

Efficacy and safety of left atrial appendage occlusion in atrial fibrillation patients with chronic kidney disease: a systematic review and meta-analysis

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Atrial fibrillation (AF) is the most common arrhythmia among the elderly, and more frequently occur in those with chronic kidney disease (CKD). Left atrial appendage occlusion (LAAO) is used as a mechanical alternative approach for prevention of AF-related thromboembolisms. This meta-analysis was conducted to provide suggestions for the clinical application of LAAO in AF patients with CKD. The incidence of perioperative adverse events and other clinical effects after operation was by a single rate meta-analysis. Results showed that incidence of adverse events in the perioperative period after LAAO was generally low, with only pericardial effusion / tamponade (1.90%) and mortality rate (1.10%). During the follow-up period, the incidence of stroke/transient ischemic attack (TIA) and bleeding were 2.17% and 4.53%, respectively. A low incidence rate of adverse events was found in the perioperative period following LAAO. These results indicate that LAAO more effectively prevents the occurrence of stroke/TIA and minimizes bleeding events than oral anticoagulants.

Keywords

Atrial fibrillation; chronic kidney disease; left atrial appendage occlusion

1. Introduction

Atrial fibrillation (AF) is the most common cardiac rhythm disorder, with a prevalence of 1-2% in the general population (Dalia et al., 2020). AF patients have a 3-5 times higher risk of ischemic stroke relative to healthy individuals (Malyszko et al., 2018). Moreover, AF associated cardiogenic cerebral infarction has high recurrence rate and poor prognosis (Akagi et al., 2019).

The global incidence rate of adult chronic kidney disease (CKD) is about 13.4% (Noble and Taal, 2019). Relative to the general population, arrhythmias are considerably higher in CKD patients with a prevalence rate in the range of 19-24% (Malyszko et al., 2018). AF and CKD have common risk factors, and both are associated with increased risk of thromboembolism, stroke, car-

diovascular morbidity and mortality (Coleman et al., 2019; Potpara et al., 2018).

Oral anticoagulants reduce the risk of stroke by two-thirds in AF patients (Mtwesi and Amit, 2019). However, oral anticoagulants undergo varying degrees of kidney clearance, and are associated with a higher risk of bleeding in CKD patients (Shin et al., 2018). In AF patients, most of the thrombus forms in the left atrial appendage. Thus, left atrial appendage occlusion (LAAO) has emerged as a mechanical alternative intervention to prevent AF-related thromboembolisms (Kreidieh et al., 2015). Patients fitted with LAAO devices do not require prolonged oral anticoagulants, but may only need single antiplatelet therapy or no therapy (Boersma et al., 2019). Such patients consistently exhibit low rates of stroke and major bleeding events. Therefore, LAAO is suitable for patients contraindicated for oral anticoagulants, end-stage renal disease, recurrent gastrointestinal hemorrhage, and prior intracranial hemorrhage (Black-Maier et al., 2019). Here, we performed a meta-analysis to determine the efficacy and safety of LAAO in CKD patients with AF.

2. Methods

2.1 Search strategy and eligibility criteria

This systematic review and meta-analysis adhered to preferred reporting items for systematic reviews and meta-analyses guidelines (PRISMA) (Shamseer et al., 2015), and was performed in line with a prespecified protocol. Two investigators (Haifu Zhang and Qinxia Zhang) searched the PubMed, Google scholar, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and OVID to identify relevant studies. The following key medical subject headings (MeSH) terms and Emtree terms were used: atrial fibrillation, atrial appendage, kidney OR renal, and oral anticoagulants. The search was restricted to randomized controlled trials (RCTs) and clinical research published from inception up to April 1, 2020. Reference lists of selected studies and previous reviews were manually screened to identify potential eligible trials. Case reports, editorials, expert opinions, review articles, editorials, guidelines, and non-English studies were excluded.

CKD is defined as an estimated glomerular filtration rate

Table 1. Characteristics of 7 studies included in the review

Study	Study design	Age	Male (%)	CHADS-VASc/ CHADS	HAS-BLED	Treatment group (n)	Renal function	Previous Stroke/ TIA (%)	Previous Major Bleeding (%)
Luani et al. (2019)	cohort study	75.9 ± 6.7	57.5	4.5 ± 1.4	3.6 ± 1.0	Watchman: 73	eGFR<60 mL/min	16.4	/
Kefer et al. (2016)	RCT	77.9 ± 7.3	54.7	4.9 ± 1.5	3.4 ± 1.3	ACP: 375	eGFR<60 mL/min	32.3	49.1
Brockmeyer et al. (2019)	cohort study	78.2 ± 7.3	49.4	4.7 ± 1.3	3.9 ± 0.9	ACP: 61 man: 5 platzer Amulet: 14	eGFR<60 mL/min	17.3	39.6
Genovesi et al. (2018)	prospective cohort study	71.8 ± 9.6	76	4.0 ± 1.5	4.4 ± 0.9	Watchman: 24 Amulet: 26	eGFR<15 mL/min, on dialysis	20	66
Xue et al. (2018)	RCT	77.0 ± 7.2	60.9	4.3 ± 1.5	4.0 ± 1.0	Watchman: 151	eGFR<60 mL/min	11.3	25.8
So et al. (2018)	retrospective study	72 ± 8	65.3	5.1 ± 1.5	3.4 ± 0.1	ACP/Amulet: 71	eGFR<60 mL/min	/	/
Della Rocca et al. (2018)	cohort study	77 ± 7	46.1	4.9 ± 1.8	3.7 ± 0.9	104	eGFR<60 mL/min	/	/

NOTE: RCT: randomized controlled trial; eGFR: estimated glomerular filtration rate; TIA: transient ischemic attack.

(eGFR) of < 60mL/min/1.73 for 3 months or more, irrespective of the cause (Tomson and Duffy, 2019). Based on eGFR (Levey et al., 2011), CKD is staged as follows: stage 3a: 45-59mL/min/1.73 m², stage 3b: 30-44mL/min/1.73 m², stage 4: 15-29 mL/min/1.73 m², stage 5: < 15mL/min/1.73 m² or on dialysis. In LAAO trials for AF, only those that included adult patients (> 18 years old), used LAAO for AF and subjects with CKD at eGFR < 60mL/min or undergoing dialysis were included.

2.2 Data abstraction and end points

Two independent investigators (Haifu Zhang and Qinxia Zhang) extracted the following data from the included studies: authors, year of publication, and baseline features, including renal function, previous stroke/transient ischemic attack (TIA), previous major bleeding, congestive heart failure and hypertension. Incidence of adverse events during the perioperative and follow-up periods were analyzed.

2.3 Quality assessment

Quality of included studies was evaluated using the Cochrane Collaboration's randomized trial bias risk assessment tool. Trials were categorized as having low, unclear, or high bias risks in the following domains: random sequence generation allocation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Quality was independently assessed by 2 investigators (Haifu Zhang and Qinxia Zhang) and any discrepancy was resolved through consensus. All eligible trials were included in the meta-analysis regardless of quality level.

2.4 Statistical analysis

The extracted data were analyzed using Microsoft Excel 2016 and Revman 5.3. The primary outcomes were the incidence of adverse events during the perioperative and follow-up periods. A

meta-analysis of single-group rates was conducted to analyze the extracted data. When an event was 0, it was corrected to 0.5 to avoid miscalculation. The inverse-variance method and random-effect approach were employed to analyze dichotomous data. $P \leq 0.05$ indicated research heterogeneity. I^2 values of 25, 50 and 75% indicated low, medium and high degree of heterogeneity, respectively.

3. Results

3.1 Search results

Our literature search retrieved 1829 relevant reports, of which 7 involved the use of LAAO in AF patients with CKD (Fig. 1). After applying the inclusion and inclusion criteria, 905 patients treated with LAAO, of which 67 were under hemodialysis were included in the final analysis. In all patient, mean score of CHADS-VASc/CHADS exceeded 4, and mean score of HAS-BLED exceeded 3.5, with high risks of thromboembolic and bleeding. The follow-up period was 1-2 years (Table 1). The quality of included trails is shown in Fig. 2. CKD patients fitted with LAAO devices exhibited improved clinical features during follow-up with low incidence of cardiogenic mortality, bleeding and stroke.

3.2 Periprocedural complications

To determine the incidence of various adverse events in the perioperative period of LAAO, the incidence of perioperative death, stroke/TIA, bleeding and pericardial effusion/tamponade were calculated. In general, we found a low rate of adverse events in the perioperative period, and renal function was not affected. After LAAO, the main adverse event was pericardial effusion/tamponade, occurring in 13 of the 670 patients, representing an incidence rate of 1.90% (OR:0.02, 95%CI: 0.00-0.10). The incidence of bleeding and stroke/TIA in the perioperative period was 1.60% (OR:0.02, 95%CI: 0.01-0.13) and 1.40% (OR:0.02, 95%CI:

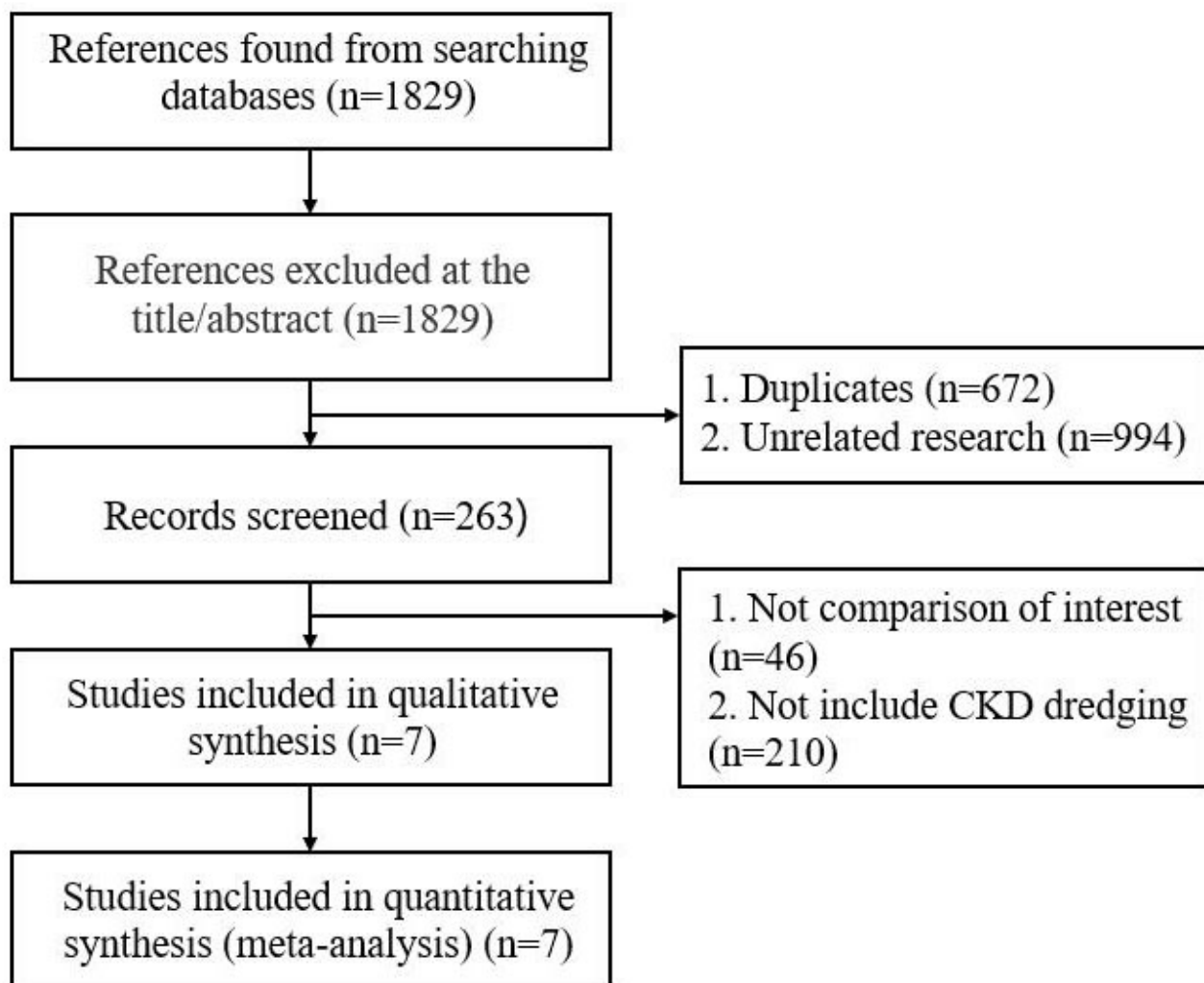


Fig. 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram. Using different keywords, a total of 1829 articles were retrieved. Through reading title, abstract and full-text, there were 7 relevant articles finally included in our meta-analysis. CKD: chronic kidney disease.

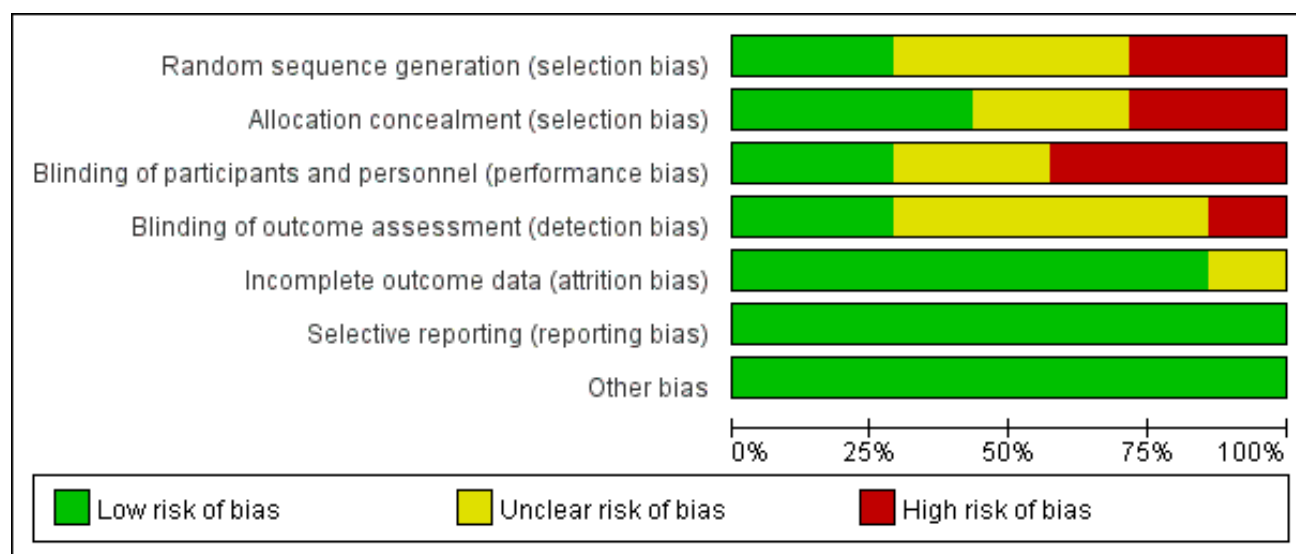


Fig. 2. Quality evaluation char. Select bias and performance bias were higher because of the inclusion of non-randomized controlled trial.

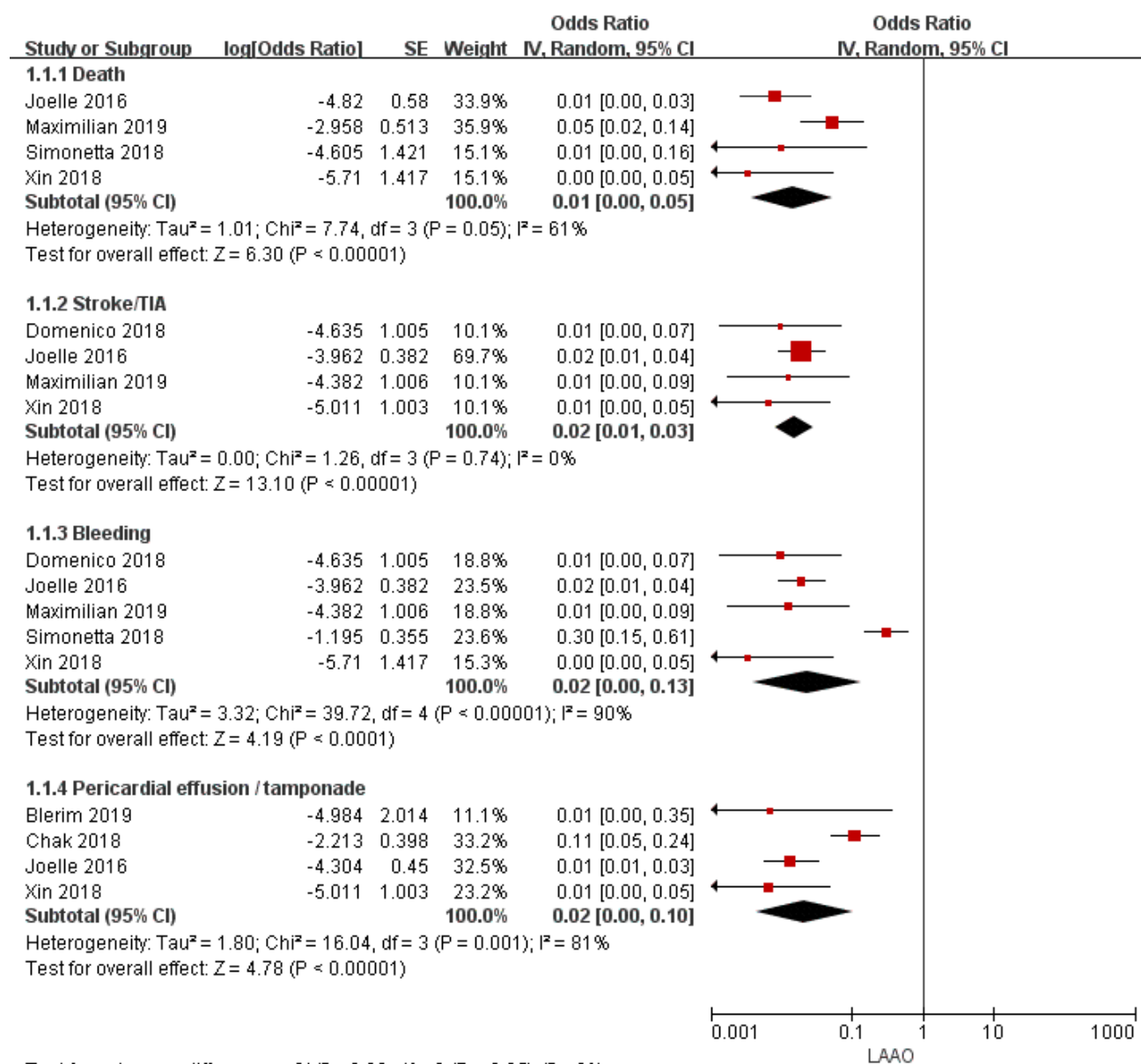


Fig. 3. Forest plots showing the effect of clinical outcomes on the overall risk of perioperative death, stroke/ transient ischemic attack, bleeding, pericardial effusion/tamponade. A total of 7 studies were included. During the perioperative period, mortality rate was 1.10% (OR:0.01, 95%CI: 0.00-0.05). The incidence of stroke/TIA and bleeding in the perioperative period was 1.40% (OR:0.02, 95%CI: 0.01-0.03) and 1.60% (OR:0.02,95%CI: 0.00-0.13). The pericardial effusion/tamponade rate was 1.90% (OR:0.02, 95%CI: 0.00-0.10).

0.01-0.03), respectively. Seven patients died during the perioperative period, representing a mortality rate of 1.10% (OR:0.01, 95%CI: 0.00-0.05) (Fig. 3).

3.3 Follow-up

The occurrence of adverse events during postoperative and follow-up periods was reported in most clinical trials. Notably, 55 among 448 patients died after LAAO treatment. Moreover, all-cause mortality of AF combined with CKD was 12.28% (OR:0.12, 95%CI: 0.09-0.17), while the cardiogenic mortality rate was 3.98% (OR:0.04, 95%CI: 0.03-0.07). Oral anticoagulants are not needed after LAAO, hence the incidence of bleeding was 4.53% (OR:0.04, 95%CI: 0.02-0.07). LAAO exhibited high safety, with a low

risk of stroke/TIA during follow-up which was 2.17% (OR:0.03, 95%CI: 0.02-0.05) (Fig. 4).

3.4 CKD vs. Non-CKD patients

The results of follow-up after LAAO in CKD versus non-CKD patients were only reported in 2 trials. Patients with CKD exhibited higher all-cause mortality rate after undergoing LAAO relative to those without CKD (12.93% vs. 6.54%; RR:2.00; 95%CI: 1.09-3.68, $P < 0.05$). There were no significant differences in stroke/TIA (RR: 0.52, $P = 0.24$), bleeding (RR: 1.02, $P = 0.96$) and cardiac death (RR: 1.34, $P = 0.65$) between CKD versus non-CKD patients (Fig. 5).

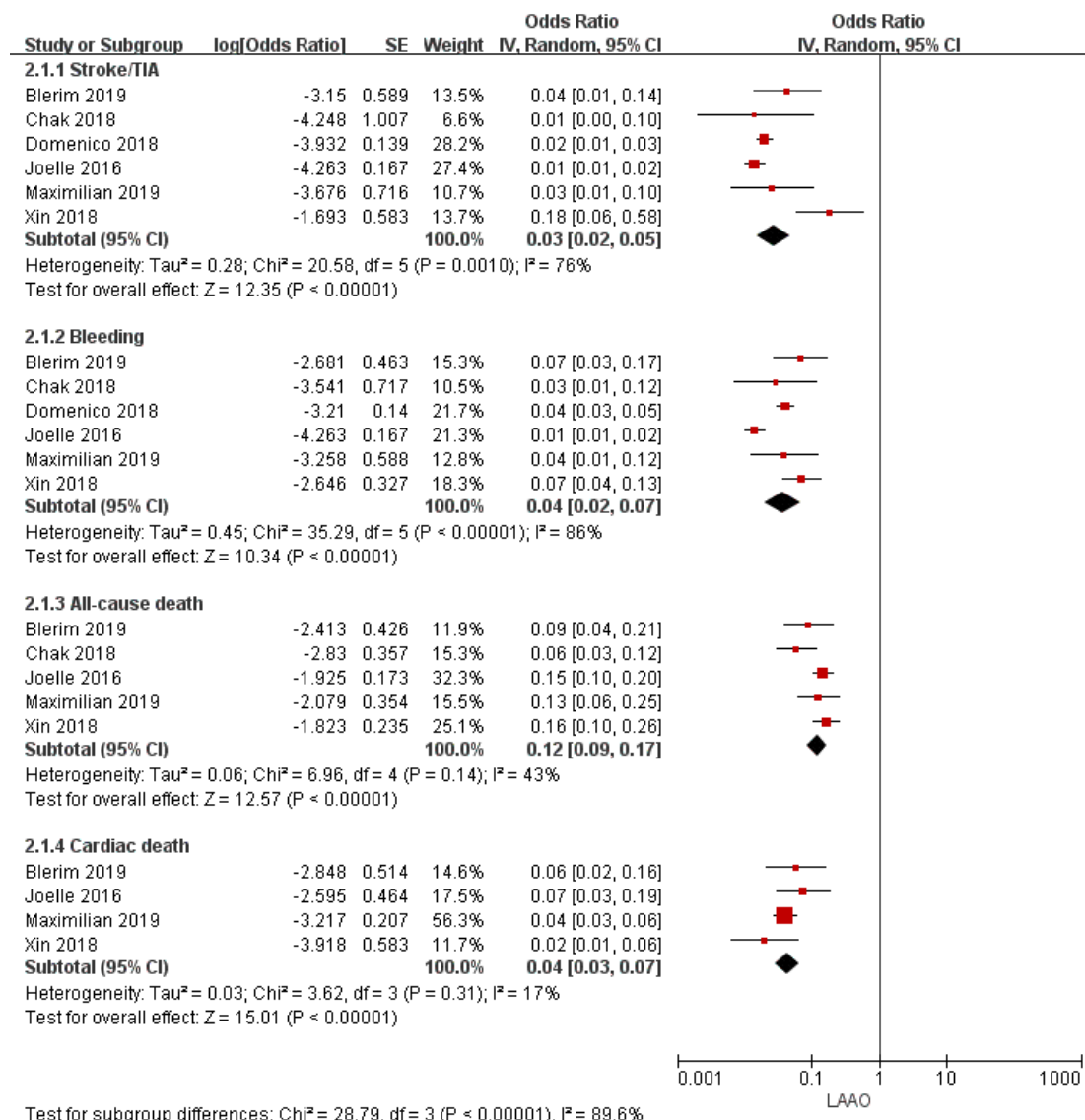


Fig. 4. A forest plot showing the effect of left atrial appendage occlusion on the overall risk of stroke/transient ischemic attack, bleeding, all-cause death and cardiogenic death in the follow up time. A total of 6 studies were included. The incidence of stroke/TIA and bleeding in the follow up time was 2.17% (OR:0.03, 95%CI: 0.02-0.05) and 4.53% (OR:0.04, 95%CI: 0.02-0.07). All-cause mortality was 12.28% (OR:0.12, 95%CI: 0.09-0.17), and the cardiogenic mortality rate was 3.98% (OR:0.04, 95%CI: 0.03-0.07) during follow-up.

4. Discussion

This meta-analysis was conducted on 7 studies reporting on the use of LAAO in AF patients with CKD. The main devices used were Watchman, ACP, and Amplatzer-Amulet. Single-rate meta-analysis revealed that incidence of perioperative adverse events was 1-2%, indicating good perioperative safety of LAAO. A low incidence of adverse events was also reported during follow-up. No significant differences in stroke/TIA, bleeding and cardiac death incidence were observed between patients with CKD and non-CKD patients.

4.1 Perioperative safety

Early use of LAAO was associated with low surgical success rate (about 90%) and high perioperative complication rates (about 8.4%) (Holmes et al., 2009). However, advances in surgical techniques and establishment of standardized operations have grad-

ually raised operation success rate to 98.5% and reduced major perioperative adverse events to 2.7% (Boersma et al., 2016).

This study shows that the incidence of pericardial effusion/tamponade in AF patients with CKD was 1.90%. The Asa Plavix Feasibility Study (Reddy et al., 2013) showed that, in patients with anticoagulation contraindications, the incidence of pericardial effusion/tamponade was 3.3% in the perioperative period. Our study revealed a perioperative mortality rate of 1.10% after LAAO, which is slightly higher than the previously reported rate in the EWOLUTION study (0.4%) (Boersma et al., 2017). In all AF patients, the incidence of perioperative stroke was 0.3-2.3%, and that of perioperative bleeding rate was about 1% (Boersma et al., 2017). Here, we find that the incidence of perioperative stroke and bleeding in AF patients with CKD was similar to that of general patients. As the application of LAAO

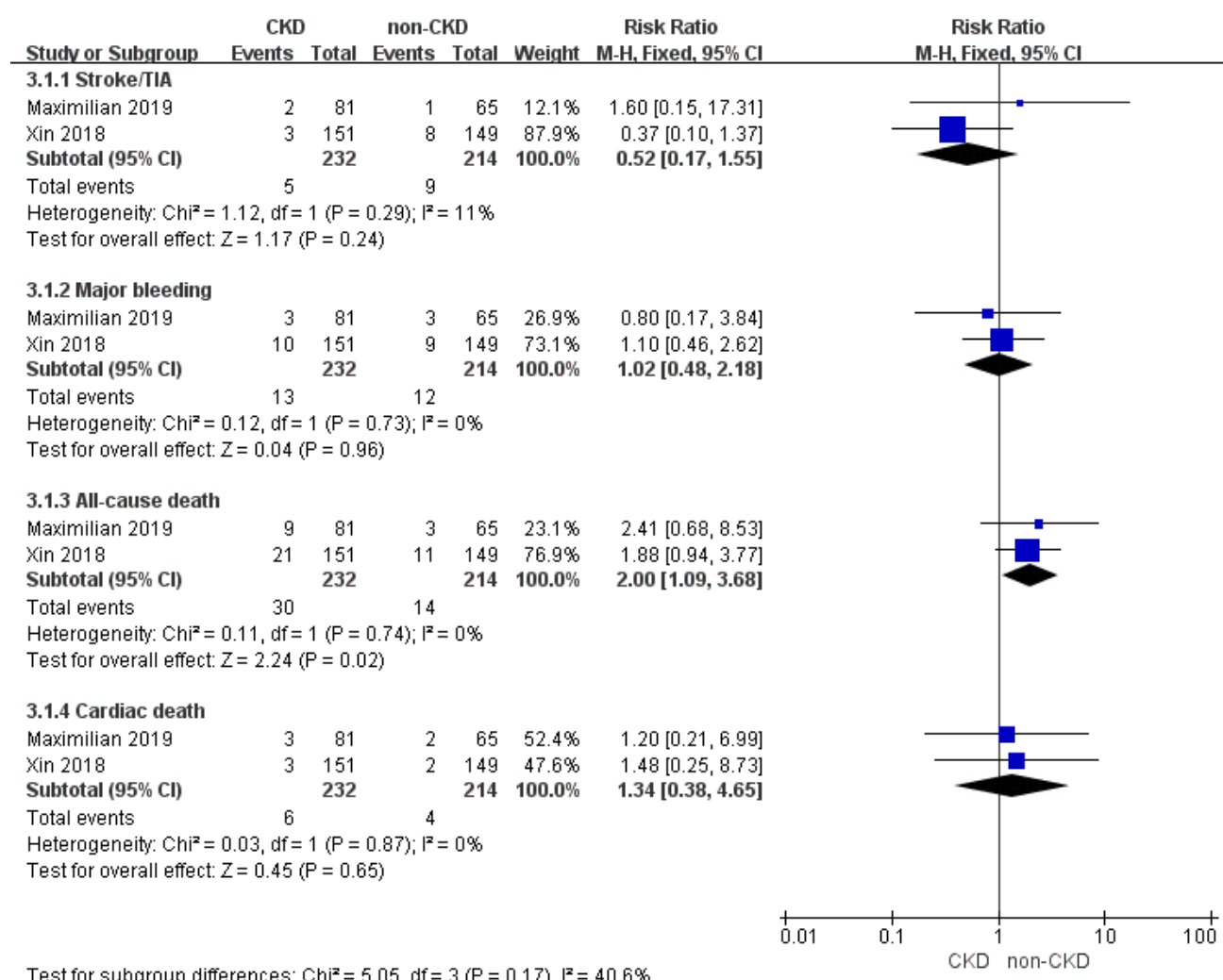


Fig. 5. Forest plots of the meta-analysis comparing the clinical outcomes after left atrial appendage occlusion in patients with or without chronic kidney disease. Patients with CKD exhibited higher all-cause mortality rate after undergoing LAAO (RR:2.00; 95%CI: 1.09-3.68, $P < 0.05$). There were no significant differences in stroke/TIA (RR: 0.52, $P = 0.24$), bleeding (RR: 1.02, $P = 0.96$) and cardiac death (RR: 1.34, $P = 0.65$).

becomes more advanced, the incidence of adverse events in the perioperative period is generally low (Bajwa et al., 2017), even in CKD patients.

Contrast-induced acute kidney injury (CI-AKI) is an important complication resulting from intravascular administration of contrast media, and is likely to occur in CKD patients (Chalikias et al., 2016). Nombela-Franco et al. (Nombela-Franco et al., 2018) reported that incidence of AKI after LAAO was 9% in general population but lower (0.8%) in patients with stage 3 CKD. Of the 905 patients included in this study, only 9 developed CI-AKI. Thus, strategies that improve perioperative management and minimize contrast media dosage are key to avoiding potential deterioration of renal function (Vuddanda et al., 2020).

4.2 Efficacy and Safety during Follow-up

The prevalence of AF in CKD patients is 15-20%, which is higher than in the general population (Kirchhof et al., 2016). AF independently increases risk of stroke by 4-5-fold (Zhang et al., 2019). Oral anticoagulants reduce risk of stroke by about two-thirds in AF patients (Mtwesi and Amit, 2019). Warfarin is still

the first-choice drug for the prevention of stroke in many types of AF (January et al., 2019). However, it interacts with food or other drugs, hence the international normalized ratio (INR) needs to be frequently monitored. Non-vitamin K antagonists of oral anticoagulants (NOACs) exhibit limited interaction with food and do not require frequent INR monitoring (La-Viola and Guerra, 2018). However, all NOACs undergo kidney clearance and are influenced by glomerular filtration rate (Shin et al., 2018). In AF patients with CKD, the annual stroke/TIA rate following NOAC and warfarin is 1.5-2.5% and 2-3%, respectively. Additionally, oral anticoagulants results in higher risk of bleeding (3-7%) in CKD patients than in non-CKD patients (about 3%) (Diener et al., 2010; Fox et al., 2011; Hohnloser et al., 2012).

The EWOLUTION trial showed that patients with a WATCHMAN LAAO device do not need oral anticoagulants and can be put on a single antiplatelet therapy or no therapy (Boersma et al., 2019). For AF patients fitted with LAAO devices who are contraindicated for anticoagulants, aspirin and clopidogrel use results in an annual incidence of stroke/embolism of 2.3% (Reddy et al., 2013). Long-term follow-up of the PREVAIL and PROTECT AF

trials showed that the LAAO group had significantly lower cardiovascular deaths (HR: 0.59, $P < 0.01$), disabling/fatal stroke (HR: 0.45, $P = 0.05$), hemorrhagic stroke (HR: 0.20, $P < 0.01$) and major bleeding (HR: 0.48, $P < 0.01$) relative to those on warfarin (Reddy et al., 2017). The PRAGUE-17 study revealed that LAAO was noninferior to NOAC in preventing ischemic/bleeding (HR: 0.84, $P = 0.004$) (Godino et al., 2020). Our data suggest that in CKD patients, the incidence of stroke/TIA (2.17%) or bleeding (4.53%) is low during follow-up period, indicating that LAAO is sufficiently safe and effective.

In this meta-analysis, the all-cause mortality was 12.28% in CKD patients and cardiogenic factors (3.98%) were the leading cause of death. During follow-up, it was observed that cardiac death was caused by heart failure and not atrial appendage occlusion devices (Kefer et al., 2016). The all-cause mortality rate when oral anticoagulants were used to prevent embolic events in AF patients with CKD stage 3 was 5-6% (Kefer et al., 2016), but it was close to 10% in AF patients with end stage renal disease (Siontis et al., 2018). Here, we find that the all-cause mortality in CKD patients was significantly higher than that of non-CKD patients, but the incidence of stroke, bleeding and cardiac death was comparable between the groups. It is worth noting that patients with eGFR of $< 30\text{ mL/min/1.73 m}^2$ had higher mortality rates relative to those with eGFR $> 30\text{ mL/min/1.73 m}^2$ reported previously (Kefer et al., 2016). In this study, many patients had eGFR $< 30\text{ mL/min/1.73 m}^2$, which may account for the higher all-cause mortality rate. Most of the trials included in this study (6/7) did not provide detailed information on renal function, hence it was not analyzed in detail.

5. Conclusions

LAAO is safe for AF patients with CKD, including during the perioperative period and long-term follow-up. In cases where surgery is needed in future, discontinuation of anticoagulants does not complicate the process. Advances in LAAO technology and standardization of surgical operations have made this technique ideal for AF patients who are contraindicated for oral anticoagulants.

Study limitations

Given that no RCTs has directly compared LAAO to oral anticoagulants in AF patients with CKD, we could not make direct comparisons. Most of the trials included in this study did not provide detailed information on renal function, hence it was not analyzed in detail.

Authors' contributions

Haifu Zhang, Qinxia Zhang, Xingwei Zhang contributed to the conception of the study; Haifu Zhang, Qinxia Zhang, Dong Yang contributed significantly to literature search and data extraction; Haifu Zhang, Qinxia Zhang, Yuanyuan Zhang performed the data analyses and wrote the manuscript; Yuanyuan Zhang, Zhao Xu, Qibin Jiao, Xingwei Zhang helped perform the analysis with constructive discussions.

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Conflict of interest

The authors declare no conflict of interest.

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