test for overall effect 2 = 0.41 ($p^2 = 0.85$);} \\ \mbox{Test for overall effect 2 = 0.41 ($p^2 = 0.85$);} \\ \mbox{Test for overall effect 2 = 0.31 ($p^2 = 0.45$);} \\ \mbox{Test for overall effect 2 = 0.21 ($p^2 = 0.45$);} \\ \mbox{Test for overall effect 2 = 0.21 ($p^2 = 0.45$);} \\ \mbox{Test for overall effect 2 = 0.21 ($p^2 = 0.45$);} \\ \mbox{Test for overall effect 2 = 0.21 ($p^2 = 0.45$);} \\ Test for overall effect 2 = 0.21 ($p^2 = 0$	$ \begin{array}{c} \label{eq:product} \begin{tabular}{ c c c c c c c c c c c c c c c c c c c$		Ruilope 2010	7	497	5	493	2.5%	1.39 [0.44, 4.35]	
Total events         DUI         DUI         Total (DUI)         Total (D	Instrume         Description         Description <thdescription< th=""> <thdescription< th=""> <t< td=""><td></td><td>Total (05% Of</td><td></td><td>E074</td><td></td><td>Encr</td><td>100 001</td><td>10470.00 1000</td><td>1</td></t<></thdescription<></thdescription<>		Total (05% Of		E074		Encr	100 001	10470.00 1000	1
Hetrogenety: Ch <sup>2</sup> = 0.53, 0 <sup>2</sup> = 0.91; 0 <sup>2</sup> = 0.95; Test for ownall effect 2 = 0.41 (0 <sup>2</sup> = 0.08); 0 <sup>2</sup> = 0.95; Test for ownall effect 2 = 0.41 (0 <sup>2</sup> = 0.08); 0 <sup>2</sup> = 0.95; Study or Subarous Events Total Weight MH. Handam 595; Cl Paradigm 2014 # 164 4203 138 4220 54.6% 120 [0.06, 1.06] Parameter 2017 3 122 10 225 21.6% 0.22 [0.06, 1.06] Parameter 2017 3 122 10 225 21.6% 0.22 [0.06, 1.06] Parameter 2017 3 122 10 225 21.6% 0.22 [0.06, 1.06] Parameter 2017 3 122 10 225 21.6% 0.22 [0.06, 1.06] Parameter 2017 3 124 100.0% 0.88 [0.42, 1.87] Total events Trad Logical Exerts Total Weight MH. Flands 595; Cl Paradigm 2016 6 497 5 493 22.8% 1.19 [0.03, 271] Parameter 2018 Character	$\frac{1}{1000} = \frac{1}{1000} = \frac{1}{10000} = \frac{1}{10000} = \frac{1}{100000} = \frac{1}{1000000} = \frac{1}{10000000000000000000000000000000000$		Total (95% CI)	200	5071	202	5090	100.0%	1.04 [0.86, 1.26]	Ť
Start or varial effect Z = 0.14 (P = 0.69)         100         001	Test for overall effect 2 = 14 (p = 0.85)       10       0.1       10       10       10         D Forest plot of back pain comparison: LC2266 group vs. ACEU/ARB group.       Risk Ratio       Risk Ratio       Risk Ratio         Study or Subgroup       6       422       447       100.05       100         Paradige 2010       6       422       10       222       10.8       223       10.9       100         Test for overall of 01       3       229       10       222       10.8       220       10.9       100         Paradige 2010       6       492       447       100.0%       0.88 (0.42, 1.87)       100       100       100         Test for overall effect 2 = 0.17, 11       5.3       153       100 <td></td> <td>Heterogeneity: Chi2 =</td> <td>209 0.53. df = 3</td> <td>(P = 0.9</td> <td>202 1): l<sup>2</sup> =</td> <td>0%</td> <td></td> <td></td> <td></td>		Heterogeneity: Chi2 =	209 0.53. df = 3	(P = 0.9	202 1): l <sup>2</sup> =	0%			
D       Forest plot of back pair comparison: LC2696 group vs. ACEU/ARB group.       E2296       ACEU/ARB       Risk Ratio         Study or Subgroup.       Events Total Weight.       M.H. Bandoma, 555. Cl.       M.H. Bandoma, 555. Cl.       M.H. Bandoma, 555. Cl.         Paradigm 2014       F       164       4203       153       120 [05, 140]       M.H. Bandoma, 555. Cl.       M.H. Bandoma, 555. Cl.         Total (955. Cl)       4229       447       100.1%       0.88 [0.42, 1.87]       100.1%       100.1	D       Forest plot of back puin comparison: LC22696 group vs. ACEU/ARB group.       Factor 12 LC2091 Forest plot of back puin comparison: LC22696 ACEU/ARB group.       Factor 12 LC2091 Forest plot of back puin comparison: LC22696 aceu plot plot plot plot plot plot plot plot		Test for overall effect:	Z = 0.41 (P	= 0.68)	.,				0.01 0.1 1 10
b         Cross port of tack pull comparison: LC2696 group vs. ACEU/ARB group.           Line         Study of Suborov         Fevents         Total         Feature         Risk Ratio         Risk Ratio           Study of Suborov         6         400 1         38 (22)         0.06, 1.49         104         AceU/ARB           Paradym 2010         6         4.97         5 (43)         225         21.6%         0.20 (0.06, 1.49)           Paradym 2010         6         4.97         5 (43)         2.85         1.19 (0.97, 3.87)           Total (65% CI)         4020         4947         100.97         0.1 <td>Lu Promes part of tack pain comparison: L-2269 group vs. ACEL/ARB group. Study or Subgroup Events. Total Events. Total Weight M-H, Random, 95% Cl Paradam, 2014 71 164 4406 Paradam, 2017 3 229 10 225 216% 0.29 (0.06, 1.49) Paradam, 2016 6 497 1000% 0.88 (0.42, 1.87) Total events 173 153 Meterogeneity: Tat' = 0.28, 0. df = 2 (P = 0.11); H = 95% Meterogeneity: Tat' = 0.28, 0. df = 2 (P = 0.11); H = 95% Total events 173 153 Meterogeneity: Tat' = 0.28, 0. df = 2 (P = 0.11); H = 95% E Forest plot of nacopharyngilis comparison: LC2566 group vs. ACEL/ARB group. LC289 Reike, Raito Study or Subgroup Events. Total Events. Total Weight M-H, Elevel, 95%, Cl Paradam, 2017 3 142 0 143 0.35% rob (0.37, 1.39) (0.48, 3.40) Total events 2017 16 229 12 225 6.2% 1.31 (0.53, 271) Raito 2017 3 142 0 143 0.35% rob (0.37, 1.32) (1.49, 3.40) Total events 100 P events. Total Events. Total Events. Total Weight M-H, Elevel, 95%, Cl Paradam, 2017 16 229 12 225 6.2% 1.31 (0.53, 271) Raito 2017 3 142 0 (1.43, 0.35% rob (0.37, 1.32) (1.49, 1.40) Total events 2017 16 229 (1.206) group vs. ACEL/ARB group. LC2806 ACEL/ARB Risk Raito Study or Subgroup Events. Total Events. Total Weight M-H, Elevel, 39%, Cl Paradam, 2017 16 229 (1.206) group vs. ACEL/ARB group. LC2806 ACEL/ARB Risk Raito Study or Subgroup Events. Total Events. Total Weight M-H, Elevel, 39%, Cl Paradam, 2017 17 148 (2.8, 2.30) 224 (2.206 group vs. ACEL/ARB group. LC2806 ACEL/ARB Risk Raito Study or Subgroup Events. Total Events. Total Weight M-H, Elevel, 39%, Cl Paradam, 2017 13 142 (1.04, 0.2%, 7.650, 0.37, 1.350, 21 Paradam, 2017 13 142 (1.04, 0.2%, 7.650, 0.37, 1.350, 21 Paradam, 2017 13 142 (1.04, 0.2%, 7.650, 0.37, 1.350, 0.41 Paradam, 2017 13 142 (1.04, 0.2%, 7.650, 0.37, 1.350, 0.41 Paradam, 2017 13 142 (1.04, 0.2%, 7.650, 0.37, 1.350, 0.41 Paradam, 2017 13 142 (1.04, 0.2%, 7.650, 0.37, 1.350, 0.41 Paradam, 2017 13 142 (1.04, 0.2%, 7.650, 0.37, 1.350, 0.41 Paradam, 2017 13 142 (1.04, 0.2%, 7.350, 0.37, 0.41, 0.41, 0.350, 0.41, 0.41, 0.44, 1.</td> <td>-</td> <td>Demot 1 . 21</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>A (101/100</td> <td>Favours [LG2696] Favours [ACEI/ARB]</td>	Lu Promes part of tack pain comparison: L-2269 group vs. ACEL/ARB group. Study or Subgroup Events. Total Events. Total Weight M-H, Random, 95% Cl Paradam, 2014 71 164 4406 Paradam, 2017 3 229 10 225 216% 0.29 (0.06, 1.49) Paradam, 2016 6 497 1000% 0.88 (0.42, 1.87) Total events 173 153 Meterogeneity: Tat' = 0.28, 0. df = 2 (P = 0.11); H = 95% Meterogeneity: Tat' = 0.28, 0. df = 2 (P = 0.11); H = 95% Total events 173 153 Meterogeneity: Tat' = 0.28, 0. df = 2 (P = 0.11); H = 95% E Forest plot of nacopharyngilis comparison: LC2566 group vs. ACEL/ARB group. LC289 Reike, Raito Study or Subgroup Events. Total Events. Total Weight M-H, Elevel, 95%, Cl Paradam, 2017 3 142 0 143 0.35% rob (0.37, 1.39) (0.48, 3.40) Total events 2017 16 229 12 225 6.2% 1.31 (0.53, 271) Raito 2017 3 142 0 143 0.35% rob (0.37, 1.32) (1.49, 3.40) Total events 100 P events. Total Events. Total Events. Total Weight M-H, Elevel, 95%, Cl Paradam, 2017 16 229 12 225 6.2% 1.31 (0.53, 271) Raito 2017 3 142 0 (1.43, 0.35% rob (0.37, 1.32) (1.49, 1.40) Total events 2017 16 229 (1.206) group vs. ACEL/ARB group. LC2806 ACEL/ARB Risk Raito Study or Subgroup Events. Total Events. Total Weight M-H, Elevel, 39%, Cl Paradam, 2017 16 229 (1.206) group vs. ACEL/ARB group. LC2806 ACEL/ARB Risk Raito Study or Subgroup Events. Total Events. Total Weight M-H, Elevel, 39%, Cl Paradam, 2017 17 148 (2.8, 2.30) 224 (2.206 group vs. ACEL/ARB group. LC2806 ACEL/ARB Risk Raito Study or Subgroup Events. Total Events. Total Weight M-H, Elevel, 39%, Cl Paradam, 2017 13 142 (1.04, 0.2%, 7.650, 0.37, 1.350, 21 Paradam, 2017 13 142 (1.04, 0.2%, 7.650, 0.37, 1.350, 21 Paradam, 2017 13 142 (1.04, 0.2%, 7.650, 0.37, 1.350, 0.41 Paradam, 2017 13 142 (1.04, 0.2%, 7.650, 0.37, 1.350, 0.41 Paradam, 2017 13 142 (1.04, 0.2%, 7.650, 0.37, 1.350, 0.41 Paradam, 2017 13 142 (1.04, 0.2%, 7.650, 0.37, 1.350, 0.41 Paradam, 2017 13 142 (1.04, 0.2%, 7.650, 0.37, 1.350, 0.41 Paradam, 2017 13 142 (1.04, 0.2%, 7.350, 0.37, 0.41, 0.41, 0.350, 0.41, 0.41, 0.44, 1.	-	Demot 1 . 21						A (101/100	Favours [LG2696] Favours [ACEI/ARB]
LC2696         ACEURABE         Risk Ratio         Risk Ratio         MH. Random, 55% Cl         MH. Ratio, 55% Cl         MH. Ratio, 55% Cl         MH. Ratio, 55% Cl         MH. Ratio, 55% Cl           Parameter 2017         3         229         10         225         10%         0.29 (10%, 1.04)         10%	LC2096         ACELIARB         Risk Ratio         Risk Ratio         Risk Ratio           Study or Subgroup         Feature 11 and Weight         M-H. Random	D	Forest plot of back	pain com	parison	LCZ	.696 g	roup vs.	ACEI/ARB group	
Study or Subgroup         Events         Total         Weight         MH. Random. 95% Cl           Paradym 2014         # 164         4203         136         4201         56.5%         0.2010.66.106           Rulings 2010         6         447         10.05%         0.25         21.6%         0.2910.80.1.06           Rulings 2010         6         447         100.0%         0.88 [0.42, 1.67]         1.00           Total (95% Ch)         422         4947         100.0%         0.88 [0.42, 1.67]         1.00           Total events         173         153         153         1.00         1.00         1.00           Total events         Total         2.02         C.111/1 (* 95%)         1.00         1.00         1.00           E         Forest plot of asopharyngitis comparison: LCZ506 group vs. ACEL/ARB         Risk Reatio         Risk Reatio         Risk Reatio           Study or Subgroup         EC296         ACEL/ARB         Risk Reatio         Risk Reatio         Risk Reatio           Paradigm 2014         # 204         4203         175         4220         69.6%         0.82 [0.80, 0.91         0.01         0.1         0.1         0.01         0.1         0.01         0.01         0.01         0.01	Study of Subarous         Events         Total         Fearling         Total         Fearling         Meth. Random. 359; Cl.           Paradigm 2010         6         407         5         435; 2.0         100         5         455; 1.0           Pransiding 2010         6         407         5         432; 2.0         0.01			LCZ696	A	CEI/A	RB		Risk Ratio	Risk Ratio
Parameter 2017       3       229       10       222       225       225       226       220       100       220       100       220       100       220       100       220       100       220       100       220       100       220       100       220       100	remember 2017       102       4000       100       1.20 (10.61, 160)         Parameter 2017       6       497       5       463       22.65%       0.20 (10.61, 160)         Total (6%) C)       4220       4447       100.0%       0.88 (0.42, 1.87)         Total (6%) C)       4220       447       100.0%       0.88 (0.42, 1.87)         Heterogeneity: Tati = 0.28; C/H = 4.50, df = 2 (P = 0.11); P = 55%       Test for overall effect 2 = 0.33 (P = 0.74)       Test for overall effect 2 = 0.33 (P = 0.74)         E       Forest plot of macopharynghis comparison: LCZ696 group vs. ACEL/ARB group.       Risk Ratio       Risk Ratio       MH. Flord, 95% Cl         Study or Subaroup. Fvents Total Events Total Weight MH. Flord, 95% Cl       MH. Flord, 95% Cl       MH. Flord, 95% Cl       MH. Flord, 95% Cl         Forest plot of bronchitis comparison: LCZ696 group vs. ACEL/ARB group.       Lc22690 Favours (LC2690 Favours (LC2690 Favours (LC2690 Forours (LC2690	-	Study or Subgroup	Events T	otal Ev	120	Total 4220	Weight	M-H, Random, 95% (	M-H. Random, 95% Cl
Rulepsize       Constrained (1) (0) (0) (0) (0) (0) (0) (0) (0) (0) (0	Patispe 2010         6         407         5         433         22.8%         110 [037, 3.87]           Total events         173         153         153         153         153         153           E Forest plot of nasopharyngitis companison: LCZ696 group vs. ACEI/ARB group.         Risk Ratio         Risk Ratio         Risk Ratio         Risk Ratio           Stady or Subarous         Events         120         104         120         103         132         104         100           Fatio 2017         16         142         120         120         100, 73         132         104         120         100         120         101         100         100           Fatio 2014         163         232         144         203         234         203         234         233         245         120         120         100         100         100         100         100		Parameter 2014 #	164 4	203	10	+229	21.6%	0.29 0.08 1.49	<b>_</b>
Total (95% Cl)       4929       4947       100.0%       0.88 [0.42, 1.87]         Total events       173       153         Heterogeneity: Trait = 0.26; Chi* = 4.50, df = 2 (P = 0.11); P = 55%       0.01       0.1	Total (95%, CI)       4220       4447       100.0%, 0.88 (0.42, 1.87)         Test or evental effect 2 = 0.33 (P = 0.74)       103       104       1		Ruilope 2010	6	497	5	493	23.8%	1.19 [0.37, 3.87	
Total (95% C)       423       4447       100.0%       0.88 [0.42, 1.87]         Total events       20,82 ChP = 4.50, df = 2 (P = 0.11); P = 5%,       10.1       1       10.1       10.0         Test for overall effect 2 = 0.32 (ChP = 4.50, df = 2 (P = 0.11); P = 5%,       Risk Ratio       Risk Ratio       Risk Ratio         Study or Subgroup       EC2596       ACEI/ARB       Risk Ratio       Risk Ratio       Risk Ratio         Paradigm 2014       # 204 4203       175 4220       69.9%, 1.17 (0.86, 1.43)       Risk Ratio       Risk Ratio         Paradigm 2014       # 204 4203       175 4220       69.9%, 1.17 (0.86, 1.43)       Risk Ratio       Risk Ratio         Total events       Total events       Total (95%, Cl)       5071       5090       100.0%, 1.20 (1.00, 1.45)       100         F forest plot of bronchitis comparison: LC2596       ACEI/ARB       Risk Ratio       Risk Ratio       Risk Ratio         Study or Subgroup       Events       Total Weight, MH-H Exed, 95%, Cl       M-H, Fixed, 95%, Cl       M	Total (eSS: Cl)       423       4447       100.%       0.88 [6.42, 1.87]         Total events       100       100       100       100       100         Fest for varial fields: 2 = 0.32 (bF) = 4.50, df = 2 (P = 0.11); P = 5%,       0.1       100       100       100         E Forest plot of nasopharyngitis comparison: LCZ566 group vs. ACEU/ARB group.       LCZ566       ACEU/ARB       Risk Ratio       Risk Ratio       Risk Ratio         Stady or Subgroup       E Varial Events       Total events </td <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>									
Total events       173       153         Heterogeneity: Tau* = 0.28, Ch* = 4.50, df = 2 (# = 0.11); P = 56%       0.01       0.1       100         E Forest plot of macopharyngits comparison: LCZ696 group vs. ACEU/ARB group.       LCZ296       ACEU/ARB       Risk Ratio         Study or Subgroup       Events       Total       Vigint       M-H. Excel .95% CI       M-H. Excel .95% CI         Paranter: 2017       16       229       8.9%, 1.17 (0.66, 1.43, 2.71)       Risk Ratio       M-H. Excel .95% CI         Paranter: 2017       16       229       12       22.5       6.2%, 1.31 (0.33, 2.71)         Ratiopa 2010       9.497       7.483       3.5%       1.28 (0.48, 3.40)         Total (95% CI)       5071       5090       100.0%       1.20 (1.00, 1.45)         Total (95% CI)       5071       5090       100.0%       2.02 (0.80, 0.98)         Rulopa 2010       5       497       6       432       2.5%       0.62 (0.80, 0.98)         Rulopa 2011       1.02       2.02       5.5%       0.62 (0.80, 0.98)       0.01       0.1       1.0       100         Ferrost plot of fuzziness comparison: LCZ506 group vs. ACEL/ARB       Risk Ratio       Nisk Ratio       Nisk Ratio       Nisk Ratio       Nisk Ratio         Stud	Total events       173       153       163       153       163       153       163       153       163       153       163       153       163       153       163       153		Total (95% CI)	4	929		4947	100.0%	0.88 [0.42, 1.87]	-
Prest Rovers (Lo22, 0, 1, 1, 2, 2, 0, 1, 2, 2, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1,	Participation (1, 1, 1, 1, 2, 2, 2, 1, 2, 1, 2, 1, 2, 1, 2, 1, 2, 1, 2, 1, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2, 2,		Total events	173	4.50 46	153	- 0.44	12 - 500/		
E Forest plot of nasopharyngitis comparison: LCZ696 group vs. ACEL/ARB group.       E/E2696       Aceu/ARB         Study or Subgroup       Events Total       Events Total       Weight       M-H. Exect 95% CI         Paradign 2014       # 244 203       175       Aceu/ARB       M-H. Exect 95% CI         Paradign 2014       # 244 203       175       Aceu/ARB       M-H. Exect 95% CI         Parameter 2017       16       229       12       225       6.2%       1.31 (0.83, 2.71)         Ratio 2017       3       142       0.143       0.3%       7.05 (0.37, 13.24)         Total (95% CI)       5071       5090       100.0%       1.20 [1.00, 145]         Total venits       Intercogenetity: Ch <sup>2</sup> = 1.50, df = 3 (P = 0.68); P = 0%       Risk Ratio       Risk Ratio         Study or Subgroup       Ecrets Total Evenits       Total evenits       Total evenits       Total evenits         Study or Subgroup       Events Total       Events Total       Fisk Ratio       Risk Ratio         Study or Subgroup       Events Total       Events       Total events       Total events       Total events         Study or Subgroup       Events Total       Events       Total events       Total events       Total events       Total events         Study or Subgr	Forest plot of masopharyngits comparison: LCZ596 group vs. ACEL/ARB group.         LCZ596 ACEUARB       Risk Ratio         Blady or Subgroup - Events Total Events Total Weight M-H Event 395 CL         Paradigm 2014 # 204 4203 175 4229 80.% 1.17 (0.86, 1.43)         Paradigm 2014 # 204 4203 175 4229 80.% 1.17 (0.86, 1.43)         Paradigm 2014 # 229 12 225 6.2% 1.31 (0.63, 2.71)         Method 2014 # 203 175 4229 80.% 1.17 (0.86, 1.43)         Paradigm 2017 16 229 17 2225 6.2% 1.31 (0.63, 3.40)         Total (95% CL) 5071 5090 100.0% 1.20 (1.00, 1.45)         Total events Total Events Total Weight M-H Event 395% CL         Blady or Subgroup Events Total Weight M-H Event 395% CL         Blady or Subgroup Events Total Weight M-H Event 395% CL         Blady or Subgroup Events Total Weight M-H Event 395% CL         Blady or Subgroup Events Total Weight M-H Event 395% CL         Blady or Subgroup Events Total Weight M-H Event 395% CL         Blady or Subgroup Events Total Weight M-H Event 395% CL         Blady or Subgroup Events Total Weight M-H Event 395% CL         Blady or Subgroup Events Total Weight M-H Event 395% CL         Blady or Subgroup Events Total Weight M-H Event 395% CL         Blady or Subgroup Events Total Weight M-H Event 395% C		Heterogeneity: Tau* = 0	.26; Chi* =	4.50, df =	= 2 (P	= 0.11)	; 1* = 56%		0.01 0.1 1 10
E Fores plot of nasopharyngitis comparison: LCZ696 group vs. ACEL/ARB group. LCZ996 ACEU/ARB Risk Ratio Study or Subgroup Events Total Events Total Weight M-H. Fixed, 55% CI Paradigm 2014 # 204 4203 175 4229 89.9% 1.17 [046, 1.43] Parameter 2017 16 1229 12 225 6.2% 1.17 [046, 1.43] Parameter 2017 16 1229 12 225 6.2% 1.128 [048, 304] Total (95% CI) 5071 5090 100.0% 1.20 [1.00, 1.45] Total (95% CI) 5071 5090 100.0% 1.20 [1.00, 1.45] Total (95% CI) 5071 5090 100.0% 0.22 [0.68, 0.98] Total (95% CI) 5497 8 493 3.8% 0.22 [0.68, 0.98] Total (95% CI) 5497 8 493 3.8% 0.22 [0.68, 0.98] Total (95% CI) 5497 8 493 3.8% 0.22 [0.68, 0.98] Total (95% CI) 5497 8 493 3.8% 0.22 [0.68, 0.98] Total (95% CI) 5497 8 493 3.8% 0.22 [0.68, 0.98] Total (95% CI) 5497 8 493 3.8% 0.22 [0.68, 0.98] Total (95% CI) 5497 8 493 3.8% 0.22 [0.68, 0.98] Total (95% CI) 5497 8 493 3.8% 0.22 [0.68, 0.98] Total (95% CI) 5497 8 493 3.8% 0.22 [0.68, 0.98] Total (95% CI) 5497 8 493 3.8% 0.22 [0.68, 0.98] Total (95% CI) 5497 8 493 3.8% 0.22 [0.68, 0.98] G Forest plot of dizziness comparison: LCZ696 group vs. ACEL/ARB group. LCZ696 ACEU/ARB Risk Ratio Study or Subgroup Events Total Events Total Weight M-H. Fixed, 55% CI Paradigm 2014 # 266 4203 226 4229 9.25% 1.30 [109, 1.55] Parameter 2017 12 229 12 225 55% 0.98 [0.63, 1.152] Total events 284 222 55.5% 0.98 [0.63, 1.152] Total events 284 222 57.5% 0.98 [0.61, 1.52] Parameter 2017 12 4229 12 227 52% 0.98 [0.61, 1.52] Total events 284 222 57.5% 0.98 [0.61, 1.52] Total events 284 222 57.5% 0.98 [0.61, 1.52] Parameter 2017 13 422 0 143 0.2% 7.05 [0.37, 135.24] Rulops 2010 3 497 4 493 1.8% 0.74 [0.17, 3.31] Total (95% CI) 5071 5090 100.0% 0.99 [0.71, 1.52] Parameter 2017 14 228 0.2% 7.3% 0.98 [0.61, 1.52] Parameter 2017 14 228 0.2% 7.3% 0.98 [0.61, 1.52] Parameter 2017 14 228 0.2% 7.3% 0.98 [0.61, 1.52] Parameter 2017 14 228 0.004 7.94 0.99 [0.62, 7.136] Paradigm 2014 103 4203 106 4229 7.92% 1.40 [0.63, 5.61] Paradigm 2014 103 4203 106 4229 7.92% 1.40 [0.63, 5.61] Paradigm	E Forest plot of nasopharyngitis comparison: LCZ596 group vs. ACEL/ARB group. LCZ96 ACEL/ARB Risk Ratio Paradigm 2014 # 204 4200 117 4222 80.9%, 1.17[0.96,1.43] Paradigm 2014 # 204 4200 117 4222 80.9%, 1.17[0.96,1.43] Paradigm 2014 # 204 4200 117 4222 80.9%, 1.17[0.96,1.43] Paradigm 2010 9 497 7 403 3.6%, 1.28[0.48,3.40] Total (95% CI) 5071 5090 100.0%, 1.20[1.00,1.45] Total (95% CI) 5071 5090 100.0%, 1.20[1.00,1.45] Total (95% CI) 5071 5090 100.0%, 1.20[1.00,1.45] Total (95% CI) 4700 4722 100.0%, 0.82[0.88, 0.99] Total events 188 4203 224 4229 06.5%, 0.82[0.88, 0.99] Total events 188 4203 224 4229 06.5%, 0.82[0.88, 0.99] Total events 188 4203 224 4229 06.5%, 0.82[0.88, 0.99] Total events 188 232 Heterogeneity: Ch <sup>2</sup> = 2.4, df = 1(P = 0.82); P = 0% Test for overall effect Z = 2.44 (P = 0.03) Total events 188 232 Heterogeneity: Ch <sup>2</sup> = 2.4, df = 1(P = 0.82); P = 0% Test for overall effect Z = 2.44 (P = 0.03) G Forest plot of dizziness comparison: LCZ696 group vs. ACEL/ARB group. LC2696 ACEL/ARB Risk Ratio Study or Subgroup Events Total Weight M-H.Fixed.95% CI Paradigm 2014 # 264 403 206 4229 225% 1.001 0.01 0.1 0.1 0.1 0.1 0.1 0.1 0.1			0.00 (i	0.14)					Favours [LCZ696] Favours [ACEI/ARB]
LC2296         ACEUARB         Risk Ratio         Risk Ratio           Study or Subgroup         Events         Total         Vents         Total         Vents         Total         Vents         Total         Vents         Total         Vents	LC2696 ACEI/ARB Reis Reis Reis AcEi/ARB Reis Reis AcEi/ARB Reis Reis AcEi/ARB Reis	Е	Forest plot of nasop	haryngitis	s compa	rison	LCZ	696 grou	p vs. ACEI/ARB g	oup.
Study or Subgroup         Events         Total         Weight         MH-Liked. 35% CL         MH-Liked. 35% CL           Parameter 2017         3         142         02         133         0.3%         7.05         0.37         0.43         0.3%         0.10         0.53         0.44         0.44         0.42         0.42         0.43         0.3%         7.05         0.37         0.53         0.44         0.44         0.43         0.3%         7.05         0.37         0.53         0.44         0.44         0.44         0.44         0.45         0.44         0.44         0.44         0.44         0.44         0.45         0.44         0.44         0.45         0.44	Study or Subgroup         Events         Total         Weight         M-H. Fixed         55:0         M-H. Fixed         95:0           Parameter 2017         16         229         12         226         6.2%         1.31 [0.63, 2.71]           Ratio 2017         142         0.43         0.3%         750 [0.3, 13:52]         1.31 [0.63, 2.71]           Ratio 2017         13         142         0.43         0.3%         750 [0.3, 13:52]           Total (95% CI)         5071         5090         100.0%         1.20 [1.00, 1.45]         1.0         0.1         0.1         0.1         0.1         0.0         1.0         1.0         1.00			LCZ696	5 /	ACEI//	ARB		Risk Ratio	Risk Ratio
Paradign 2014 #       204       4200       175       4229       82.95%       1.17 [D.96, 1.43]         Parameter 2017       13       142       225       62.97       1.31 [D.83, 2.17]         Ratic 2017       3       142       0       143       0.3%       7.05 [D.37, 135, 2.4]         Ruicpe 2010       9       497       7       493       3.6%       1.28 [D.48, 3.40]         Total (95% CI)       5071       5090       100.0%       1.20 [1.00, 1.45]         Total (95% CI)       5071       5090       100.0%       1.20 [1.00, 1.45]         Extraction overail effect: Z = 1.92 (P = 0.05); P = 0%       10       10       10       10         Study or Subgroup       Cents Total       Weight       M-H. Fixed, 35% CI       M-H. Fixed, 35% CI       M-H. Fixed, 35% CI         Paradigm 2014       #       143       4203       2.4229       96.5%       0.42 [D.68, 0.98]       0.01       0.1       10       10       100         Forest plot of dizzines comparison: LCZ696 group vs. ACEI/ARB group.       LCZ6866       ACEI/ARB       Cital (95% CI)       4167       10       100       100       Favours [LCZ686]       Favours [LCZ686]       Favours [LCZ686]       Favours [LCZ686]       Favours [LCZ686]       Favo	Paraging 2014 #       204 4203       175 4229       62%       1.17 [068, 1.43]         Parameter 2017       16 429       12 225       6.2%       1.31 [063, 2.71]         Ratio 2017       3 142       0.143       0.3%       7.05 [03, 155.24]         Ratio 2017       3 142       0.143       0.3%       7.05 [03, 155.24]         Total (95% C)       5071       5090 100.0%       1.20 [1.00, 1.45]         Total (95% C)       5071       5090 100.0%       ACEI/ARB       Risk Ratio         Heterogeneity: Ch <sup>2</sup> = 1.59.2 (P = 0.65)       Favours [LC2596]       Favours [LC2596]       Favours [LC2596]         For cest plot of bronchitis comparison: LC2696 group vs. ACEI/ARB group.       NLS 200, 68, 0.98]       NH. Fixed, 55% CI         Total (95% C)       4700       4722 100.0%       0.82 [0.68, 0.98]       NH. Fixed, 55% CI         Total (95% C)       4700       4722 100.0%       0.82 [0.8, 0.98]       NH. Fixed, 55% CI         Study or Subgroup       Events       Total (95% C)       100       Favours [LC2596]       Favours [LC2596]         Study or Subgroup       Events       Total (95% C)       5071       5090 100.0%       1.28 [1.08, 1.52]       NH. Fixed, 55% CI         Pandigm 2014       # 249       0.2%       7.56 [0.37, 155.54]	_	Study or Subgroup	Events 1	Total E	rents	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
Parameter 2017       16       229       12       225       6.2%       1.31       1063.2.71         Raito 2017       3       142       0.143       0.3%       7.05       0.53       0.53       0.44         Ruitope 2010       9       497       7       493       3.6%       1.28       0.44, 3.40         Total events       232       194         Heterogeneity: Ch <sup>2</sup> = 1.50, df = 3 (P = 0.68); P = 0%       0.01       0.01       Favours [LC2696]       Favours (LC2696]	Parameter 2017       16       229       12       225       6.2%       1.31 [0.63, 2.71]         Ratio 2017       3       142       0.143       0.3%       7.05 [0.37, 135.24]         Ratio 2010       9       497       7       433       3.8%       1.28 [0.48, 3.40]         Total events       232       194       142       0.143       0.3%       1.20 [1.00, 1.45]         Total events       232       194       142       0.01       0.1       10         Fet for overall effect: Z = 150 (ff = 0.05); F = 0%       CEL/ARB       Risk Ratio       Risk Ratio         Study or Subgroup       Events Total Events       Total (95% CI)       470       4722       100.0%       0.82 [0.88, 0.99]         Total 6% CI)       470       4722       100.0%       0.82 [0.88, 0.98]       100       100         Study or Subgroup       Events Total Events       Total 6% CI       470       4722       100.0%       0.82 [0.8, 0.98]         Total 6% CI)       470       4722       100.0%       0.82 [0.8, 0.98]       100       144       165 CI         Budy or Subgroup       Events Total Events Total Weight       MH + Exed 5% CI       MH + Exed		Paradigm 2014 #	204 4	4203	175	4229	89.9%	1.17 [0.96, 1.43]	
Ratio 2017       3       142       0       143       0.3%       7.05 [0.37, 155.24]         Ratiope 2010       9       497       7       493       3.6%       1.28 [0.48, 3.40]         Total (95% Cl)       5071       5090       100.0%       1.20 [1.00, 1.45]         Total (95% Cl)       5071       5090       100.0%       1.20 [1.00, 1.45]         Test for overall effect: Z = 1.92 (P = 0.05)       0.01       0.1       0.1       10         F Forest plot of bronchitis comparison: LCZ696 accEl/ARB       Risk Ratio       Risk Ratio       Risk Ratio         Study or Subgroup       Events       Total (95% Cl)       4700       4722       100.0%       0.82 [0.68, 0.99]         Total (95% Cl)       4700       4722       100.0%       0.82 [0.68, 0.99]       MH. Fixed, 95% Cl       MH. Fixed, 95% Cl         Paracigm 2014       # 100       492       9.0%       0.82 [0.68, 0.99]       1.00 [1.00, 1.55]         Forest plot of dizziness comparison: LCZ696 group vs. ACEL/ARB group.       LCZ2696       ACEI/ARB       Risk Ratio         Study or Subgroup       Events       Total Weight       MH. Fixed, 95% Cl       MH. Fixed, 95% Cl         Paracigm 2014       126 4229       222       5.5%       0.98 [0.67, 1.52]       MH. F	Ratio 2017       3       142       0       143       0.3%       7.05 [0.37, 155.24]         Rule 2010       9       497       7       493       3.6%       1.28 [0.48, 3.40]         Total (95% CI)       5071       5090       100.0%       1.20 [1.00, 1.45]         Total (95% CI)       5071       5090       100.0%       1.20 [1.00, 1.45]         Total (95% CI)       100       Forest plot of bronchitis comparison: LCZ696 group vs. ACEL/ARB group.       CC2696       ACEI/ARB       Risk Ratio         Study or Subaroup       Events       Total (95% CI)       4700       4722       100.0%       0.82 [0.68, 0.99]         Rolique 2010       5       477       8 493       3.5%       0.82 [0.68, 0.99]       M.H. Fixed, 95% CI       M.H. Fixed, 95% CI         Total (95% CI)       4700       4722       100.0%       0.82 [0.68, 0.99]       M.H. Fixed, 95% CI       M.H. Fixed, 95% CI         Parametry culf       LC2.2696       ACEI/ARB       Risk Ratio       Risk Ratio         Study or Subaroup       Events Total       Weight M.H. H. Exed, 95% CI       M.H. Fixed, 95% CI         Parametry culf       122       228       5.50       96 [0.45, 214]       M.H. Fixed, 95% CI         Paradign 2014       264 <th< td=""><td></td><td>Parameter 2017</td><td>16</td><td>229</td><td>12</td><td>225</td><td>6.2%</td><td>1.31 [0.63, 2.71]</td><td></td></th<>		Parameter 2017	16	229	12	225	6.2%	1.31 [0.63, 2.71]	
Ruliope 2010       9       497       7       493       3.5%       1.28 [0.48, 3.40]         Total (95% CI)       5071       5090       100.0%       1.20 [1.00, 1.45]         Total (95% CI)       5071       5090       100.0%       1.20 [1.00, 1.45]         Test for overall effect: Z = 1.52 (P = 0.65)       CEVARB       Risk Ratio         F Forest plot of bronchitis comparison: LCZ696 group vs. ACEU/ARB group.       LC2696 ACEVARB       Risk Ratio         Study or Subgroup       Events       Total (95% CI)       MH. Fixed, 95% CI         Paradigm 2014 #       183       4203       224       4229       96.5%       0.82 [0.68, 0.99]         Total (95% CI)       4700       4722       100.0%       0.82 [0.68, 0.99]       MH. Fixed, 95% CI         Total (95% CI)       4700       4722       100.0%       0.82 [0.68, 0.99]       MH. Fixed, 95% CI         Total (95% CI)       4700       4722       100.0%       0.82 [0.68, 0.99]       MH. Fixed, 95% CI         Total (95% CI)       108       C229       6.25%       1.30 [1.09, 1.55]       Paradigm 2014       HE e0.62); Paradigm 2014       HE e0.62); Paradigm 2014       MH. Fixed, 95% CI         Study or Subgroup       Events       Total Weight       MH. Fixed, 95% CI       MH. Fixed, 95%	Number 2010       9       497       7       493       3.6%       1.28 [0.48, 3.40]         Total (95%, Cl)       5071       5090       100.0%       1.20 [1.00, 1.45]         Total events       232       194         Heterogeneity: Ch <sup>12</sup> = 1.50, df = 3 (P = 0.68); P = 0%       0.01       0.1       1       10         Test for overall effect Z = 1.90 (F = 0.68); P = 0%       CEUARB       Risk Ratio       Risk Ratio         Study or Subgroup       C2696       ACEUARB       Risk Ratio       Risk Ratio         Total (95%, Cl)       4700       4722       100.0%       0.82 [0.88, 0.99]       MH. Fixed, 95% Cl         Paradigm 2014       #       148       4203       224       4229       96.5%       0.82 [0.88, 0.99]         Total (95%, Cl)       4700       4722       100.0%       0.82 [0.88, 0.99]       MH. Fixed, 95% Cl         Test for overall effect Z = 2.14 (P = 0.03)       CEUARB       Risk Ratio       Risk Ratio         Study or Subgroup       Cornets Total       Weight       MH. Fixed, 95% Cl       MH. Fixed, 95% Cl         Paradigm 2014       226       ACEUARB       Risk Ratio       Risk Ratio         Study or Subgroup       Forest plot of headache comparison: LCZ696 group vs. ACEU/ARB group.       C2696 <td></td> <td>Ratio 2017</td> <td>3</td> <td>142</td> <td>0</td> <td>143</td> <td>0.3%</td> <td>7.05 [0.37, 135.24]</td> <td></td>		Ratio 2017	3	142	0	143	0.3%	7.05 [0.37, 135.24]	
Total (95% CI)       5071       5090       100.0%       1.20 [1.00, 1.45]         Total events       232       194         Heterogenety: Ch <sup>2</sup> = 1.50, (P = 0.05)       0.01       0.1       10         F Forest plot of bronchitis comparison: LCZ696 group vs. ACEI/ARB group.       Risk Ratio       Risk Ratio         Study or Subgroup       Events       Total Events       764       95% CI         Paradigm 2014 #       183       4203       224       4229       96.5%       0.82 [0.68, 0.99]         Rule pe 2010       5       497       6       493       3.5%       0.62 [0.20, 1.89]         Total (95% CI)       4700       4722       100.0%       0.82 [0.68, 0.98]       MH. Fixed, 95% CI         Heterogenety: Ch <sup>2</sup> = 0.24, let 1 = 0.63, let 1 = 0.66, let 1 = 0.05%       0.01       0.1       0.1       0.1       10       10         G       Forest plot of dizziness comparison: LCZ696 group vs. ACEI/ARB group.       LCZ696       ACEI/ARB       Risk Ratio       Risk Ratio         Study or Subgroup       LCZ696 droup vs. ACEI/ARB       Risk Ratio       Risk Ratio       Risk Ratio         Study or Subgroup       LCZ696 group vs. ACEI/ARB       Risk Ratio       Risk Ratio       Risk Ratio         Study or Subgroup       Events	$ \begin{array}{c} \mbox{Total (95% Cl)} & 5071 & 5090 & 100.0\% & 1.20 [1.00, 1.45] \\ \mbox{Total events} & 232 & 144 \\ \mbox{Hetrogenehy: Ch^P = 1.50, df = 2 (P = 0.68); P = 0\% \\ \mbox{Test for overall effect Z = 1.52 (P = 0.05) \\ \mbox{Test for overall effect Z = 1.52 (P = 0.05) \\ \mbox{LC2696} & ACEUARB & Risk Ratio \\ \mbox{Subgroup} & Events & Total Events & Total Weight & M-H, Fixed, 95% Cl \\ \mbox{Paradigm 2014 } & 133 4203 & 224 422 9 65.\% & 0.82 [0.68, 0.99] \\ \mbox{Rulope 2010} & 5 & 497 & 8 & 493 & 3.5\% & 0.62 [0.20, 1.88] \\ \mbox{Test for overall effect Z = 1.4 (P = 0.62); P = 0\% \\ \mbox{Test for overall effect Z = 0.4 (f = 1 (P = 0.62); P = 0\% \\ \mbox{Test for overall effect Z = 0.4 (f = 1 (P = 0.62); P = 0\% \\ \mbox{Test for overall effect Z = 2.14 (P = 0.62); P = 0\% \\ \mbox{Test for overall effect Z = 2.14 (P = 0.62); P = 0\% \\ \mbox{Test for overall effect Z = 2.14 (P = 0.62); P = 0\% \\ \mbox{Test for overall effect Z = 2.14 (P = 0.62); P = 0\% \\ \mbox{Test for overall effect Z = 2.14 (P = 0.62); P = 0\% \\ \mbox{Test for overall effect Z = 2.14 (P = 0.62); P = 0\% \\ \mbox{Test for overall effect Z = 2.14 (P = 0.62); P = 0\% \\ \mbox{Test for overall effect Z = 2.26, df = 3 (P = 0.52); P = 0\% \\ \mbox{Test for overall effect Z = 2.28 (P = 0.004) \\ \mbox{H is Ratio } \mbox{Ratio overall effect Z = 2.88 (P = 0.004) \\ \mbox{H is Ratio } \mbox{Ratio overall effect Z = 2.88 (P = 0.004) \\ \mbox{H is Ratio } \mbox{Signorup } \mbox{LC2696 group vs. ACEL/ARB group. \\ \mbox{LC2696 ACEUARB } \mbox{Odds Ratio } \Odds Ra$		Ruilope 2010	9	497	7	493	3.6%	1.28 [0.48, 3.40]	
Total events       232       194       Total function       Total provider         Total events       232       194       Total function       Total provider       Total provider         Test for overall effect: 2 = 1.50, df = 3 (P = 0.68); P = 0%       Total provider       Total provider <t< td=""><td>Total events       222       194       100 more intermediation intermediatintermediatexemetation intermediatintexemetation inte</td><td></td><td>Total (95% CI)</td><td></td><td>5071</td><td></td><td>5090</td><td>100.0%</td><td>1.20 [1.00, 1.45]</td><td>•</td></t<>	Total events       222       194       100 more intermediation intermediatintermediatexemetation intermediatintexemetation inte		Total (95% CI)		5071		5090	100.0%	1.20 [1.00, 1.45]	•
Heterogeneity: Ch <sup>2</sup> = 1.50, df = 3 (P = 0.68); P = 0%       0.01       0.01       0.01       10       10       10         F Forest plot of bronchittis comparison: LC2696 accEl/ARB       Risk Ratio       Risk Ratio       Risk Ratio       Risk Ratio         Study or Subgroup       Events       Total       Events       Total       Events       Total       Events       Total       Events       Total       Favours [LC2696]       ACEI/ARB       Risk Ratio         Study or Subgroup       Events       108       232       Hoterogeneity: Ch <sup>2</sup> = 0.24, df = 1 (P = 0.62); P = 0%       0.01       0.1       0.1       10       10       100         Feetorest plot of dizziness comparison: LC2696 group vs. ACEI/ARB group.       Events       Total events       108       232       Hoterogeneity: Ch <sup>2</sup> = 0.44 (P = 0.63); P = 0%       10.01       0.1       10       10       100         Feroest plot of dizziness comparison: LC2696 group vs. ACEI/ARB group.       Events       Total events       Total events       Total events       128       7.05 (0.1)       0.1       0.1       10       100       Favours [LC2696]       ACEI/ARB       Risk Ratio         Study or Subgroup       Events       Total Weight       MH-L Fixed, 95% Cl       MH-L Fixed, 95% Cl       MH-L Fixed, 95% Cl       MH-L Fixed, 95% Cl <td><math display="block">\begin{array}{c} \text{Heterogeneity: } Ch^2 = 1.50, df = 3 (P = 0.68); P = 0\% \\ Test for overall effect: Z = 1.92 (P = 0.05) \\ \hline 0.01 &amp; 0.1 &amp; 1 &amp; 0 \\ \hline 0.01 &amp; 0.1 &amp; 1 &amp; 0 \\ \hline 0.01 &amp; 0.1 &amp; 1 &amp; 0 \\ \hline 0.01 &amp; 0.1 &amp; 1 &amp; 0 \\ \hline 0.01 &amp; 0.1 &amp; 0 \\ \hline 0.01 &amp; 0 \\ </math></td> <td></td> <td>Total events</td> <td>232</td> <td></td> <td>194</td> <td></td> <td></td> <td></td> <td></td>	$\begin{array}{c} \text{Heterogeneity: } Ch^2 = 1.50, df = 3 (P = 0.68); P = 0\% \\ Test for overall effect: Z = 1.92 (P = 0.05) \\ \hline 0.01 & 0.1 & 1 & 0 \\ \hline 0.01 & 0.1 & 1 & 0 \\ \hline 0.01 & 0.1 & 1 & 0 \\ \hline 0.01 & 0.1 & 1 & 0 \\ \hline 0.01 & 0.1 & 0 \\ \hline 0.01 & 0 \\ $		Total events	232		194				
Test for overall effect: Z = 1.92 (P = 0.05)       UT       1 <td< td=""><td>Test for overall effect: Z = 1.92 (P = 0.05)       U1       1       1       1       100       1       1       100       1       1       100       100       1       100       1       100       100       1       100       <td< td=""><td></td><td>Heterogeneity: Chi<sup>2</sup> = '</td><td>.50, df = 3</td><td>(P = 0.68</td><td>3); 1<sup>2</sup> =</td><td>0%</td><td></td><td></td><td></td></td<></td></td<>	Test for overall effect: Z = 1.92 (P = 0.05)       U1       1       1       1       100       1       1       100       1       1       100       100       1       100       1       100       100       1       100 <td< td=""><td></td><td>Heterogeneity: Chi<sup>2</sup> = '</td><td>.50, df = 3</td><td>(P = 0.68</td><td>3); 1<sup>2</sup> =</td><td>0%</td><td></td><td></td><td></td></td<>		Heterogeneity: Chi <sup>2</sup> = '	.50, df = 3	(P = 0.68	3); 1 <sup>2</sup> =	0%			
Forest plot of bronchitis comparison: LCZ696 group vs. ACEI/ARB group.         LC2696 ACE/ARB Risk Ratio         Study or Subgroup Events Total Weight MH. MH, Fixed, 95% CL       MH, Fixed, 95% CL         Paradigm 2014 #       183 4203       224 4229       96.5%       0.82 [0.68, 0.99]         Total (95% CL)       4700       4722       100.0%       0.82 [0.68, 0.99]         Total (95% CL)       4700       4722       100.0%       0.82 [0.68, 0.99]         Total (95% CL)       4700       4722       100.0%       0.82 [0.68, 0.99]         Total (95% CL)       4700       4722       100.0%       0.82 [0.68, 0.99]         Total (95% CL)       4710       100       100       100         Favours [LC2696       ACEI/ARB       Risk Ratio       Risk Ratio         Study or Subgroup       Events       Total Weight       H-Fixed, 95% CL       M-H-Fixed, 95% CL         Paradigm 2014       122 (229       22.5%       1.30 [1.09, 1.55]       Parameter 2017       14 (P = 0.03)       Paradigm 2014       100 tot         Study or Subgroup       Events       Total Weight       M-H-Fixed, 95% CL       M-H-Fixed, 95% CL         Paradigm 2014       1342       0.44 229       222       5.5%       0.99 [0.47, 1.31]       0.1	F       Forest plot of bronchitis comparison: LCZ696 group vs. ACEI/ARB group.         LC2696       ACE/ARB       Risk Ratio         Study or Subgroup       Events Total Veight MH- Eved, 95% CI       M-H. Eved, 95% CI         Paradigm 2014 #       183 4203       224 4229       96.5%       0.82 [0.68, 0.99]         Rulope 2010       5 497       6 493       3.5%       0.62 [0.20, 1.88]         Total (95% CI)       4700       4722 100.0%       0.82 [0.68, 0.99]         Total (95% CI)       6403       232         Heterogeneity: Ch <sup>2</sup> = 0.24, df = 1 (P = 0.62); I <sup>2</sup> = 0%       Total (95% CI       M-H. Fixed, 95% CI         Study or Subgroup       Events       Total Veints       Total Veints       Total (95% CI         Study or Subgroup       Events       Total Veints       Total Veints       Total Veints       Total Veints         Study or Subgroup       Events       Total Veints       Total (95% CI       M-H. Eved, 95% CI       M-H. Ev		Test for overall effect:	Z = 1.92 (P	= 0.05)					0.01 0.1 1 10 Favours [LCZ696] Favours [ACEI/ARB]
P F Prest pix of utroitmus of migration. LC2696       ACEL/ARB       Risk Ratio       Risk Ratio         Study or Subgroup       Events       Total Weight       M-H. Fixed. 95% CI       M-H. Fixed. 95% CI         Paracigin 2014 #       183 4203       224 429       96.5%       0.82 [0.68, 0.99]         Total (95% CI)       4700       4722 100.0%       0.82 [0.68, 0.99]         Total (95% CI)       4700       4722 100.0%       0.82 [0.68, 0.99]         Total (95% CI)       11 (P = 0.62), I <sup>P</sup> = 0%       0.01       0.1       1       10         Test for overall effect: Z = 2.14 (P = 0.03)       CEI/ARB       Risk Ratio       Risk Ratio         Study or Subgroup       LC2696       ACEI/ARB       Risk Ratio       Risk Ratio         Study or Subgroup       LC2696       ACEI/ARB       Risk Ratio       Risk Ratio         Study or Subgroup       LC2696       ACEI/ARB       Risk Ratio       Risk Ratio         Study or Subgroup       Events       Total sevents       CEI/ARB       Risk Ratio         Paradigm 2014       229       12 225       55% 0.98 [0.64.5.14]       Risk Ratio         Ratio 2017       3       142       0       1.28 [1.08, 1.52]       Intervieweits       Intervieweits       224       222 <td>LC2096 ACEUARB Risk Ratio Study or Subgroup Events Total Events Total Weight M-H. Fixed, 95% Cl M-H. Fixed,</td> <td>F</td> <td>Farrest allet of house</td> <td>1.:::- · · · · ·</td> <td></td> <td>1.07</td> <td><i>(0)</i></td> <td></td> <td>ACEI/ADD</td> <td>· arous [concel] · arous [ream aro]</td>	LC2096 ACEUARB Risk Ratio Study or Subgroup Events Total Events Total Weight M-H. Fixed, 95% Cl M-H. Fixed,	F	Farrest allet of house	1.:::- · · · · ·		1.07	<i>(0)</i>		ACEI/ADD	· arous [concel] · arous [ream aro]
Liczege         ACEL/ARB         Takk Ratio         Mikk Ratio           Paradigm 2014 #         183 4203         224 4229         96.5%         0.82 [0.68, 0.99]           Rulope 2010         5         497         8         493 3.5%         0.62 [0.62, 0.98]           Total (95% CI)         4700         4722 100.0%         0.82 [0.68, 0.99]         0.01         0.1           Total (95% CI)         4700         4722 100.0%         0.82 [0.68, 0.98]         0.01         0.1         1         10           Total (95% CI)         4700         4722 100.0%         0.82 [0.68, 0.98]         0.01         0.1         1         10         100           Fest for overall effect 2 = 2.14 (P = 0.03)         CEI/ARB         Risk Ratio         Risk Ratio         Risk Ratio           Study or Subgroup         Events Total Events         Total (95% CI)         ACEI/ARB         Risk Ratio         Risk Ratio           Study or Subgroup         Events         Total (95% CI)         10         10         100           Paradigm 2014         266         4203         206         429         92.5%         1.30 [1.00, 1.55]         MH.F Eved, 95% CI           Paradigm 2014         264         493         1.8%         0.75 (0.37, 135.24]         0.1	LC2696       ACEL/ARB       Task Ratio       MHx Rate       Misk Ratio         Paradigm 2014 #       183 4203       224 4229       96.5%       0.82 [0.68, 0.99]         Ruitope 2010       5       497       8       493       3.5%       CL       MHx Fixed, 35% CL         Paradigm 2014 #       183 4203       224       4229       96.5%       0.82 [0.68, 0.99]         Total (95% Cl)       4700       4722       100.0%       0.82 [0.68, 0.99]         Total vents       188       232         Heterogeneity: Ch <sup>2</sup> = 2.44 (P = 0.03)       CEI/ARB       Risk Ratio         Study or Subgroup       LC2696       ACEI/ARB       Risk Ratio         Ratio 2017       3       142       0       143       0.2%       7.05 [0.37, 135 24]         Paradigm 2014       128 (1.96, 1.52]       Total events       224       222       225       7.5%       0.98 [0.47, 1.29]         Para	r	Forest plot of brond	mus com	parison:	LCZ	090 g	roup vs.	ACEI/ARB group.	
			Study of Subaroup	LCZ696	5 /	ACEI//	ARB	Weight	Risk Ratio	Risk Ratio
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Ruitope 2010       5       497       3.5%       0.62 [0.00, 1.88]         Total (95% CI)       4700       4722       100.0%       0.82 [0.68, 0.98]         Total (95% CI)       4700       4722       100.0%       0.82 [0.68, 0.98]         Total events       188       232         Heterogenety: Ch <sup>2</sup> - 0.24 (1 + [0 - 0.03)       0.1       0.1       0.1       1       10       100         Fest for overall effect: Z = 2.14 (P = 0.03)       LCZ696       ACEI/ARB       Risk Ratio       Risk Ratio         Study or Subgroup       LCZ696       ACEI/ARB       Risk Ratio       Risk Ratio       Risk Ratio         Study or Subgroup       LCZ696       ACEI/ARB       Risk Ratio       Risk Ratio       Risk Ratio         Study or Subgroup       Loc 2696       ACEI/ARB       No 174 [0.17, 3.31]       101       0.1       1.1       10       100         Farours [LCZ696]       13 (100, %       1.28 [1.08, 1.52]       Interception (1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1	-	Paradiam 2014 #	193	4203	224	4220	96 5%	0.82 [0.68, 0.00]	M-H, Fixed, 95% Cl
Total (95% Cl)       4700       4722       100.0%       0.82 [0.88, 0.98]         Total events       168       232         Heterogeneity: Ch <sup>2</sup> = 0.24, df = 1 (P = 0.62); P = 0%       0.01       0.1       0.1       10         Test for overall effect: 2 = 2.14 (P = 0.03)       CZ296 G 203       0.62 [0.88, 0.98]       0.01       0.1       10       100         Favours [LC22696 C 203       2.14 (P = 0.03)       CZ296 C 203       2.14 (P = 0.03)       0.01       0.1       0.1       10       100         Study or Subgroup       Events       Total events       Total (P = 0.02)       1.30 [109, 1.55]       Parameter 2017       12 229       2.25 5.5%       0.39 [0.45, 2.14]       0.01       0.1	$\begin{array}{c c c c c c c c c c c c c c c c c c c $		Ruilope 2010	5	497	8	493	3.5%	0.62 [0.20, 1.88]	
Total (95% CI)       4700       4722       10.0%       0.82 [0.68, 0.98]         Total events       188       232         Heterogeneity: Chi* = 0.24, df = 1 (P = 0.62); P = 0%       0.01       0.1       0.1       10         Test for overall effect: Z = 2.14 (P = 0.03)       Events       Total events       100         LCZ2696       ACEU/ARB       Risk Ratio       Risk Ratio         Study or Subgroup       Events       Total Vents       101 (0.1, 10, 10, 10, 10, 10, 10, 10, 10, 10, 1	Total (95% CI)       4700       4722       100.0%       0.82 [0.68, 0.98]         Total events       168       232         Heterogeneity: Chi* = 0.24, df = 1 (P = 0.62); I* = 0%       0.01       0.1       10         Test for overall effect: Z = 2.14 (P = 0.03)       Events: Total Events. Total Weight       MH. Eixed, 95%, CI         Study or Subgroup       Events: Total Events. Total Weight       MH. Eixed, 95%, CI       MH. Eixed, 95%, CI         Paradigm 2014       268       4229       92.5%       1.30 (10.0, 1.55)         Paradigm 2014       3 497       4 493       1.8%, 0.74 (0.17, 3.31]         Total (95%, CI)       5071       5090       100.0%       1.28 [1.08, 1.52]         Total (95%, CI)       5071       5090       100.0%       1.28 [1.08, 1.52]         Total (95%, CI)       5071       5090       100.0%       1.28 [1.08, 1.52]         Total (95%, CI)       5071       5090       100.0%       1.28 [1.08, 1.52]         Total (95%, CI)       5071       5090       100.0%       1.28 [1.08, 1.52]         Total (95%, CI)       5071       5090       100.0%       1.28 [1.08, 1.32]         Paradigm 2014       103       4029       229       72.5%       1.40 (0.61, 3.22]         Paradig									
Total events       168       232         Heterogenetity: Ch <sup>2</sup> = 2.24 (P = 0.03)       0.1       0.1       0.1       0.0         G       Forest plot of dizziness companison: LCZ696 group vs. ACEI/ARB group.       LCZ696 ACEI/ARB       Risk Ratio       Risk Ratio         Study or Subgroup       LC2696 ACEI/ARB       Risk Ratio       Niek Ratio       Niek Ratio         Paradigm 2014       # 229       92.5%       1.30 [1.00, 1.55]       M-H. Fixed, 95% CL         Paradigm 2017       3       142       0       143       0.2%       7.05 [0.37, 135 24]         Ruitope 2010       3       497       4       433       1.2%       0.98 [0.44, [0.17, 3.31]         Total (95% Cl)       5071       5090 100.0%       1.28 [1.08, 1.52]       1.0       1.0       100         Total veents       224       225       7.5% (1.464, Ratio       0.464 Ratio       0.01       0.1       1.0       100         Fevours [LC2696 Favours [ACEI/ARB]       0.464 Ratio       0.01       0.1       1.0       100       100         Favours [LC2696 Favours [ACEI/ARB]       0.464 Ratio       0.046 Ratio       0.046 Ratio       0.046 Ratio       0.046 Ratio       0.01       0.1       1.0       1.0       100       100       100	Total events       188       232         Heterogenetic; Ch <sup>2</sup> = 2.24 (P = 10.63);       0.1       0.1       100         Ferrest plot of dizziness companison: LCZ696 group vs. ACEL/ARB group.       LCZ696       ACEI/ARB       Risk Ratio         Study or Subgroup       LCZ696       ACEI/ARB       Risk Ratio       Risk Ratio         Paradigm 2014       #       264       225       55:0       0.98 [0.45, 2.14]         Ratio 2017       3       142       0       143       0.2%       7.05 [0.37, 135, 2.4]         Ruiope 2010       3       497       4       493       1.8%       Orf [0.17, 3.31]         Total events       264       222       225       f.5% (D)       0.1       10       100         Ferrowers (LC2696       for 0.0%       1.28 [1.08, 1.52]       101       10       100         Total events       264       222       225       f.5% (D)       0.01       1.1       10       100         Ferrowers (LC2696       for 0.0%       1.28 [1.08, 1.52]       0.01       0.1       1.01       100         Ferrowers (LC2696 for 0.0%       0.28 [0.74, 1.29]       0.40 (6.13, 3.22]       0.40 (6.13, 3.22]       0.40 (6.13, 3.22]       0.40 (6.13, 3.22]       0.40 (6.13, 3.22]		Total (95% CI)	4	4700		4722	100.0%	0.82 [0.68, 0.98]	•
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{array}{c c c c c c c c c c c c c c c c c c c $		Total events	188		232				
Favours [LC2696] Favours [LC2696] Favours [LC2696]         Favours [LC2696] Favours [LC2696] Favours [LC2696]         G Forest plot of dizziness comparison: LC2696 group vs. ACEI/ARB group.         LC2696 ACEI/ARB Risk Ratio         Study or Subgroup       Events Total Events Total Weight M-H. Fixed, 95% CI         Paradigm 2014 #       268 4223       92.5%       1.30 [1.09, 1.55]         Paradigm 2014 #       229 15.2%       0.98 [0.45, 2.14]       1.44         Ratio 2017       3 142       0 143       0.2%       7.05 [0.37, 135, 2.4]         Ratio 2010       3 497       4 493       1.8%       0.74 [0.17, 3.31]         Total (95% CI)       5071       5090 100.0%       1.28 [1.08, 1.52]       1.01         Total events       284       222       1.28 [1.08, 1.52]       1.01       1.01         Feroversi [LC2696]       Favours [LC2696]       Favours [LC2696]       Favours [LC2696]       Favours [LC2696]       Favours [LC2696]         Hetrogenetic: Ch <sup>2</sup> = 2.68 (P = 0.004)       Study or Subgroup       Events Total Events Total Eventh       Odds Ratio       Odds Ratio         Study or Subgroup       Events Total Eventh       Total (95% CI)       5071       5090 100.0%       0.99 [0.47, 1.26]       Favours [experimental]       Favours [control] </td <td>Favours [LCZ696]         Favours [LCZ696]         Favours [LCZ696]         Favours [LCZ696]         Study or Subgroup       Events Total Events Total Weight M-H. Eixed, 95% CI         M-H. Eixed, 95% CI         Parameter 2017       12 225 55%       1.30 [109, 155]         Parameter 2017       12 225 55%       0.90 [03, 135 24]         Total (95% CI)       5071       5090 100.0%       1.22 [1.08, 1.52]         Total (95% CI)       5071       5090 100.0%       1.22 [1.08, 1.52]         Total (95% CI)       5071       5090 100.0%       1.22 [1.08, 1.52]         Total (95% CI)       5071       5090 100.0%       1.22 [1.08, 1.52]         Total (95% CI)       5071       5090 100.0%       1.22 [1.08, 1.32]         Parameter 2017       1.4 229       1.22 269 [.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2</td> <td></td> <td>Heterogeneity: Chi<sup>e</sup> = 1</td> <td>J.24, df = 1 7 = 2.14 / P</td> <td>(P = 0.6)</td> <td>2); 1* =</td> <td>0%</td> <td></td> <td></td> <td>0.01 0.1 1 10 1</td>	Favours [LCZ696]         Favours [LCZ696]         Favours [LCZ696]         Favours [LCZ696]         Study or Subgroup       Events Total Events Total Weight M-H. Eixed, 95% CI         M-H. Eixed, 95% CI         Parameter 2017       12 225 55%       1.30 [109, 155]         Parameter 2017       12 225 55%       0.90 [03, 135 24]         Total (95% CI)       5071       5090 100.0%       1.22 [1.08, 1.52]         Total (95% CI)       5071       5090 100.0%       1.22 [1.08, 1.52]         Total (95% CI)       5071       5090 100.0%       1.22 [1.08, 1.52]         Total (95% CI)       5071       5090 100.0%       1.22 [1.08, 1.52]         Total (95% CI)       5071       5090 100.0%       1.22 [1.08, 1.32]         Parameter 2017       1.4 229       1.22 269 [.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2		Heterogeneity: Chi <sup>e</sup> = 1	J.24, df = 1 7 = 2.14 / P	(P = 0.6)	2); 1* =	0%			0.01 0.1 1 10 1
G       Forest plot of dizziness comparison: LCZ696 group vs. ACEI/ARB group.         LC2696       ACEI/ARB       Risk Ratio       Risk Ratio         Study or Subgroup       Events Total Events. Total Verified 5% CI       M-H, Fixed 5% CI       M-H, Fixed 5% CI         Paradigm 2014       # 266       4203       206       4229       92.5%       1.30 [1:00.155]         Paradigm 2014       # 266       4203       206       4229       92.5%       0.98 [0.45, 214]         Ratio 2017       3       142       0       143       0.2%       7.56 [0.37, 135.24]         Ratiope 2010       3       497       4       493       1.8%       0.74 [0.17, 3.31]         Total (95% CI)       5071       5090 100.0%       1.28 [1.08, 1.52]       0.01       0.1       1.1       10       100         Total (95% CI)       5071       5090 100.0%       1.28 [1.08, 1.52]       0.01       0.1       1.1       10       100         Total (95% CI)       5071       5090 100.0%       0.28 [1.08, 1.52]       0.01       0.1       0.1       0.1       0.1       0.1       0.1       0.1       0.1       0.1       0.1       0.1       0.1       0.1       0.1       0.1       0.1       0.1       <	G Forest plot of dizziness comparison: LCZ696 group vs. ACEL/ARB group. LC2696 ACEL/ARB Risk Ratio Risk Ratio Study or Subgroup Events Total Events Total Venth H.H. Fixed 55% CI Parandigm 2014 # 266 4203 206 4229 92.5% 1.30 [1.00.1.55] Parandigm 2014 # 266 4203 206 4229 92.5% 1.30 [1.00.1.55] Parandigm 2017 12 229 12 225 55% 0.98 [0.45.2.14] Ratio 2017 13 142 0 143 0.2% 7.05 [0.37, 135.24] Ratio 2017 3 142 0 143 0.2% 7.05 [0.37, 135.24] Total (95% CI) 5071 5090 100.0% 1.28 [1.08, 1.52] Total events 128 (P = 0.04) H Forest plot of headache comparison: LCZ696 group vs. ACEL/ARB group. LC2696 ACEL/ARB Odds Ratio Odds Ratio Study or Subgroup Events Total Events Total Events Total Venth Total (95% CI) Paradigm 2014 103 4203 106 4229 79.2% 0.98 [0.74, 1.29] Parameter 2017 14 129 10 225 7.3% 1.40 [0.61, 3.22] Ratio 2017 3 142 6 143 4.5% 0.49 [0.12, 2.01] Rutope 2010 12 497 12 493 9.0% 0.99 [0.47, 1.26] Total events 132 134 Heterogeneity: Ch <sup>2</sup> = 162, d = 3 (P = 0.66); P = 0% 15 Forest plot of influenza comparison: LCZ696 group vs. ACEL/ARB group. LC2696 ACEL/ARB Odds Ratio Odds Ratio 0.01 0.1 1 0.1 1 0 100 Favours [cc2690 Favours [control]] 1 Forest plot of influenza comparison: LCZ696 group vs. ACEL/ARB Odds Ratio MH, Fixed 35% CI Paradigm 2014 159 4203 132 4229 91.5% 1.32 [0.48, 1.44] Heterogeneity: Ch <sup>2</sup> = 162, d = 3 (P = 0.66); P = 0% Total (95% CI) 590 100.0% 1.22 [0.38, 1.54] Parameter 2017 7 229 5 225 3.5% 1.38 [0.48, 4.44] Rutops 2010 8 497 7 493 5.0% 1.14 [0.41, 3.16] Total (95% CI) 4929 4947 100.0% 1.22 [0.38, 1.54] Paradigm 2014 159 4203 152 4229 91.5% 1.32 [0.48, 1.54] Paradigm 2017 7 229 5 225 3.5% 1.39 [0.48, 4		. Sat for overall ellect.	= - 2.14 (P	0.00)					Favours [LCZ696] Favours [ACEI/ARB]
Control of control contrecont control control control control contr	Controls provide an acceleration of the provide and provide an acceleration of the provide and	G	Forest plot of dizzi	ness comr	aricon.	I CZ	696 a	NOR VE	ACEI/APB group	
LC2090         ACEUARD         Nisk Ratio           Study or Subgroup         Events         Total (events         Total (events         Total (events         Total (events         222           Paradigm 2014         #         266         4223         92.5%         1.30 [1.09, 1.55]         MH. Fixed, 95% C I           Paradigm 2014         #         229         1.2 225         5.5%         0.98 [0.45, 2.14]           Ratic 2017         3         142         0         143         0.2%         7.05 [0.37, 135, 24]           Total (95% CI)         5071         5090         100.0%         1.28 [1.08, 1.52]         1.00           Total events         264         222         1.00         1.28 [1.08, 1.52]         1.00           Total events         264         222         1.00         1.01         1.00           Test for ovental effect: 2 = 2.48 (P = 0.00.40)         VEX         Odds Ratio         Odds Ratio           Study or Subgroup         Events         Total (95% CI)         5071         5090 100.0%         0.99 [0.44, 2.23]           Paradigm 2014         103         4223         106         4225         7.3%         0.49 [0.12, 2.01]           Raio 2017         14         229         102         <	LL 2095         ALCENARD         Nisk Ratio           Study or Subgroup         Events         Total (RS), CI         M-H, Fixed, 95%, CI           Paradigm 2014         229         12,25         55%, O.98 [0.45, 2.14]           Ratio 2017         3         142         0         143         0.2%, 7.06 [0.37, 135, 2.4]           Ruitope 2010         3         497         4         93         1.8%         0.74 [0.17, 3.31]           Total (8%, CI)         5071         5090         100.0%         1.28 [1.08, 1.52]         1.01         1.01           Total (9%, CI)         5071         5090         100.0%         1.28 [1.08, 1.52]         1.01         1.01           Total (9%, CI)         5071         5090         100.0%         1.28 [1.08, 1.52]         1.01         1.01           Total (9%, CI)         5071         5090         100.0%         1.28 [1.08, 1.52]         1.01         1.01           Test for overall effect: Z = 2.88 (P = 0.004)         LC2696         Group vs. ACEL/ARB group.         LC2696         CdEl/ARB         Odds Ratio           Study or Subgroup         Events         Total (8%, CI)         5071         5090         100.0%         0.99 [0.41, 2.2]         1.01         1.00           Paradigm 201	0	a orea pior or ulzzi	Longer		0000	o zo gi	oup vs.	Bish D	
Paradigm 2014         #         2006         4229         225%         1.30 [109].155]           Parameter 2017         12         229         12         225         5.5%         0.98 [0.45, 2.14]           Ratio 2017         12         229         12         225         5.5%         0.98 [0.45, 2.14]           Ratio 2017         3         142         0.1         143         0.2%         7.06 [0.37, 155.24]           Ruicope 2010         3         497         4         493         1.8%         0.74 [0.17, 3.31]           Total events         284         222         Heterogenetity: Ch <sup>2</sup> = 2.88 (P = 0.52); P = 0%         1.28 [1.08, 1.52]           Test for overall effect: Z = 2.88 (P = 0.004)         LC2696         ACEU/ARB         Odds Ratio           Study or Subaroup         Events         Total         Vents         Total           LC2666         ACEU/ARB         Odds Ratio         Odds Ratio         Odds Ratio           Study or Subaroup         Events         Total         Vents         Total         Vent	Paradigm 2014         # 12         2006         4229         925%         1.30 [109, 1.55]           Parameter 2017         12         229         12         225         5.5%         0.98 [0.45, 2.14]           Raio 2017         3         142         0         143         0.2%         7.05 [0.37] 155.24]           Raio 2017         3         142         0         143         0.2%         7.05 [0.37] 155.24]           Raio 2017         3         497         4         493         1.8%         0.74 [0.17, 3.31]           Total events         284         222         128         128 [1.06, 1.52]         101         10           Total events         284         222         101         0.1         0.1         10           Total events         284         222         0.480         Odds Ratio         Odds Ratio           Study or Subgroup         Events         Total Weight         MH. Fixed, 95% CI         MH. Fixed, 95% CI           Paradim 2014         103         4203         106         4229         73%         0.40 [0.12, 201]           Ruio 2010         12         497         12         493         9.0%         0.99 [0.47, 1.29]           Paradign 2014		Study or Subgroup	Evente T	otal E	ente	Total	Weigh*	M-H. Fixed 95% C	RISK KAUO M-H. Fiyad 95% Cl
Parameter 2017       12       229       12       225       5.5%       0.98 [0.45, 2:14]         Railo 2017       3       142       0       143       0.2%       7.05 [0.37, 135, 24]         Ruilope 2010       3       442       0       143       0.2%       7.05 [0.37, 135, 24]         Total (95% CI)       5071       5090       100.0%       1.28 [1.08, 1.52]         Total events       284       222         Heterogeneity: Ch <sup>2</sup> = 2.2, 88 (P = 0.004)       0.01       0.1       10         Feroversi [LCZ696]       Favours [LCZ696]       Fevours [LCZ696]       Fevours [LCZ696]         Study or Subgroup       ECZ696       ACEI/ARB       Odds Ratio       Odds Ratio         Study or Subgroup       12       497       12       297       9.0%       0.49 [0.12, 2.01]         Paradigm 2014       103       4203       106       4229       79.2%       0.98 [0.74, 1.29]         Paradigm 2010       12       497       12       493       9.0%       0.99 [0.44, 2.23]         Total events       132       134       Heterogeneity: Ch <sup>2</sup> = 1.62, df = 3 (P = 0.66); P = 0%       0.01       0.1       1       10       100         Total events       132	Parameter 2017       12       229       12       225       5.5%       0.38 [0.45, 214]         Ratio 2017       3       142       0       143       0.2%       7.05 [0.37, 155 24]         Ratio 2017       3       142       0       143       0.2%       7.05 [0.37, 155 24]         Ruilope 2010       3       497       4       93       1.6%       0.74 [0.17, 3.31]         Total (95% CI)       5071       5090       100.0%       1.28 [1.08, 1.52]         Total events       244       222         Heterogenetic, CH* = 2.26, B(P = 0.004)       0.01       0.1       1       10       100         Fest for overall effect: Z = 2.88 (P = 0.004)       CZ696       ACEU/ARB       Odds Ratio       Odds Ratio         Study or Subgroup       Events       Total (95% CI)       5071       5090       100.0%       0.99 [0.77, 1.26]         Paradigm 2014       103       4203       106       422       79.2%       0.98 [0.44, 2.33]         Total (95% CI)       5071       5090       100.0%       0.99 [0.77, 1.26]       0.01       0.1       1.0       10       100         Favours [control]       10       100       90       90.99 [0.47, 1.26]       0.01		Paradigm 2014 #	266 4	1203	206	4229	92.5%	1.30 [1.09, 1.55]	
Ratic 2017       3       142       0       143       0.2%       7.05 [0.37, 135, 24]         Ruicope 2010       3       497       4       493       1.8%       0.74 [0.17, 3.31]         Total (9%, C1)       5071       5090       100.0%       1.28 [1.08, 1.52]         Total events       264       222         Hetrogeneity: Ch <sup>2</sup> = 22.6, df = 3 (P = 0.52); P = 0%       0.01       0.1       1       10       100         Test for overal effect; Z = 2.84 (P = 0.04)       CZE966       ACEI/ARB       Odde Ratio       Odde Ratio       Odde Ratio         Study or Subgroup       Events Total Events Total Eventh Total Weinh MH. Fixed, 35% C1       MH. Fixed, 35% C1       MH. Fixed, 35% C1         Paradigm 2014       103       4223       106       425       7.3%       1.40 [0.61, 3.22]         Ratic 2017       14       229       10       225       7.3%       1.40 [0.61, 3.22]         Parameter 2017       14       29       100       0.09 [0.74, 1.29]       100       100         Total (95%; C1)       5071       5090       100.0%       0.99 [0.44, 2.23]       100       100       100       100         Total (95%; C1)       5071       5090       100.0%       0.99 [0.71, 1.26]	Ratio 2017       3       142       0       143       0.2%       7.05 [0.37, 135, 24]         Ruitope 2010       3       497       4       493       1.8%       0.74 [0.17, 3.31]         Total (9%, C1)       5071       5090       100.0%       1.28 [1.08, 1.52]         Total (9%, C1)       5071       5090       100.0%       1.28 [1.08, 1.52]         Hetrogeneity: CH <sup>2</sup> = 2.26 (1 = 3 (P = 0.52); P = 0%       10       0.1       0.1       10         Fest for overal effect: Z = 2.88 (P = 0.004)       CZE596       Group vs. ACEL/ARB group.       CZE696       ACEL/ARB       Odds Ratio         Study or Subgroup       Events Total Events Total Eventh Total Weight M-H. Fixed, 95% C1       M-H. Fixed, 95% C1       M-H. Fixed, 95% C1         Paradigm 2014       103       4203       106       422 9       90.90 (0.4), 2.23]         Paradigm 2014       132       134       Hetrogeneity CH <sup>2</sup> = 1.62, 016); P = 0.9%       100.0%       0.99 [0.47, 1.26]         Total (95% C1)       5071       5090       100.0%       0.99 [0.47, 1.26]       0.01       10         Total (95% C1)       267 - 0.66; P = 0.9%       100.0%       0.99 [0.47, 1.26]       0.01       10       100         Festor overal effect: Z = 0.10 (P = 0.92); P = 0.%       122		Parameter 2017	12	229	12	225	5.5%	0.98 [0.45, 2.14]	- <b>F</b>
Ruilope 2010       3       497       4       493       1.8%       0.74 [0.17, 3.31]         Total events       264       222         Heterogenetity: Ch <sup>1</sup> = 2.86, df = 3 (P = 0.52); I <sup>2</sup> = 0%,       0.01       0.1       0.1       10         Test for overall effect: 2 = 2.88 (P = 0.004)       CZ696       ACEU/ARB       Odds Ratio       Odds Ratio         H Forest plot of headache comparison: LCZ696 group vs. ACEU/ARB group.       LCZ696       ACEU/ARB       Odds Ratio       Odds Ratio         Study or Subarou       Events       Total Weight       M-H. Fixed, 95% CI       M-H. Fixed, 95% CI         Paradign 2014       103 4203       106 4229       73%       1.40 [0.61, 3.22]       M-H. Fixed, 95% CI         Parameter 2017       14       229       10       225       7.3%       1.40 [0.61, 3.22]         Ruilope 2010       12       497       12       493       9.0%       0.99 [0.41, 2.20]         Ferours [coperimental]       5071       509       100.0%       0.99 [0.77, 1.26]       0.01       1       10       100         Total events       132       134       Heterogenetity: Ch <sup>2</sup> = 1.62, df = 3 (P = 0.66); F = 0%       0.04 ds Ratio       0.04 ds Ratio       0.04 ds Ratio         I Forest plot of influenza comparison:	Rulicpe 2010       3       497       4       493       1.8%       0.74 [0.17, 3.31]         Total events       254       222         Heterogeneity: Ch <sup>2</sup> = 2.28, df = 3 (P = 0.52); P = 0%, Test for overall effect: Z = 2.38 (P = 0.004)       1.28 [1.08, 1.52]         H Forest plot of headache comparison: LCZ696 group vs. ACEL/ARB group.       0.01       0.1       10       10         Study or Subgroup       Events       Total events       0.04 exet       0.9% (0.41, 1.29)       0.9% (0.41, 1.29)         Paradign 2014       10       420       10       422       7.3% (0.40) (0.1, 3.22)       0.41       1.40 (0.61, 3.22)         Parameter 2017       13       142       6       143       4.5% (0.49) (0.12, 2.01)       10       10       100         Total (95% Cl)       5071       5090       100.0% (0.99 (0.41, 2.23)       0.01       0.1       1       10       100         Total (95% Cl)       5071       5090       100.0% (0.99 (0.47, 1.26)       0.01       0.1       1       10       100         Fevours (experimental)       Favours (control)       10       100       100       Favours (experimental)       Favours (control)       100       100       100       Favours (experimental)       Favours (experimental)       Favours		Ratio 2017	3	142	0	143	0.2%	7.05 [0.37, 135.24]	
Study or Subgroup         5071         5090         100.0%         1.28         1.08         1.52           Heterogeneity: Ch <sup>2</sup> = 2.28         (P = 0.52); P = 0%         0.01         0.1         100         100           Heterogeneity: Ch <sup>2</sup> = 2.68         (P = 0.02); P = 0%         0.01         0.1         100         100           Hortsongeneity: Ch <sup>2</sup> = 2.68         (P = 0.004)         CZ696         CRU/ARB         Odds Ratio         Odds Ratio           Study or Subgroup         Excession Total Weight MH-Fixed .95% CI         MH-Fixed .95% CI         MH-Fixed .95% CI         Favours [ACEI/ARB]           Paradigm 2014         103         4203         106         4229         79.2%         0.98 [0.74, 1.29]         0.01         0.1         1.0         100           Paradigm 2014         103         4203         106         4229         79.2%         0.98 [0.74, 1.29]         0.04         8.40         0.04         8.40           Paradigm 2014         103         4203         106         4229         79.2%         0.49 [0.13, 22]         1.0         1.0         1.0         1.0         1.0         1.0         1.0         1.0         1.0         1.0         1.0         1.0         1.0         1.0         1.0         1.0	Total (95% CI)       5071       5090       100.0%       1.28 [1.08, 1.52]         Total events       284       222         Total events       216 3 (P = 0.52); P = 0%       0.1       0.1       10       100         Test for overall effect: Z = 2.88 (P = 0.004)       0.1       0.1       0.1       10       100         H       Forest plot of headache comparison: LCZ696 group vs. ACEL/ARB group.       LCZ696       ACEI/ARB       Odds Ratio       Odds Ratio         Study or Subgroup       Events       Total (95% CI)       0.22       7.3%       1.40 (b1.3, 22)       MH. Fixed, 95% CI       MH. Fixed, 95% CI         Paradigm 2014       103       4203       100 422       7.9%       0.98 (0.74, 1.29)         Paradigm 2014       103       4203       102 25       7.3%       1.40 (b1.3, 22)         Ratio 2017       3       142       6       143       4.5%       0.49 (0.12, 2.01)         Rulico 2010       12       497       100.0%       0.99 (0.47, 1.26)       0.01       0.1       100         Feavours [coperimental]       Favours [coperimental]       Favours [control]       100       100       100       100         Feature 2017       7       29       9.0%       0.99 (0.47, 1.		Ruilope 2010	3	497	4	493	1.8%	0.74 [0.17, 3.31]	
Total events         284         222           Heterogeneity: Ch <sup>2</sup> = 226, df = 3 (P = 0.52); I <sup>2</sup> = 0%,         0.01         0.1         1         100           Test for overall effect: 2 = 226, df = 3 (P = 0.52); I <sup>2</sup> = 0%,         0.01         0.1         1         100           Fest for overall effect: 2 = 226, df = 3 (P = 0.04)         0.01         0.1         1         100           Favours [LC2696]         Favours [LC2696]         Favours [LC2696]         Favours [LC2696]         Favours [LC2696]           Study or Subgroup         Events: Total Weinhl         MH, Fixed 35% Cl         MH, Fixed 35% Cl           Paradigm 2014         103         420         106         4229         79.2%         0.98 [0.74, 129]           Parameter 2017         14         220         10         225         7.3%         0.49 (0.81, 3.29]           Ratio 2017         3         142         6         143         4.5%         0.49 (0.12, 2.01]           Ruipope 2010         12         497         12         493         9.0%         0.99 [0.44, 2.23]           Total (95% Cl)         5071         5090         100.0%         0.99 [0.77, 1.26]         0.01         0.1         10         100           Testor ovenal lefter, 2 = 0.068; !F = 0%         Fa	$\begin{array}{c c c c c c c c c c c c c c c c c c c $		Total (95% CI)	5	5071		5090	100.0%	1.28 [1.08. 1.52]	•
Heterogeneity: Ch <sup>III</sup> = 228, df = 3 (P = 0.52); I <sup>II</sup> = 0%         101         Test for overal effect: Z = 2.88 (P = 0.004)         Interpretation of the state	Heterogeneity: Ch <sup>2</sup> = 2.26, df = 3 (P = 0.52); l <sup>2</sup> = 0%       0.01       0.1       10       10         Test for overal effect: Z = 2.88 (P = 0.004)       0.04       10       10       10       10         H Forest plot of headache comparison: LCZ696 proup vs. ACEI/ARB odds Ratio       0.04       0.01       0.1       10       10       10         Budy or Subgroup       Events       Total       Events       Total       Weight       M-H. Fixed, 95% CI       M-H. Fixed, 95% CI         Paradign 2014       103       4203       106       4229       792%       0.98 (0.44, 1.29)         Paradign 2014       103       124       143       4.5% 0.98 (0.44, 2.23)       0.01       0.1       10       10         Total (95% CI)       5071       5090       100.0%       0.99 (9.44, 2.23)       0.01       0.1       10       100         Ferocurs (experimental)       132       134       134       0.045%       0.99 (9.44, 2.23)       0.01       0.1       10       100         For overail effect: Z = 0.10 (P = 0.92); P = 0%       104       10       100       100       100       100       100       100       100       100       100       100       100       100       100       100 <td< td=""><td></td><td>Total events</td><td>284</td><td></td><td>222</td><td></td><td></td><td></td><td> *</td></td<>		Total events	284		222				*
UUT 100 100 100 100 100 100 100 100 100 Favours [ACEI/ARB]         UUT 100 100 100 100 100 100 100 100 100 10	Test for overall effect: Z = 2.88 (P = 0.004)       UUT U, 1 1 100 Favours [LC22696] Favours [LC2496] Favours [LC2498B]         H Forest plot of headache comparison: LC2696 group vs. ACEL/ARB group. LC2696 ACEL/ARB Odds Ratio         Study or Subgroup       CACEL/ARB Odds Ratio         Odds Ratio     <		Heterogeneity: Chi <sup>2</sup> = 2	.26, df = 3 (	(P = 0.52	2);  2 =	0%			
Introduction of the adache comparison: LCZ696 group vs. ACEU/ARB group.         LCZ696 ACEU/ARB Odds Ratio         Odds Ratio <th< td=""><td>H       Forest plot of headache comparison: LCZ696 group vs. ACEI/ARB group.         LC2696       ACEI/ARB       Odds Ratio         Study or Subgroup       Events       Total       Weight       M-H. Fixed, 95% CI         Paradign 2014       103 4203       106 4229       79.2%       0.98 [0.74, 1.29]         Parameter 2017       14 229       10       225       7.3%       1.40 [0.61, 3.22]         Ratio 2010       12 497       12 493       9.0%       0.99 [0.44, 2.23]         Total (95% CI)       5071       5090       100.0%       0.99 [0.44, 2.23]         Total (95% CI)       5071       5090       100.0%       0.99 [0.44, 2.23]         Total (95% CI)       5071       5090       100.0%       0.99 [0.77, 1.26]         Total (95% CI)       5071       5090       100.0%       0.99 [0.44, 2.23]         Total (95% CI)       5071       5090       100.0%       0.99 [0.44, 2.23]         Total (95% CI)       5071       5090       100.0%       0.99 [0.44, 2.23]         Total (95% CI)       200 = 0.51, H= 0.0%       0.01       0.1       1.0         Forest plot of influenza comparison: LCZ696 group vs. ACEI/ARB group.       0.01       0.1       H.Fixed, 95% CI         Paradigm 2014</td><td></td><td>Test for overall effect: 2</td><td>z = 2.88 (P</td><td>= 0.004)</td><td></td><td></td><td></td><td></td><td>Favours [LCZ696] Favours [ACEI/AR8]</td></th<>	H       Forest plot of headache comparison: LCZ696 group vs. ACEI/ARB group.         LC2696       ACEI/ARB       Odds Ratio         Study or Subgroup       Events       Total       Weight       M-H. Fixed, 95% CI         Paradign 2014       103 4203       106 4229       79.2%       0.98 [0.74, 1.29]         Parameter 2017       14 229       10       225       7.3%       1.40 [0.61, 3.22]         Ratio 2010       12 497       12 493       9.0%       0.99 [0.44, 2.23]         Total (95% CI)       5071       5090       100.0%       0.99 [0.44, 2.23]         Total (95% CI)       5071       5090       100.0%       0.99 [0.44, 2.23]         Total (95% CI)       5071       5090       100.0%       0.99 [0.77, 1.26]         Total (95% CI)       5071       5090       100.0%       0.99 [0.44, 2.23]         Total (95% CI)       5071       5090       100.0%       0.99 [0.44, 2.23]         Total (95% CI)       5071       5090       100.0%       0.99 [0.44, 2.23]         Total (95% CI)       200 = 0.51, H= 0.0%       0.01       0.1       1.0         Forest plot of influenza comparison: LCZ696 group vs. ACEI/ARB group.       0.01       0.1       H.Fixed, 95% CI         Paradigm 2014		Test for overall effect: 2	z = 2.88 (P	= 0.004)					Favours [LCZ696] Favours [ACEI/AR8]
H       Forest plot of headache comparison: LCZ696 group vs. ACEU/ARB group.         LCZ696       ACEU/ARB       Odds Ratio         Study or Subgroup       Events       Total       Events       Total         Paradign 2014       103       4203       106       4229       79.2%       0.98 (0.74, 1.29)         Paradign 2014       103       4203       102       225       7.3%       1.40 (0.61, 3.22)         Ratio 2017       3       142       6       143       4.5%       0.49 (0.12, 2.01)         Ruito 2010       12       497       12       493       9.0%       0.99 (0.44, 2.23)         Total (8%, Cl)       5071       5090       100.0%       0.99 (0.77, 1.26)         Total (8%, Cl)       5071       5090       100.0%       0.99 (0.77, 1.26)         Total (8%, Cl)       5071       5090       100.0%       0.99 (0.77, 1.26)         Total (8%, Cl)       5071       5090       100.0%       0.99 (0.77, 1.26)         Total events       132       134       Heterogeneity: Ch <sup>2</sup> = 162.d = 3 (P = 0.66); P = 0%       0.01       0.1       10       100         Fest for lot of influenza comparison: LCZ696 group vs. ACEL/ARB group.       LC2696       ACEL/ARB       Odds Ratio       Odd	H       Forest plot of the leadache comparison: LC2696 proup vs. ACEL/ARB group.         LC2696       ACELVARB       Odds Ratio         Study or Subgroup       Events       Total       Events       Total         Paradigm 2014       103       4203       106       4229       792%       098 (0.74, 1.29)         Parameter 2017       14       229       7.3%       1.40 (0.61, 3.22)       MH. Fixed, 95% CI         Ratio 2017       3       142       6       143       4.5%       0.49 (0.12, 2.01]         Rulope 2010       12       497       12       493       0.9%       0.99 (0.44, 2.23)         Total (95% CI)       5071       5090       100.0%       0.99 (0.77, 1.26)         Total (95% CI)       5071       5090       100.0%       0.99 (0.77, 1.26)         Total (95% CI)       5071       5090       100.0%       0.99 (0.77, 1.26)         Total (95% CI)       5071       5090       100.0%       0.99 (0.77, 1.26)         Total (95% CI)       5071       5090       100.0%       0.99 (0.44, 2.23)         Udd or Subgroup       Events       Total Weinht       MH. Fixed, 95% CI       MH.H. Exed, 95% CI         Paradigm 2014       159       4202       15%					_				. arous (concert i arous (roni/Arb)
LC2696         ACEI/ARB         Odds Ratio           Study or Subgroup         Freents Total Eventh Tedal Weight MH-Fixed, 95% CI         MH-Fixed, 95% CI           Parandigm 2014         103         4203         106         4229         79,2%         0.98 (p.74, 1.29)           Parandigm 2014         103         4203         106         4229         79,2%         0.98 (p.74, 1.29)           Parandigm 2017         14         229         70,2%         0.98 (p.74, 1.29)         100           Ratio 2017         3         142         6         143         4.5%         0.49 (p.13, 22, 01)           Total (95% CI)         5071         5090         100.0%         0.99 (p.44, 2.23)         100           Total (95% CI)         5071         5090         100.0%         0.99 (p.77, 1.26)         100           Test for ovarial effect, 2 = 0.06 (p. P = 0.92)         134         100         100         100           Test for ovarial effect, 2 = 0.06 (p. P = 0.92)         CZE/56 group vs. ACEI/ARB group.         Codds Ratio         Cdds Ratio           LC2696         ACEUARB         Odds Ratio         Odds Ratio         Cdds Ratio           L100 to 1 influenza comparison: LC2696 group vs. ACEI/ARB group.         LC2696 ACEUARB         Odds Ratio           L	$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Η	Forest plot of head	ache comp	parison:	LCZ	696 g	roup vs.	ACEI/ARB group.	
Study or subaroup         Events         Total         Weight         MH. Fixed, 95% CI         M.H. Fixed, 95% CI           Paradigm         2014         103         4229         79.2%         0.98 [0.74, 1.29]           Parameter 2017         14         229         10         225         7.3%         1.40 [0.61, 3.22]           Parameter 2017         3         142         6         143         4.5%         0.49 [0.12, 201]           Ruice 2010         12         497         12         493         9.0%         0.99 [0.44, 2.23]           Total (95% CI)         5071         5090         100.0%         0.99 [0.77, 1.26]           Total (95% CI)         5071         5090         100.0%         0.99 [0.77, 1.26]           Total (95% CI)         5071         5090         100.0%         0.99 [0.77, 1.26]           Test for overall effect Z = 0.10 (P = 0.92)         100         10         100           Favours [coperimental]         Favours [control]         Favours [control]           I         Forest plot of influenza comparison: LCZ696 aroup vs. ACEI/ARB group.         Odds Ratio         Odds Ratio           Study or Subgroup         Events         Cod dvalk Ratio         Odds Ratio	Study or studproup         Events         Total         Events         Total         Weight         M-H. Fixed, 95% CI         M-H. Fixed, 95% CI           Paramiler 2017         14         229         10         225         7.3%         1.40 [0.61, 3.22]           Parameter 2017         14         229         10         225         7.3%         1.40 [0.61, 3.22]           Ratio 2017         3         142         6         143         4.5%         CI           Ruito 2017         12         493         9.0%         0.99 [0.44, 2.23]         Image: Comparison of the comparison of th			LCZ696	A	CEI/A	RB		Odds Ratio	Odds Ratio
reargent 2017       14       229       100       42.07       14.20       101.322         Parameter 2017       3       14.22       10.025       7.36       1.40       10.51       3.221         Ratio 2017       3       14.22       10.025       7.36       0.98       1.40       10.51       3.221         Ratio 2017       3       14.2       6       14.3       4.5%       0.49       10.15       3.221         Ratio 2010       12       497       12       493       9.0%       0.99       10.42       2.23         Total (8%) CI)       5071       5090       100.0%       0.99       10.77       1.26         Total events       132       134       134       14       10.0%       0.99       10.77       1.26         Test for varial effect Z = 0.10 (P = 0.92)       0.50       0.01       0.1       1       10       100         Fest for varial effect Z = 0.10 (P = 0.92)       0.42       2.29       9.50       0.404 s Ratio       0.404 s Ratio </td <td>For analysis 2017       103       4209       100       9225       7.3%       0.38 [0./4, 1.29]         Parameter 2017       3       142       6       143       0.518       3.22]         Ratio 2017       3       142       6       143       0.518       3.22]         Ratio 2017       3       142       6       143       4.558       0.49 [0.12, 2.01]         Ruice 2010       12       497       12       939       0.96       0.99 [0.44, 2.33]         Total (95% CI)       5071       5090       100.0%       0.99 [0.77, 1.26]         Ital events       132       134         Heterogenety: Ch² = 1.62, (13 (P = 0.69); P = 0%)       0.01       0.1       10       100         Favours [control]       I       Favours [control]       Favours [control]       100       100         Faradigm 2014       159       4203       132       4229       91.5%       1.22 [0.96, 1.54]       0dd Ratio         Paradigm 2014       159       4203       132       4229       91.5%       1.22 [0.96, 1.54]       1.54         Paradigm 2014       159       4203       132       422 [0.91, 1.54]       1.44       1.44       0.41       1.41 [0.41, 3.16]</td> <td>-</td> <td>Study or Subgroup</td> <td>Events Te</td> <td>otal Ev</td> <td>ants 100</td> <td>1 otal</td> <td>weight</td> <td>M-H. Fixed, 95% Cl</td> <td>M-H, Fixed, 95% Cl</td>	For analysis 2017       103       4209       100       9225       7.3%       0.38 [0./4, 1.29]         Parameter 2017       3       142       6       143       0.518       3.22]         Ratio 2017       3       142       6       143       0.518       3.22]         Ratio 2017       3       142       6       143       4.558       0.49 [0.12, 2.01]         Ruice 2010       12       497       12       939       0.96       0.99 [0.44, 2.33]         Total (95% CI)       5071       5090       100.0%       0.99 [0.77, 1.26]         Ital events       132       134         Heterogenety: Ch² = 1.62, (13 (P = 0.69); P = 0%)       0.01       0.1       10       100         Favours [control]       I       Favours [control]       Favours [control]       100       100         Faradigm 2014       159       4203       132       4229       91.5%       1.22 [0.96, 1.54]       0dd Ratio         Paradigm 2014       159       4203       132       4229       91.5%       1.22 [0.96, 1.54]       1.54         Paradigm 2014       159       4203       132       422 [0.91, 1.54]       1.44       1.44       0.41       1.41 [0.41, 3.16]	-	Study or Subgroup	Events Te	otal Ev	ants 100	1 otal	weight	M-H. Fixed, 95% Cl	M-H, Fixed, 95% Cl
Ratio 2017       3       142       6       143       4,5%       0,49 [0,12, 2,01]         Ratio 2010       12       497       12       493       9,0%       0,99 [0,44, 2,23]         Total (95% Cl)       5071       5090       100.0%       0,99 [0,44, 2,23]         Total (95% Cl)       5071       5090       100.0%       0,99 [0,44, 2,23]         Total (95% Cl)       5071       5090       100.0%       0,99 [0,77, 1,26]         Test for overall effect 2 = 0.069; P = 0%       0.01       0.1       1       10         Test for overall effect 2 = 0.069; P = 0%       0.01       0.1       100       100         Test for overall effect 2 = 0.069; P = 0%       0.01       0.1       10       100       100         I Forest blot of influenza comparison: LC2696 group vs. ACEL/ARB group.       LC2696 ACEUARB       Odds Ratio       0.046 Ratio         Study or Subgroup       Events Total Events Total Events Total Events Total Events Office 0.9% CL       M-H Events 0.9% CL       M-H Events 0.5% CL         Parandigm 2014       159       403       132       4229       91.5%       1.38 [0.43, 4.44]         Parandigm 2017       7       225       5       3.5%       1.38 [0.43, 4.44]       10         Parandigm 2010 </td <td>Ratio 2017       3       142       6       143       4.5%       0.49 [0.12, 2.01]         Ruliope 2010       12       497       12       493       9.0%       0.49 [0.12, 2.01]         Total (95% CI)       5071       509 100.0%       0.99 [0.44, 2.23]         Total events       132       134         Heterogeneity: Ch<sup>2</sup> = 162, df = 3 (P = 0.66); P = 0%       0.01       0.1       10         Test for overal effect: Z = 0.10 (P = 0.92)       Parours [experimental]       Favours [experimental]       Favours [control]         I       Forcest hold of influenza comparison: LCZ596 group vs. ACEL/ARB group.       Odds Ratio       Odds Ratio       Odds Ratio         Study or Subgroup       Events       Total Events       Total Weight       M-H. Fixed, 95%; CL       M-H. Fixed, 95%; CL         Paradigm 2014       159       420       915, 132       126 (96, 1.54)       127 (96, 1.54)         Paradigm 2014       159       429       4947       100.0%       1.22 [0.96, 1.53]         Total (95%; CL)       429       4947       100.0%       1.22 [0.98, 1.53]         Total (95%; CL)       429       4947       100.0%       1.22 [0.98, 1.53]         Total (95%; CL)       144       Hetorogeneity: Ch<sup>2</sup> = 0.07, df = 2 (P = 0.97); P = 0%<td></td><td>Parameter 2017</td><td>103 4</td><td>203 229</td><td>100</td><td>4229</td><td>7.3%</td><td>0.96 [0.74, 1.29] 1.40 [0.61 3.221</td><td><b>——</b></td></td>	Ratio 2017       3       142       6       143       4.5%       0.49 [0.12, 2.01]         Ruliope 2010       12       497       12       493       9.0%       0.49 [0.12, 2.01]         Total (95% CI)       5071       509 100.0%       0.99 [0.44, 2.23]         Total events       132       134         Heterogeneity: Ch <sup>2</sup> = 162, df = 3 (P = 0.66); P = 0%       0.01       0.1       10         Test for overal effect: Z = 0.10 (P = 0.92)       Parours [experimental]       Favours [experimental]       Favours [control]         I       Forcest hold of influenza comparison: LCZ596 group vs. ACEL/ARB group.       Odds Ratio       Odds Ratio       Odds Ratio         Study or Subgroup       Events       Total Events       Total Weight       M-H. Fixed, 95%; CL       M-H. Fixed, 95%; CL         Paradigm 2014       159       420       915, 132       126 (96, 1.54)       127 (96, 1.54)         Paradigm 2014       159       429       4947       100.0%       1.22 [0.96, 1.53]         Total (95%; CL)       429       4947       100.0%       1.22 [0.98, 1.53]         Total (95%; CL)       429       4947       100.0%       1.22 [0.98, 1.53]         Total (95%; CL)       144       Hetorogeneity: Ch <sup>2</sup> = 0.07, df = 2 (P = 0.97); P = 0% <td></td> <td>Parameter 2017</td> <td>103 4</td> <td>203 229</td> <td>100</td> <td>4229</td> <td>7.3%</td> <td>0.96 [0.74, 1.29] 1.40 [0.61 3.221</td> <td><b>——</b></td>		Parameter 2017	103 4	203 229	100	4229	7.3%	0.96 [0.74, 1.29] 1.40 [0.61 3.221	<b>——</b>
Ruilope 2010         12         497         12         493         9.0%         0.99 [0.44, 2.23]           Total (95% Cl)         5071         5090         100.0%         0.99 [0.77, 1.26]           Total events         132         134           Heterogenetic, Ch <sup>2</sup> = 1.62, (1.67, 1.26]         0.01         0.1         1         10           Test for overall effect. Z = 0.10 (P = 0.92)         0.01         0.1         1         10         100           I         Forest plot of influenza comparison: LCZ696 group vs. ACEI/ARB group.         0.045 Ratio         Odds Ratio         0         0         0 dds Ratio         0         0         0 dds Ratio         0         95% Cl         M-H. Fixed, 95% Cl         M-H. F	Ruitope 2010         12         497         12         493         9.0%         0.99 [0.44, 2.23]           Total (95% CI)         5071         5090         100.0%         0.99 [0.77, 1.26]           Total events         132         134           Heterogeneity: Chi <sup>2</sup> = 1.62, df = 3 (P = 0.66); P = 0%         0.01         0.1         1         10           Test for overall effect. Z = 0.10 (P = 0.92)         0.01         0.1         1         10         100           Fervours [experimental]         Favours [control]         0.01         0.1         1         10         100           Study or Subgroup         Events         Total Events         Total Weight         M-H. Fixed, 95% CI         M-H. Fixed, 95%		D-1- 0047		142	6	143	4.5%	0.49 [0.12, 2.01]	
Total (95% CI)         5071         5090         100.0%         0.99 [0.77, 1.26]           Total events         132         134           Heterogeneity: Ch <sup>2</sup> = 1.62, df = 3 (P = 0.66); P = 0%         0.01         0.1         10           Test for overal effect Z = 0.10 (P = 0.52);         0.01         0.1         10         10           Fest for overal effect Z = 0.10 (P = 0.52);         LCZ696         ACEI/ARB         Odds Ratio         Odds Ratio           LCZ696         ACEI/ARB         Odds Ratio         Odds Ratio         Odds Ratio         Odds Ratio           Study or Subgroup         Events         Total VHM H.F. Fixed, 5% CI         M-H.F. Fixed, 5% CI         M-H.F. Fixed, 5% CI           Paradigm 2014         159         4203         132         4229         91.5%         1.32 [0.64, 3.44]           Parameter 2017         7         229         5         255         3.5%         1.38 [0.43, 4.44]           Ruilope 2010         8         497         7         493         5.0%         1.14 [0.41, 3.16]	Total (95% CI)         5071         5090         100.0%         0.99 [0.77, 1.26]           Total events         132         134           Heterogeneity: Ch <sup>2</sup> = 16.2 (1.67)         166 (2.76)         100           Test for overall effect. Z = 0.10 (P = 0.92)         0.01         1         100           Forest plot of influenza commarison: LCZ696 aroup vs. ACEL/ARB eroup.         CZ696         ACE/ARB         Odds Ratio           Odds Ratio         Odds Ratio         Odds Ratio         Odds Ratio         Odds Ratio           Paradigm 2014         159 4203         132 4229 91.5%         1.32 (0.94).444         100           Paradigm 2010         8 497         7 493         5.0%         1.44 (0.41, 3.16)         1.14 (0.41, 3.16)           Total (95% Cl)         4929         4947         10.0%         1.22 [0.36, 1.53]         1.01 <td></td> <td>Ratio 2017</td> <td>3</td> <td>1000</td> <td>12</td> <td>493</td> <td>9.0%</td> <td>0.99 [0.44, 2.23]</td> <td>-+</td>		Ratio 2017	3	1000	12	493	9.0%	0.99 [0.44, 2.23]	-+
Iotal (95% CI)         5071         5090         100.0%         0.99 [0.77, 1.26]           Total events         132         134           Heterogeneity: Ch <sup>2</sup> = 162, df = 3 (P = 0.66); F = 0%         0.01         0.1         10         100           Test for overall effect: Z = 0.10 (P = 0.92)         Favours [experimenta]         Favours [control]         100           I         Forest plot of influenza comparison: LCZ696 group vs. ACEL/ARB group.         Odds Ratio         Odds Ratio           LC2696         ACEUARB         Odds Ratio         Odds Ratio           Paradigm 2014         159         4203         132         4229         91.5%         122 [0.96, 1.54]           Paradigm 2014         159         4203         132         4229         91.5%         139 [0.43, 4.44]           Ruilope 2010         8         497         7         493         5.0%         1.14 [0.41, 3.16]	I totai (sys, ci)     5071     5090     100.0%     0.99 [0.77, 1.26]       Totai events     132     134       Heterogeneity, Chi² = 162, df = 3 (P = 0.66); P = 0%     0.01     0.1     10       Test for overall effect. Z = 0.10 (P = 0.92)     Parours [experimental]     Favours [experimental]       I Forest hold of influenza comparison: LCZ509 & group vs. ACEL/ARB group.     Odds Ratio       Study or Subgroup     Events     Total Weight. MH. Fixed. 95%; CL       Paradigm 2014     159     4229     15%       Parameter 2017     7     228     5       Total (95% Cl)     4929     4947     100.0%       Total (95% Cl)     4929     4947     100.0%       Test or overall effect. Z = 0.07, df = 2 (P = 0.97); P = 0%     100     1.14 [0.41, 3.16]		Ruilope 2010	12	497	12				
10ait events         1.32         1.34         1.34           Heterogeneity: Ch <sup>2</sup> = 1.62, (H = 3 (P = 0.66); P = 0%)         0.01         0.1         100           Test for overall effect: Z = 0.10 (P = 0.92)         0.01         1         10         100           I         Forest plot of influenza commarism: LCZ696 group vs. ACEL/ARB group. LC2696 ACEL/ARB velot.         Odds Ratio         0.0ds Ratio         0.0ds Ratio           Study or Subgroup.         Events Total Events         Total Events         Total 22 (9.65, 1.54)         100           Paradigm 2014         159         4203         132         4229         91.5%         1.39 (0.34, 4.44)           Paradigm 2017         7         229         5.255         3.5%         1.36 (0.34, 4.44)           Ruilope 2010         8         497         7         493         5.0%         1.14 [0.41, 3.16]	10at events         1.32         1.34           Heterogeneity: Ch <sup>2</sup> = 16.2 (# 3 (P = 0.66); # = 0%);         0.01         0.1         100           Test for overall effect: Z = 0.10 (P = 0.92);         0.01         1         10         100           Forest plot of influenza comparison: LCZ696 acroup vs. ACEL/ARB group.         0.01         1         10         100           Study or Subproup.         Events         Total         Events         0.04         H.Fixed, 95% CI         M.H.Fixed, 95% CI           Paradigm 2014         159         4209         158, 122 (0.96, 1.54)         1         1.14 (0.41, 3.16)         1           Total (95% Cl)         4929         4947         10.0%         1.22 (0.38, 1.53)         1         1         1         1         1         1         0.01         0.1         1         1         0         1         0.01         0.1         1         0.01         0.1         1         0         0         1         1         0         1         1         0         1         1         0         1         1         0         1         1         1         1         1         1         1         1         1         1         1         1         1 <td< td=""><td></td><td>Ruilope 2010</td><td>12</td><td>497</td><td>12</td><td></td><td></td><td>A AA IA</td><td><b>A</b></td></td<>		Ruilope 2010	12	497	12			A AA IA	<b>A</b>
Index ur = 0 (r = 0.00), r = 0.00, r = 0.	Image 100, 101     1     100       Test for overall effect: 2 0.10 (P = 0.92).     0.01     0.1     1     100       Forest plot of influenza comparison: LCZ696 eroup vs. ACEL/ARB group.     Dodds Ratio     Odds Ratio       Study or Subgroup     Events Total Events Total Weight     M-H. Fixed, 95% Cl     M-H. Fixed, 95% Cl       Parameter 2017     7     229     5     225     3.5%     1.32 (0.96, 1.54)       Parameter 2017     7     229     5     225     3.5%     1.38 (0.43, 4.44)       Ruilope 2010     8     497     7     493     5.0%     1.14 (0.41, 3.16)       Total events     174     144     144     144     1.17 (0.0%)     1.22 (0.96, 1.53)       Test for overall effect: 2 - 1.75 (P = 0.08)     0.01     0.1     0.1     1     100		Ratio 2017 Ruilope 2010 Total (95% CI)	12 5	497 071	12	5090	100.0%	0.99 [0.77, 1.26]	<b>•</b>
Forest plot of influenza comparison: LCZ696 group vs. ACEI/ARB group. LCZ696 ACEI/ARB Odds Ratio         Favours [experimental]         Favours [control]           I Forest plot of influenza comparison: LCZ696 accEI/ARB group.         Odds Ratio         Odds Ratio         Odds Ratio           Study or Subgroup         Events         Total         Events         Total         Events         Odds Ratio           Paradigm 2014         169         4203         132         4229         91.5%         1.38 [0.43, 4.44]         Parameter 2017         7         229         5         2.5%         1.38 [0.43, 4.44]         Parameter 2017         Paradigm 2010         8         497         7         493         5.0%         1.14 [0.41, 3.16]         Parameter 2017         7         249         5.0%         1.38 [0.43, 4.44]         Parameter 2017         Parameter 2017         7         249         5.0%         1.14 [0.41, 3.16]         Parameter 2017         Parameter 2	Forest nlot of influenza comparison: LCZ696 eroup vs. ACEI/ARB eroup.           Forest nlot of influenza comparison: LCZ696 acEuARB Odds Ratio           Study or Subgroup Events Total Events Total Weight MH. Fixed, 95% CI           Paradigm 2014         159 4203         132 4229         15%         122 (096, 1.54)           Parameter 2017         7         228         5         25% of 1.38 [0.43, 4.44]           Ruilope 2010         8         497         7         493         5.0%         1.14 [0.41, 3.16]           Total (95% CI)         4929         4947         100.0%         1.22 [0.98, 1.53]         1.01         0.01         0.1         1         100         100         100         100         100         100         100         0.01         0.1         <		Ratio 2017 Ruilope 2010 Total (95% CI) Total events	3 12 51 132 62 df = 2 df	497 071 P = 0.60	134	5090	100.0%	0.99 [0.77, 1.26]	• · · · · · · · · · · · · · · · · · · ·
I Forest plot of influenza comparison: LCZ696 group vs. ACEU/ARB group. LC2696 ACEU/ARB volume and the second of	I Forest plot of influenza commarison: LCZ696 arcupu x. ACEU/ARB group.           Odds Ratio           Odds Ratio           Odds Ratio           Data Study or Subgroup         Events Total Events Total Weight M-H Fixed 95% CI         M-H. Fixed 95% CI           Paradigm 2014         159 4220 132 4229 91.5%         Lag 2006 1.54]           Paradigm 2017 7 229 5 225 3.5%         1.38 [043, 4.44]           Total (95% CI)         4947 100.0%         1.22 [0.38, 1.53]           Total events         Total events         174         144           Heterogeneity: Chi* = 0.07, df = 2 (P = 0.97); l* = 0%         Odd Stature E C 26001         Expressive 10.001           Total events         174         144           Heterogeneity: Chi* = 0.07, df = 2 (P = 0.97); l* = 0%           Odd Stature E C 26001         Expressive 10.001		Ratio 2017 Ruilope 2010 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2	5 12 50 132 .62, df = 3 (0 2 = 0, 10 /P -	497 071 P = 0.66 = 0.92)	134 ;; l² = (	5090 )%	100.0%	0.99 [0.77, 1.26]	01 0.1 1 10 1
LC2696         ACEUARB         Odds Ratio         Odds Ratio           Study or Subcroup         Events         Total Version         Study of Subcroup         Study of Subcroup           Paradigm 2014         159         4203         132         4229         91.5%         122 [0.96, 1.54]           Paradigm 2014         159         4203         132         4229         91.5%         132 [0.43, 4.44]           Parameter 2017         7         229         5         25%         1.5%         1.38 [0.43, 4.44]           Ruilope 2010         8         497         7         493         5.0%         1.14 [0.41, 3.16]	LC2696         ACEUARB         Odds Ratio           _Study or Subgroup         Events         Total         Events         Total         Weight         M-H, Fixed, 95% CI         M-H, Fix		Ratio 2017 Ruilope 2010 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2	12 12 132 .62, df = 3 (l : = 0.10 (P =	497 071 P = 0.66 = 0.92)	134 ; I <sup>2</sup> = (	5090 )%	100.0%	0.99 [0.77, 1.26]	01 0.1 1 10 1 Favours [experimental] Favours [control]
Study or Subgroup         Events         Total         Weight         M-H. Fixed, 95% Cl         M-H. Fixe	Study or Subgroup         Events         Total         Weight         M-H. Fixed, 95% CI         M-H. Fixed, 95% CI           Paradigm 2014         159         4209         152         429         5         225         3.5%         1.38 [0.43, 4.44]           Parameter 2017         7         229         5         225         3.5%         1.38 [0.43, 4.44]           Ruiope 2010         8         497         7         493         5.0%         1.14 [0.41, 3.16]           Total (95% CI)         4929         4947         100.0%         1.22 [0.38, 1.53]         1.01         1.01         1.01           Total (95% CI)         4929         4947         100.0%         1.22 [0.38, 1.53]         1.01 <td>I</td> <td>Ratio 2017 Ruilope 2010 Total (95% CI) Total events Heterogeneity: Chi<sup>2</sup> = 1 Test for overall effect: 2 Forest plot of influe</td> <td>12 132 .62, df = 3 (( = 0.10 (P = nza compa</td> <td>497 071 P = 0.66) = 0.92) arison: 1</td> <td>134 ;; I<sup>2</sup> = ( LCZ6</td> <td>5090 )% 96 gr</td> <td>100.0% oup vs. 4</td> <td>0.99 [0.77, 1.26]</td> <td>01 0.1 1 10 1 Favours [experimental] Favours [control]</td>	I	Ratio 2017 Ruilope 2010 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2 Forest plot of influe	12 132 .62, df = 3 (( = 0.10 (P = nza compa	497 071 P = 0.66) = 0.92) arison: 1	134 ;; I <sup>2</sup> = ( LCZ6	5090 )% 96 gr	100.0% oup vs. 4	0.99 [0.77, 1.26]	01 0.1 1 10 1 Favours [experimental] Favours [control]
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Parameter 2017 7 229 5 225 3.5% 1.39 [0.43, 4.44] Ruilope 2010 8 497 7 493 5.0% 1.14 [0.41, 3.16]	Parameter 2017         7         229         5         25         3.5%         1.39 (0.43, 4.44)           Ruilope 2010         8         497         7         493         5.0%         1.14 [0.41, 3.16]           Total (95% CI)         4929         4947         100.0%         1.22 [0.96, 1.53]           Total events         174         144           Heterogeneity: Chi² = 0.07, df = 2 (P = 0.97); l² = 0%         0.01         0.1         0.1         1         10         100           Test for ovall effect: Z = 1.75 (P = 0.08)         C26001 Encourse (C26001 Encourse)         C26001 Encourse (C26001 Encourse)         C26001 Encourse         C260	I	Railo 2017 Ruilope 2010 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2 Forest plot of influe <u>Study or Subgroup</u>	3 12 50 132 .62, df = 3 (( = 0.10 (P = nza compa LCZ69 Events	497 071 P = 0.66) = 0.92) arison: 1 6 <u>Total E</u>	134 ; I <sup>2</sup> = ( LCZ6 ACEI/	5090 )% 96 gr ARB Tota	100.0% oup vs. <i>i</i>	0.99 [0.77, 1.26] ACEI/ARB group. Odds Ratio M-H. Fixed. 95% C	01 0.1 1 0 1 Favours (experimental) Favours (control) Odds Ratio M-H. Fixed, 95% Cl
ruilope zo to o 491 / 493 3.0% 1.14 [U.41, 3.10]	Total (95% CI)         4929         4937         1.18 [0.41, 3.16]           Total (95% CI)         4929         4947         100.0%         1.22 [0.38, 1.53]           Total vents         174         144         Heterogeneity: Chi <sup>2</sup> = 0.07, df = 2 (P = 0.97); l <sup>2</sup> = 0%         0.01         0.1         1         10         00           Test for ovall effect: 2 = 1.75 (P = 0.08)         0.01         0.1         0.1         0.1         10.100	I	Railo 2017 Ruilope 2010 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2 Forest plot of influe <u>Study or Subgroup</u> Paradigm 2014	3 12 50 132 62, df = 3 (l = 0.10 (P = nza comp: LCZ69 Events 159	497 071 P = 0.66 = 0.92) arison: 1 6 <u>Total E</u> 4203	134 ;; I <sup>2</sup> = ( LCZ6 ACEI/ <u>Events</u> 132	5090 )% 96 gr ARB Tota 4229	100.0% oup vs. <i>A</i> Weight 91.5%	0.99 [0.77, 1.26] ACEI/ARB group. Odds Ratio M-H. Fixed. 95% C 1.22 [0.96, 1.54]	01 0.1 1 10 1 Favours [experimental] Favours [control] Odds Ratio M-H, Fixed, 95% GI
	Total (95% CI)         4929         4947         100.0%         1.22 [0.98, 1.53]           Total events         174         144           Heterogeneity: Chi <sup>2</sup> = 0.07, df = 2 (P = 0.97); P = 0%         0.01         0.1         1         1         0         100           Test for overall effect: 2 = 1.75 (P = 0.08)         0.01         0.1         0.1         0.1         100         100	Ι	Ratio 2017 Ruilope 2010 Total (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2 Forest plot of influe <u>Study or Subgroup</u> Paradigm 2014 Parameter 2017	3 12 54 132 .62, df = 3 (l = 0.10 (P = nza compa LCZ69 Events 159 7	497 071 P = 0.66] = 0.92) arison: 1 6 <u>Total E</u> 4203 229 497	134 ; I <sup>2</sup> = ( LCZ6 ACEI/ vents 132 5	5090 )% 96 gr ARB Tota 4229 225	100.0% oup vs. 4 Weight 91.5%	0.99 [0.77, 1.26] CEI/ARB group. Odds Ratio M-H. Fixed, 95% C 1.22 [0.96, 1.54] 1.39 [0.43, 4.44]	01 0.1 1 0 1 Favours [experimental] Favours [control] Odds Ratio M-H. Fixed, 55% Cl
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Heterogeneity: Chi <sup>2</sup> = 0.07, df = 2 (P = 0.97); l <sup>2</sup> = 0%	Test for overall effect: Z = 1.75 (P = 0.08)	Ι	Ratio 2017 Ruliope 2010 Total (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2 Forest plot of influe <u>Study or Subgroup</u> Paradigm 2014 Parameter 2017 Ruliope 2010 Total events	5 12 5 132 .62, df = 3 (( = 0.10 (P = 128 comp LCZ69 Events 159 7 8	497 071 P = 0.66 = 0.92) arison: 1 6 <u>Total E</u> 4203 229 497 4929	134 ; I <sup>2</sup> = ( LCZ6 ACEI/ ivents 132 5 7 144	5090 )% 96 gr ARB 10ta 4229 225 493 4947	100.0% Oup vs. 4 Weight 91.5% 5.0% 100.0%	0.99 [0.77, 1.26] ACEI/ARB group. Odds Ratio M-H. Fixed. 95% C 1.22 [0.96, 1.54] 1.39 [0.43, 4.44] 1.14 [0.41, 3.16] 1.22 [0.98, 1.53]	01 0.1 1 10 1 Favours [experimental] Favours [control] Odds Ratio M-H. Fixed, 55% Cl
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#: The data of Paradigm-HF study in this part was from Supplementary Appendix of their article.

Figure 3: Forest plots depicting the comparison of LCZ696 and a placebo or ACEI/ARB on other adverse effects.

renal impairment were less [9], or at least no more [10], frequent in the LCZ696 group than in the ACEI/ARB group. In the present study, we only aimed to consider the effect of LCZ696 on renal dysfunction, so we extracted the relevant data of the PARAMOUNT study and the PARADIGM-HF study. The result again confirmed the significant protective effect of LCZ696 on renal function over ACEI or ARB alone. However, since the data we used were from the 2 above studies, it cannot be seen as a new discovery, and the conclusion still need to be confirmed by new investigations.

The most important finding in the present metaanalysis is the confirmation of LCZ696 on any adverse event, serious adverse event and discontinuation of treatment for any adverse event. Integrating all of the 6 studies, we found that no matter compared of a placebo or ACEI/ARB, LCZ696 didn't increase the risk of any adverse events, which proved the safety of the drug. Simultaneously, to our surprise, fewer patients displayed serious adverse events, and fewer patients stopped their study medication for an adverse event in the LCZ696 group than in the ACEI/ARB group. Even compared with the placebo group, LCZ696 treatment also showed a smaller risk of discontinuation of the medication, which greatly encouraged us. In addition, we also summarized the results of other adverse effects repeatedly mentioned in the studies. Compared with the ACEI/ARB group, LCZ696 decreased the occurrence of the risk of bronchitis, but increased the occurrence of the risk of dizziness, which might need us to pay more attention. There was no difference for cough, upper respiratory tract inflammation, diarrhoea, back pain, nasopharyngitis, headache and influenza.

It is worth mentioning that Neprilysin is a major enzyme responsible for the degradation of Amyloid  $\beta$  (A $\beta$ ) peptide. Accumulation of toxic levels of  $A\beta$  in the brain leads to the dementia cases in the elderly population. In the previous study, although neprilysin knockout in mice has been confirmed to be responsible for the impairment of cognitive function [20], neprilysin overexpression did not improve deficits in spatial learning and memory in neprilysin transgenic mice [21]. The authors claimed that cognition, memory, and dementia-related adverse events were not increased in the LCZ696 group in the PARADIGM-HF study in their reply to reviewers [9]. And they thought that it was possible that cognitive decline related to vascular disease might be reduced by LCZ696. In addition, none of the 6 studies included in the present meta-analysis related the occurrence of the cognitive function impairment. Another large doubleblind, parallel-group RCT, the PARAGON-HF study, which enrolled 4300 patients over a maximum follow-up period of 57 months, including repeated measurements of cognitive function in patients, might provide more evidences in cognitive function.

There are a number of limitations to our metaanalysis. First, in order to minimize the heterogeneity and bias, we used strict selection criteria, and thus only 6 randomized controlled trials of LCZ696 met the inclusion criteria. Furthermore, although the number of participants included in the study reached 11,821, most of them were from the PARDIGM-HF study. In addition, except for PARDIGM-HF study (27 months) and Parameter study (52 weeks), the other studies were generally short, so the results on the adverse effects only reflected the short-term effects of LCZ696. Therefore, we are anticipating the new larger trials of LCZ696, such as the PARAGON study and the UKHARP study, which will provide more useful information for us.

## **MATERIALS AND METHODS**

# Data source, search strategy, and inclusion criteria

EMBASE, PubMed and the Cochrane Library of Trials were carefully searched from April 2010 to May 2017 for the study. The following search terms or key words were used alone or in combination: 'sacubitril/ valsartan', 'LCZ696', 'neprilysin inhibitor', 'AHU377', 'valsartan', 'enalaprilat', 'hypertension' and 'heart failure'. After initially identifying 1072 potential trials, 336 duplicate documents were identified and 724 documents that were not clinical trials were excluded. The remaining 12 trials were carefully evaluated and 6 trials were excluded because there were less than 100 participants or they were non-controlled trials. Finally, a total of 6 eligible RCTs with 11,821 patients were included (Figure 4). All the 6 articles were published in English, conducted on human subjects, and classified as RCTs (Table 1). All of the 6 studies were at a lower risk of bias. These studies were conducted according to published protocols and randomization, double blinding, controlling, intention-to treat (ITT) were all performed for all of these studies. Risk of bias analysis was shown in Figures 5 and 6.

#### Data synthesis and statistical analysis

All analyses were performed using RevMan software version 5.3. Pooled risk ratios (RR) with 95% CIs were presented for dichotomous outcomes (e.g. AEs, serious AEs, and discontinuation of participants in the trials, as well as hypotension, renal impairment and hyperkalemia). The results of the included studies were performed with fixed-effect models (Mantel–Haenszel method) [22] or random-effect models in cases of significant heterogeneity between estimates [23]. We used the I<sup>2</sup> statistics to assess the magnitude of heterogeneity: 25%, 50%, and 75%

Table 1: Baseline characteristics of the 4 included trials

Study	Country	Population	LCZ696 Dose (mg/d)	Control group and Dose (mg/d)	Age	LCZ696 group (n)	Control group (n)	Follow up	End-point
Ruilope 2010	18 countries	Hypertension	100-400 mg qd	Valsartan 80–320mg qd/ AHU377 200mg qd/ placebo	18–75 y	497	493/165/172	8 w	Sitting diastolic blood pressure
Paramount 2012	13 countries	Heart Failure	200 mg bid	Valsartan 160 mg bid	$\geq 40 \text{ y}$	149	152	36 w	Death
Kavio 2014	5 Asian countries	Hypertension	100-400 mg qd	placebo	$\geq 18 \text{ y}$	297	92	8 w	Diastolic BP
Paradigm 2014	47 countries	Heart Failure	200 mg bid	Enalapril 10 mg bid	18–96 y	4187	4212	27 m	Death
Ratio 2017	9 countries	Hypertension	400 mg qd	Valsartan 320 mg qd	≥18 y	142	143	8 w	Sitting systolic blood pressure
Parameter 2017	12 countries	Hypertension	400 mg qd	Olmesartan 40mg qd	$\geq$ 60 y	229	225	52w	central aortic systolic pressure

represented low, moderate, and high degrees of heterogeneity respectively. The effect model chosen was based on the analysis results: the fixed effect model was used if  $I^2 < 50\%$ and the random effect model was used if  $I^2 \ge 50\%$  [24].



Figure 4: Flow diagram of the study selection process.



Figure 5: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Figure 6: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

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# **CONFLICTS OF INTEREST**

None declared.

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