Mortality Risk Associated With Long-acting Injectable Antipsychotics: A Systematic Review and Meta-analyses of Randomized Controlled Trials

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Long-acting injectable (LAI) antipsychotics (LAI-APs) have several advantages over oral medications, but deaths reported in Japan during the early post-marketing phase vigilance period have raised safety concerns. We conducted a series of meta-analyses to assess whether LAI-APs affect the mortality of patients with schizophrenia. Three categorical meta-analyses of randomized controlled trials (RCTs) were performed to compare all-cause death (primary outcome) and death due to suicide: individual and pooled LAI-APs vs placebo, individual and pooled LAI-APs vs oral antipsychotics (OAPs), and head-to-head comparisons of LAI-APs. The risk ratios (RRs) and 95% CIs were calculated. We identified 52 RCTs (53 comparisons; total participants = 17 416, LAI-APs = 11 360, OAP = 3910, and placebo = 2146; mean study duration [wk]: LAI-APs vs placebo = 28.9, LAI-APs vs OAPs = 64.5). Neither pooled nor individual LAI-APs (aripiprazole, fluphenazine, olanzapine, paliperidone, and risperidone) differed from the placebo regarding the incidences of all-cause death (pooled LAI-APs: RR = 0.64, P = .37) and death due to suicide (pooled LAI-APs: RR = 0.98, P = .98). However, in a subgroup meta-analysis of only short-duration RCTs (≤13 wk), pooled LAI-APs exhibited a trend toward lower incidence of all-cause death than placebo (RR = 0.29, P = .08). Pooled LAI-APs (aripiprazole, fluphenazine, haloperidol, olanzapine, paliperidone, risperidone, and zuclopenthixol) did not differ from pooled OAPs regarding all-cause death (pooled LAI-APs: RR = 0.71, P = .30) and death due to suicide (pooled LAI-APs: RR = 0.94, P = .91). Individual LAI-APs and OAPs were associated with similar risks of death. Data for head-to-head comparisons of individual LAI-APs were insufficient. In conclusion, there was no significant difference between LAI-APs and placebo or OAPs regarding all-cause death and death due to suicide.

Key words: long-acting injectable antipsychotics/mortality/schizophrenia/meta-analysis/systematic review

Introduction

People with schizophrenia have a substantially higher risk of early death in comparison with the general population[1,2] (standardized mortality ratio = 3.6–3.7[3,4]). Probable causes for this increased mortality include a greater risk of various comorbid somatic conditions[5–7] and higher incidence of suicide.[8,9] Second-generation antipsychotics (SGAs) are known to induce severe adverse events such as metabolic syndrome and diabetes, which are important risk factors for cardiovascular and cerebrovascular diseases.[10] Moreover, patients with schizophrenia often lead a more sedentary lifestyle and are less motivated to improve their physical condition because of the effects of medication and/or their symptoms, which further increase their risk of developing metabolic syndrome.[11] A meta-analysis by Saha et al pertaining to mortality associated with schizophrenia reported that all-cause mortality has increased since the late 1990s when SGAs became widely used. People with schizophrenia are at a high risk of attempting and committing suicide (10%–13%).[8] A recent systematic review reported that suicide risk in patients with schizophrenia is particularly associated with affective symptoms, history of suicide attempt, and number of psychiatric hospitalizations for relapse.[12] A meta-analysis concluded that antipsychotics are superior to placebo for relapse prevention with large effect size (risk ratio [RR] = 0.40; 95% CI = 0.33−0.49; number needed to treat to benefit = 3).[13] In addition, several Finnish nationwide cohort studies reported that current antipsychotic use is associated with a lower mortality risk than non-antipsychotic use.[14–16] A recent observational cohort study of schizophrenia in Sweden reported that moderate- (0.5–1.5 defined daily dose/d, ATC/DDD Index, http://www.whocc.no/atc_ddd_index/) and high-dose antipsychotics (≥1.5 defined daily dose/d) are associated with a lower overall mortality in comparison with no antipsychotic exposure (moderate: adjusted hazard

ratio [HR] = 0.59, 95% CI = 0.49–0.70; high: adjusted HR = 0.75, 95% CI = 0.63–0.89).[17] Furthermore, considering only suicide mortality, exposure to high doses of antipsychotics is associated with a lower risk of death in comparison with no antipsychotic exposure (adjusted HR = 0.43, 95% CI = 0.24–0.78).[17] Moreover, the FIN11 study provided evidence that there are significant differences in the risks of mortality associated with individual antipsychotics.[14] Considering the current use of perphenazine as the reference, the highest risk for overall mortality has been recorded with the use of quetiapine (adjusted HR = 1.41, 95% CI = 1.09−1.82) and the lowest risk with the use of clozapine (adjusted HR = 0.74, 95% CI = 0.60−0.91). All the studies cited above suggest that antipsychotic dose and type are major factors determining mortality in people with schizophrenia.

Does the form of antipsychotic drug influence mortality in people with schizophrenia? Long-acting injectable (LAI) antipsychotics (LAI-APs) are considered to have several pharmacokinetic benefits in comparison with oral antipsychotics (OAPs), including (1) an improvement in stability within the blood, (2) more consistent bioavailability, (3) more predictable medication adherence, and (4) an improvement in the pharmacokinetic profile, all of which allow for the use of lower antipsychotic dosages.[18] Consequently, the LAI-APs are expected to have greater relapse prevention[19] and reduce the incidence of adverse events[18] in comparison with OAPs. Therefore, we hypothesized that LAI-APs decrease mortality to a greater extent in comparison with OAPs, at least in part, because of these advantages over OAPs. However, a recent meta-analysis also reported that SGA-LAIs were associated with a higher incidence of extrapyramidal symptoms in comparison with OAPs (RR = 1.45, 95% CI = 1.00–2.10).[20] Moreover, from the launch of the SGA-LAI paliperidone palmitate in Japan from November 19, 2013, to May 18, 2014 (the estimated the number of users for this 6-month period was approximately 11 000), 32 patients died during the early post-marketing phase vigilance period.[21] Therefore, there is a growing concern among Japanese clinicians and patients that LAI-AP use may increase the risk of death. However, this remains unclear as no meta-analysis of LAI-AP trials regarding mortality in people with schizophrenia has been reported to date.

The overall incidence of death in randomized controlled trials (RCTs) involving pharmacotherapy for the treatment of schizophrenia is very low. Therefore, it is difficult for a single RCT to accurately estimate the risk of such rare adverse events because of low statistical power (ie, insufficient sample size).[22] A meta-analysis can increase the statistical power for group comparisons and can overcome the limitation of sample size in underpowered studies.[22] Here to determine whether LAI-APs are associated with higher mortality in people with schizophrenia, we performed several categorical meta-analyses of RCTs.

Methods

These meta-analyses were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[23]

Search Strategy and Inclusion Criteria of Studies

To identify relevant RCTs, 2 authors (T.K. and S.M.) independently searched MEDLINE, Cochrane Library, and PsycINFO without language restrictions from inception to March 8, 2016 using the following search strategy: schizophrenia AND randomized AND antipsychotic, neuroleptic or an individual LAI-AP name[24] (aripiprazole, bromperidol, clopenthixol, flupenthixol, fluphenazine, fluspirilene, haloperidol, iloperidone, olanzapine, oxyprothepin, paliperidone, penfluridol, perphenazine, pipothiazine, risperidone, or zuclopenthixol) AND depot, enanthate, decanoate, long-acting injection, microsphere, once monthly, palmitate, or pamoate. Two authors (T.K. and S.M.) independently assessed the inclusion and exclusion criteria and selected relevant studies. The references of the included articles and review articles (a list of the review articles is presented in supplementary appendix 1) were also searched for citations of further relevant published and unpublished research, such as conference abstracts.

Data Synthesis and Outcome Measures

The outcome measures were all-cause death (primary) and death due to suicide.

Data Extraction

Two authors (T.K. and S.M.) independently extracted data from the included studies. We used intention-to-treat or a modified intention-to-treat for analysis. When the data required for the meta-analysis were missing, we contacted the study investigators and requested the unpublished data. The following 3 categorical meta-analyses of RCTs were performed for evaluating each outcome: (1) individual and pooled LAI-APs vs the placebo; (2) individual and pooled LAI-APs vs OAPs; and (3) head-to-head comparisons of LAI-APs.

Meta-analytic Methods

These meta-analyses were conducted using Review Manager software (Version 5.3 for Windows, Cochrane Collaboration, http://tech.cochrane.org/Revman). The random effects model was chosen because of the potential heterogeneity across studies. The RR was estimated along with a 95% CI for each meta-analysis. We also planned to investigate study heterogeneity using a chi-square test of homogeneity ($P < .05$) together with the I^2 statistic, considering $I^2 \geq 50\%$ indicative of considerable heterogeneity.[25]

We also performed an individual subgroup meta-analyses of "pooled LAI-APs vs placebo" and "pooled LAI-APs vs OAPs" regarding the primary outcome stratified by antipsychotic group (SGAs vs first-generation antipsychotics [FGAs]), duration of study (short vs long), sponsorship (industry sponsored vs nonindustry sponsored), current disease status (studies including patients with acute symptoms vs studies including only stable patients), and the LAI-AP dose (haloperidol equivalents). We also added the following 2 subgroup meta-analyses of "pooled LAI-APs vs OAPs:" comparator antipsychotic dose (haloperidol equivalents), comparator antipsychotic group (SGAs vs others), and presentation style (published articles vs unpublished conference abstract). The antipsychotic doses were converted into haloperidol equivalents using published guidelines.[26–28] For LAI-APs, we used the manufacturers' recommended equivalent for the depot to oral conversion for the same drug and then converted into oral haloperidol equivalents. The median duration of the "pooled LAI-APs vs placebo" and "pooled LAI-APs vs OAPs" studies were used as cutoffs for distinguishing between short and long-duration studies. The subgroup analyses divided by antipsychotic dose also used a median dose of antipsychotics as cutoffs. Studies including patients with acute symptoms were those accepting patients with acutely symptomatic schizophrenia or an acute exacerbation of schizophrenia. Because the study quality regarding the use of "an unpublished conference abstract" is difficult to assess because of its incompleteness,[29] we examined a subgroup analysis regarding presentation style (published articles vs unpublished conference abstracts). For head-to-head comparisons, we conducted the following 3 subgroup meta-analyses: (1) paliperidone palmitate vs other pooled LAI-APs (aripiprazole, haloperidol, and risperidone); (2) zuclopenthixol vs other pooled LAI-APs (flupenthixol, haloperidol, and perphenazine); and (3) SGA-LAIs (paliperidone and risperidone) vs FGA-LAIs (fluphenazine/haloperidol and haloperidol). Both the funnel plot and Egger's regression test (Comprehensive Meta-Analysis Version 2.0) were used to evaluate publication bias. In addition, we assessed the methodological quality of the trials with the Cochrane risk-of-bias criteria.[22]

Results

Study Characteristics

Of 6665 hits, we removed 5270 duplicates, 1184 references based on abstract/title review, and 76 articles after a full-text review (56 review articles and 20 identical studies), retaining 135 RCTs for the systematic review (supplementary figure 1). Moreover, we retrieved 16 additional RCTs by searching through the review articles, for a total of 151 RCTs (supplementary figure 1). However, 99 articles did not report data regarding death during the study (supplementary figure 1 and appendix 2). Therefore, only 52 (participant numbers: total $n = 17\,416$; LAI-APs = 11 360; OAPs = 3910; placebo = 2146) were included in the meta-analyses (supplementary figure 1 and appendix 3). The details of each study are described in supplementary table 1. The number of studies for each individual LAI-AP and the corresponding total number of participants are as follows: aripiprazole = 6 ($n = 1493$), fluphenazine = 9 ($n = 376$), flupentixol = 1 ($n = 30$), fluphenazine/haloperidol = 1 ($n = 32$), haloperidol = 4 ($n = 342$), olanzapine = 3 ($n = 1169$), perphenazine = 1 ($n = 85$), paliperidone = 16 ($n = 4092$), risperidone = 18 ($n = 3562$), and zuclopenthixol = 4 ($n = 179$). The number of studies regarding each individual OAP and the corresponding total number of participants are as follows: aripiprazole = 3 ($n = 669$), fluphenazine = 3 ($n = 139$), haloperidol = 2 ($n = 275$), olanzapine = 4 ($n = 903$), physicians' choice among OAPs = 3 ($n = 800$), physicians' choice among SGAs = 3 ($n = 639$), pimozide = 1 ($n = 24$), risperidone = 4 ($n = 441$), and zuclopenthixol = 1 ($n = 20$). The median duration of "LAI-APs vs placebo" studies was 13 weeks and that of "LAI-APs vs OAPs" studies was 52 weeks. Patients in all studies included in the meta-analysis were adults (there were no studies that included specifically adolescent or elderly patients). The median LAI-AP dose (haloperidol equivalent) of the "LAI-APs vs placebo" studies was 4.03 mg/d and the "LAI-APs vs OAPs" studies was 3.34 mg/d. The median OAPs dose (haloperidol equivalent) of "LAI-APs vs OAPs" studies was 4.07 mg/d. One of the 52 RCTs was an unpublished conference abstract.[30] Eleven of the 52 RCTs included acute phase patients, such as patients with acutely symptomatic schizophrenia or acute exacerbation of schizophrenia. Of the 52 RCTs, 37 were industry-sponsored, and 18 were not double blinded. The detailed methodological quality of the RCTs based on the Cochrane risk-of-bias criteria are presented in supplementary figures 2 and 3.

LAI-APs vs Placebo

Neither the pooled LAI-APs nor any single individual LAI-AP (aripiprazole, fluphenazine, olanzapine, paliperidone, and risperidone) outperformed the placebo regarding the incidence of all-cause death (figure 1) and death due to suicide (supplementary figure 4). We did not find significant heterogeneity with respect to the primary outcome in the meta-analysis. In addition, we also did not detect publication bias (Egger's regression test: $P = .548$, funnel plot: supplementary figure 5). However, in a subgroup meta-analysis using only short-duration RCTs (≤13 wk), pooled LAI-APs exhibited a trend towards a lower incidence of all-cause death in comparison with the placebo (RR = 0.29; 95% CI = 0.07 − 1.16; $P = .08$; $I^2 = 0\%$; $N = 10$; $n = 4217$; table 1). We did not find significant differences in any of the other subgroup analyses between LAIs and placebo (table 1).
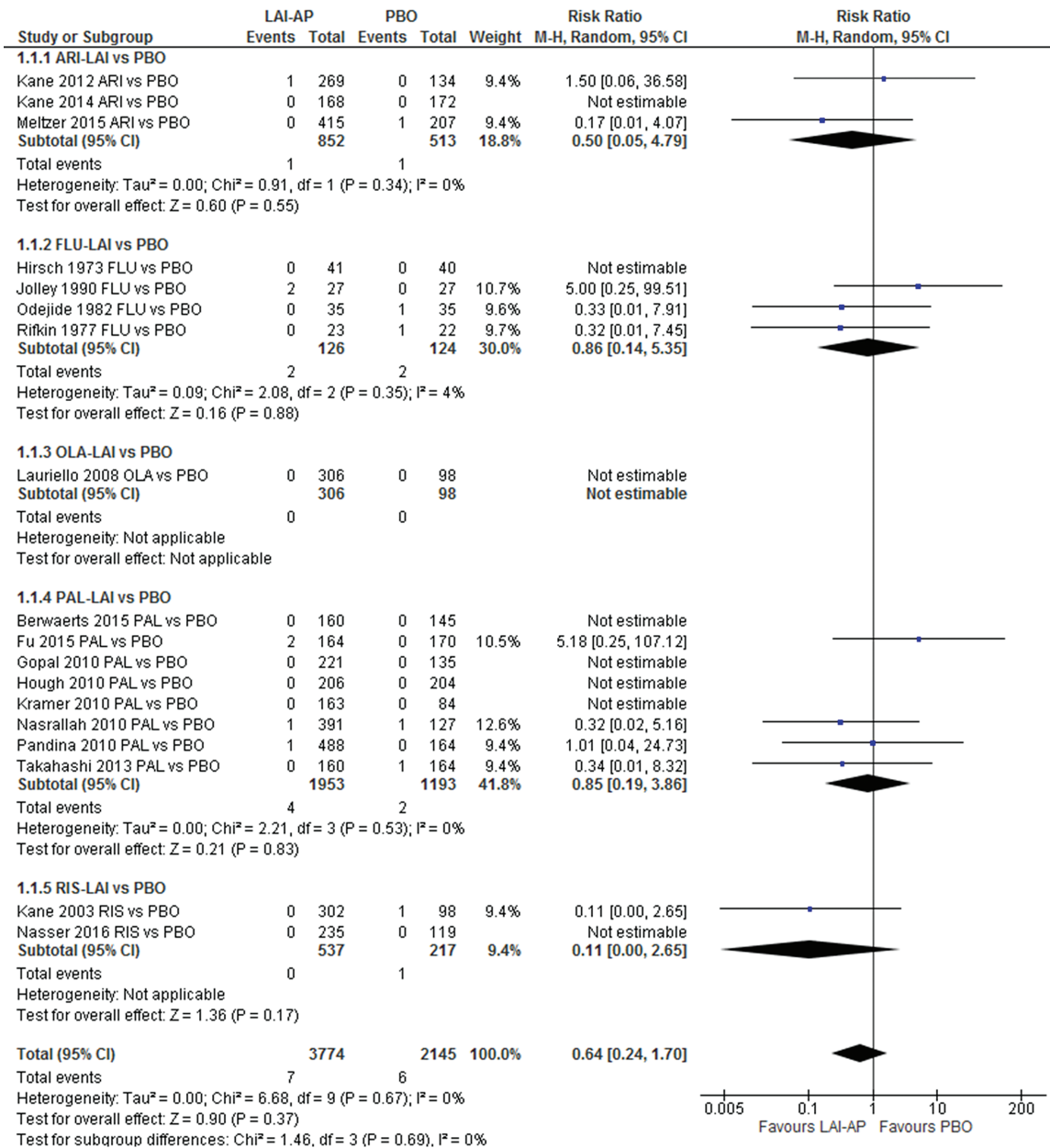
Fig. 1. All-cause death: long-acting injectable antipsychotics vs placebo. AP: antipsychotic; ARI: aripiprazole; FLU: fluphenazine; LAI: long-acting injectable; OLA: olanzapine; PAL: paliperidone; PBO: placebo; RIS: risperidone.

LAI-APs vs OAPs

Neither the pooled LAI-APs nor any single individual LAI-AP (aripiprazole, fluphenazine, haloperidol, olanzapine, paliperidone, risperidone, and zuclopenthixol) differed from OAPs regarding the incidence of all-cause death (figure 2) and death due to suicide (supplementary figure 6). We did not find significant heterogeneity with respect to the primary outcome in the meta-analysis. We did not detect publication bias (Egger's regression test: *P* = .949; funnel plot: supplementary figure 7) or significant differences in any of the subgroup analyses between the pooled LAI-APs and OAPs (supplementary table 2).

LAI-AP vs LAI-AP

The meta-analyses of the head-to-head LAI-AP comparisons did not exhibit any significant differences in all-cause death and suicide (supplementary figures 8 and 9). There were also no differences in the incidence of all-cause death in any of the subgroup meta-analyses (supplementary table 3).

Discussion

This is the first meta-analysis of RCTs (52 studies, 53 comparisons) examining the differences in mortality among people with schizophrenia treated with LAI-APs,

Table 1. The Subgroup Meta-analysis of Long-acting Injectable Antipsychotics vs Placebo

		Number of Studies	Number of Patients	Risk Ratio	95% CI	P	I^2
Antipsychotic group	Second-generation antipsychotics-long acting injectable	14	5669	0.56	0.17–1.80	.33	0%
	First-generation antipsychotics-long acting injectable	4	250	0.86	0.14–5.35	.88	4%
Duration of study	≤13 wk	10	4217	0.29	0.07–1.16	.08	0%
	>13 wk	8	1702	1.40	0.35–5.60	.64	0%
Sponsorship	Industry	14	5669	0.56	0.17–1.80	.33	0%
	Non industry	3	180	1.32	0.09–19.66	.84	35%
	Unknown	1	70	0.33	0.01–7.91	.50	not applicable
Current disease status	Acute phase	9	3827	0.72	0.16–3.28	.67	0%
	Other phase	9	2092	0.58	0.16–2.10	.41	0%
Long acting injectable-antipsychotic dose	Haloperidol equivalent > 4.03 mg/d	8	3032	1.28	0.21–7.82	.79	0%
	Haloperidol equivalent ≤ 4.03 mg/d	8	2788	0.31	0.08–1.24	.10	0%
	Unknown	2	99	1.32	0.09–19.66	.84	35%

placebo, or OAPs (total participants = 17 416; LAI-APs = 11 360, OAP = 3910, and placebo = 2146). Several clinicians and patients in Japan have concerns regarding LAI-AP safety considering the deaths reported during the early post-marketing phase vigilance period.[21] However, the results of the current study suggest that there are no significant differences in the incidence of death between LAI-APs and OAPs or the placebo treatment groups. Moreover, we identified a trend towards a lower mortality rate in the pooled LAI-APs group in comparison with the placebo within 13 weeks of treatment onset (RR = 0.29; 95% CI = 0.07−1.16; P = .08). Furthermore, it is possible that this result was a type II error because of the small sample size. According to the early post-marketing phase vigilance period regarding paliperidone palmitate in Japan, 32 Japanese patients died after paliperidone palmitate injection (over a 6-month period).[21] Of the 32 patients, the percent of males (1 patient was unknown) was 67.7% and the mean age was 51.2 years. Moreover, 37.5% patients (n = 12) were diagnosed as sudden death based on the International Classification of Diseases 10th revision. Other causes of death were suspected sudden death (12.5%, n = 4), suicide (21.9%, n = 7), suspected neuroleptic malignant syndrome (12.5%, n = 4), and physical illness such as pancreatic cancer (15.6 %, n = 5). The mean and median duration from the first paliperidone palmitate injection to death were 7.61 and 5.86 weeks, respectively. When analyzing the publicly available information regarding the deceased Japanese patients (n = 27), 33.3% of patients (n = 9) died within 4 weeks and 77.8% (n = 21) of patients died within 13 weeks after the first paliperidone palmitate injection. However, our subgroup meta-analysis (≤13 wk of treatment onset) revealed that the pooled LAI-APs trended toward a lower mortality rate in comparison with the placebo. This

evidence may be representative of conflicting findings. Therefore, our results must be discussed in light of the following limitations regarding the current study. First, all studies included in these current meta-analyses were RCTs, and most (71.2%) were industry-sponsored clinical trials. RCTs are considered to be effective for detecting large effects in homogeneous populations. Importantly, in RCTs, patients who are medically compromised have psychiatric comorbidities, including substance dependence, those who are suicidal, and who receive different co-medications, are systematically excluded. Moreover, the use of concomitant medications is limited during the study. On the other hand, when analyzing publicly available information regarding the deceased Japanese patients (n = 27), those who used antipsychotics, benzodiazepines, or mood stabilizers as concomitant medications were 85.2%, 59.3%, and 44.4%, respectively. However, detailed information regarding these drugs was unknown (ie, when the patients took these drugs, the dose of these drugs taken by the patients, and/or how long the patients took these drugs).

Moreover, the traditional RCTs of LAI-APs confirmed that the participants responded to oral same antipsychotics, and that the participants were well tolerated to the same OAPs before the LAI-APs were given. Therefore, homogeneous patient cohorts and strictly controlled clinical environments associated with RCTs may not reflect real-world practice and outcomes.[31] In fact, 1 recent meta-analysis of RCTs of LAI-APs vs OAPs regarding relapse prevention in people with schizophrenia found no evidence for the superiority of LAI-APs over OAPs.[32] However, another meta-analysis that included mirror image studies (which have been suggested to better reflect the real-world impact of LAI-APs than RCTs) concluded that LAI-APs were superior to OAPs for reducing
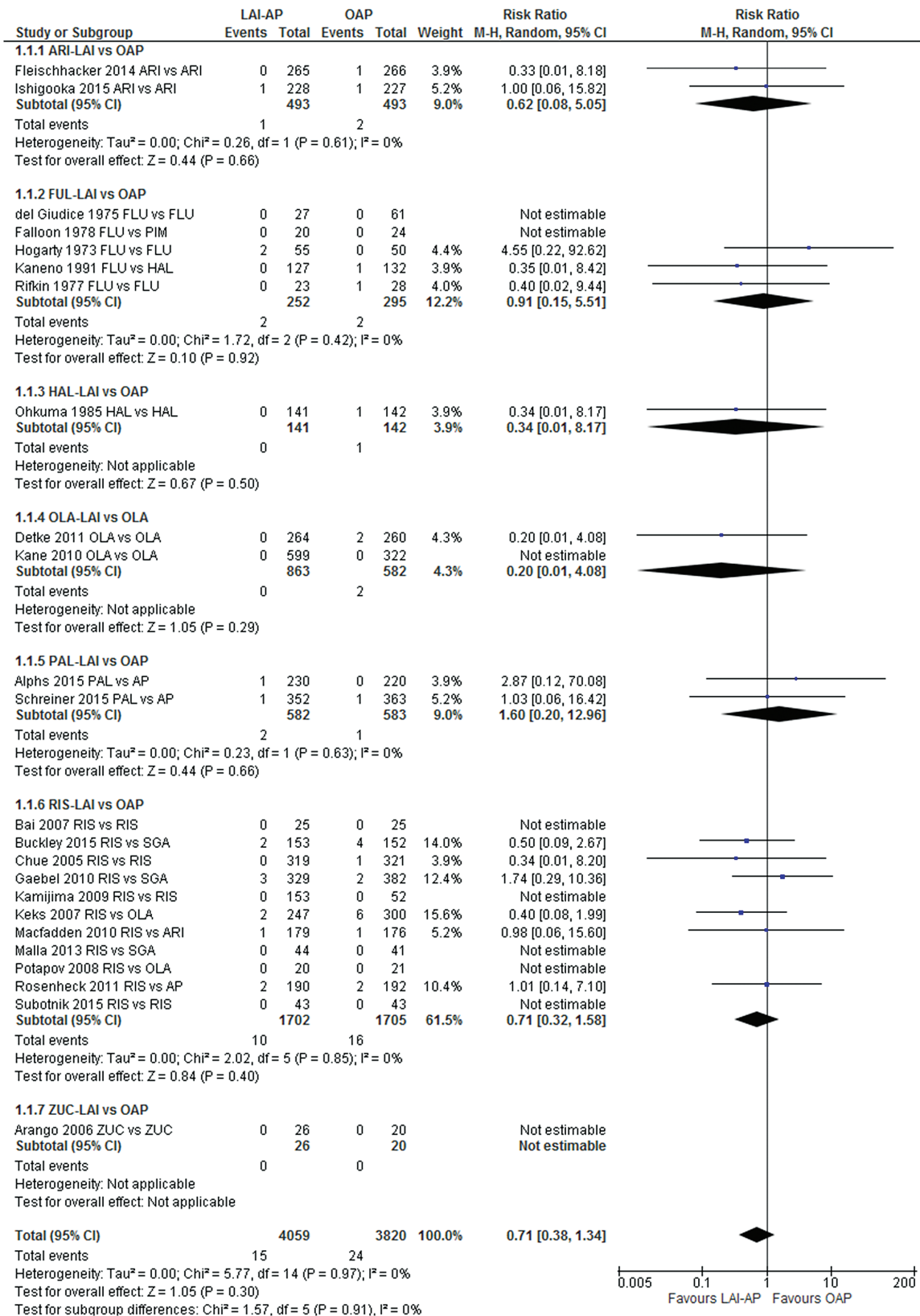
Study or Subgroup	LAI-AP Events	Total	OAP Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.1.1 ARI-LAI vs OAP							
Fleischhacker 2014 ARI vs ARI	0	265	1	266	3.9%	0.33 [0.01, 8.18]	
Ishigooka 2015 ARI vs ARI	1	228	1	227	5.2%	1.00 [0.06, 15.82]	
Subtotal (95% CI)		493		493	9.0%	0.62 [0.08, 5.05]	
Total events	1		2				
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%							
Test for overall effect: Z = 0.44 (P = 0.66)							
1.1.2 FUL-LAI vs OAP							
del Giudice 1975 FLU vs FLU	0	27	0	61		Not estimable	
Falloon 1978 FLU vs PIM	0	20	0	24		Not estimable	
Hogarty 1973 FLU vs FLU	2	55	0	50	4.4%	4.55 [0.22, 92.62]	
Kaneno 1991 FLU vs HAL	0	127	1	132	3.9%	0.35 [0.01, 8.42]	
Rifkin 1977 FLU vs FLU	0	23	1	28	4.0%	0.40 [0.02, 9.44]	
Subtotal (95% CI)		252		295	12.2%	0.91 [0.15, 5.51]	
Total events	2		2				
Heterogeneity: Tau² = 0.00; Chi² = 1.72, df = 2 (P = 0.42); I² = 0%							
Test for overall effect: Z = 0.10 (P = 0.92)							
1.1.3 HAL-LAI vs OAP							
Ohkuma 1985 HAL vs HAL	0	141	1	142	3.9%	0.34 [0.01, 8.17]	
Subtotal (95% CI)		141		142	3.9%	0.34 [0.01, 8.17]	
Total events	0		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.67 (P = 0.50)							
1.1.4 OLA-LAI vs OLA							
Detke 2011 OLA vs OLA	0	264	2	260	4.3%	0.20 [0.01, 4.08]	
Kane 2010 OLA vs OLA	0	599	0	322		Not estimable	
Subtotal (95% CI)		863		582	4.3%	0.20 [0.01, 4.08]	
Total events	0		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.05 (P = 0.29)							
1.1.5 PAL-LAI vs OAP							
Alphs 2015 PAL vs AP	1	230	0	220	3.9%	2.87 [0.12, 70.08]	
Schreiner 2015 PAL vs AP	1	352	1	363	5.2%	1.03 [0.06, 16.42]	
Subtotal (95% CI)		582		583	9.0%	1.60 [0.20, 12.96]	
Total events	2		1				
Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 1 (P = 0.63); I² = 0%							
Test for overall effect: Z = 0.44 (P = 0.66)							
1.1.6 RIS-LAI vs OAP							
Bai 2007 RIS vs RIS	0	25	0	25		Not estimable	
Buckley 2015 RIS vs SGA	2	153	4	152	14.0%	0.50 [0.09, 2.67]	
Chue 2005 RIS vs RIS	0	319	1	321	3.9%	0.34 [0.01, 8.20]	
Gaebel 2010 RIS vs SGA	3	329	2	382	12.4%	1.74 [0.29, 10.36]	
Kamijima 2009 RIS vs RIS	0	153	0	52		Not estimable	
Keks 2007 RIS vs OLA	2	247	6	300	15.6%	0.40 [0.08, 1.99]	
Macfadden 2010 RIS vs ARI	1	179	1	176	5.2%	0.98 [0.06, 15.60]	
Malla 2013 RIS vs SGA	0	44	0	41		Not estimable	
Potapov 2008 RIS vs OLA	0	20	0	21		Not estimable	
Rosenheck 2011 RIS vs AP	2	190	2	192	10.4%	1.01 [0.14, 7.10]	
Subotnik 2015 RIS vs RIS	0	43	0	43		Not estimable	
Subtotal (95% CI)		1702		1705	61.5%	0.71 [0.32, 1.58]	
Total events	10		16				
Heterogeneity: Tau² = 0.00; Chi² = 2.02, df = 5 (P = 0.85); I² = 0%							
Test for overall effect: Z = 0.84 (P = 0.40)							
1.1.7 ZUC-LAI vs OAP							
Arango 2006 ZUC vs ZUC	0	26	0	20		Not estimable	
Subtotal (95% CI)		26		20		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total (95% CI)		4059		3820	100.0%	0.71 [0.38, 1.34]	
Total events	15		24				
Heterogeneity: Tau² = 0.00; Chi² = 5.77, df = 14 (P = 0.97); I² = 0%							
Test for overall effect: Z = 1.05 (P = 0.30)							
Test for subgroup differences: Chi² = 1.57, df = 5 (P = 0.91), I² = 0%							

Favours LAI-AP   Favours OAP

Fig. 2. All-cause death: long-acting injectable antipsychotics vs oral antipsychotics. AP: antipsychotic; ARI: aripiprazole; FLU: fluphenazine; HAL: haloperidol; LAI: long-acting injectable; OAP: oral antipsychotics; OLA: olanzapine; PAL: paliperidone; PIM: pimozide; RIS: risperidone; SGA: second-generation antipsychotic; ZUC: zuclopenthixol.

relapse.[19] Thus, the traditional RCT may not be the most appropriate trial design to compare the effectiveness of LAI-APs vs OAPs because participants are strictly selected and the treatments varied.[31] Therefore, we could not deny the possibility that our results included a risk of selection bias. Moreover, because the medications may be differently dosed in clinical care settings, patients at a higher risk of death were treated in usual care settings, which could have affected the mortality rates. Further study is needed to examine that the potential effect of these factors on the risk of death. Given the above discussion, we emphasize that LAI-APs use did not increase the risk of death in comparison with OAPs or placebo when used as directed by the drug package insert. This is because the drug package insert is composed based on the industry-sponsored RCTs.

A second limitation was that the duration of studies included in the meta-analysis of LAI-APs vs placebo was relatively short (median = 13 wk, mean = 28.9 wk). The median and the mean duration of all studies included in the meta-analysis of LAI-APs vs OAPs were 52 weeks and 64.5 weeks, respectively. Therefore, because of this short duration, the evidence from our meta-analyses does not substantiate a similar death risk between LAI-APs and OAPs or placebo over several years. Third, the studies included in the current meta-analyses differed regarding patient characteristics (eg, race and ethnicity, the state of disease, antipsychotic dose, and study duration), which could generate heterogeneity when combining data. However, we did not detect significant heterogeneity regarding the primary outcome in any of the categorical meta-analyses, so we performed subgroup meta-analyses for the primary outcomes. The pooled LAI-APs group exhibited a trend towards a reduced mortality rate within 13 weeks in comparison with the placebo, while no significant differences were found in the subgroup analyzes between LAI-APs and the placebo or OAPs. Fourth, although we detected 151 RCTs of LAI-APs, we included only 52 RCTs in the meta-analysis because the articles of 99 RCTs (93 of 99 RCTs were published before the year 2000; (supplementary appendix 2) did not include any information regarding death during the study. We contacted the authors requesting raw data, but we have, in most cases, received no reply. In addition, although we searched the data using the review articles (supplementary appendix 1), we could not locate all necessary data. However, if we included the data from the 99 RCTs in the meta-analysis, the results may be different from the current results (reporting bias). Fifth, because LAI-APs may be more harmful to elderly patients than younger patients,[33] there were no RCT that included only elderly patients. Sixth, because we did not use Embase as a database for our literature search because of the limited access to our university hospital, this was a possible weakness of our literature study. Therefore, it was possible that some appropriate articles could have been missed.

To conclude, our results suggest that there is no significant difference in all-cause death and death due to suicide between LAI-APs and placebo or OAPs. On the other hand, there was a modest trend for reduced mortality in the pooled LAI-APs group in comparison with the placebo within 13 weeks. Data were insufficient for meaningful head-to-head comparisons of individual LAI-APs. Data for individual LAI-APs vs individual OAPs were also insufficient.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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