Ivabradine added to usual care in patients with heart failure: systematic review with meta-analysis and Trial Sequential Analysis

Detailed risk of bias judgements.

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Abdel-Hady 2011

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Unclear	No information
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No protocol available
Other bias	Unclear	No mention of funding or conflicts of interest

Abdel-Salam 2015

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "Randomization was performed by computer-generated allocation schedule drawn by an independent statistician."
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: "Study drugs were identical in appearance. Both the patients and the investigators performing the baseline and follow-up assessment were blinded to the treatment allocation."
Blinding of outcome assessment	Unclear	Not mentioned
Incomplete outcome data	Low	No loss to follow-up.
Selective reporting	Unclear	No protocol and serious adverse events reported inadequately
Other bias	Low	Funded by university. No conflicts of interest

Adamyan 2008

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to standard care. Therefore, the participants and personnel were probably unblinded.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information

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Other bias	Unclear	No mention of funding or conflicts of interest

Adamyan 2010		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to standard care. Therefore, the participants and personnel were probably unblinded.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Adamyan 2015		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to standard care. Therefore, the participants and personnel were probably unblinded.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Al Saadi 2013		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to carvedilol. Therefore, the participants and personnel were probably unblinded.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information

| Other bias | Unclear | No mention of funding. No conflicts of interest. |

Aroutunov 2008

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to standard care. Therefore, the participants and personnel were probably unblinded.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Babushkina 2020

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine and bisoprolol was compared to bisoprolol alone. Therefore, the participants and personnel were probably unblinded.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	No funding or conflicts of interest

Bansal 2019

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of

		interest

Barilla 2016

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "patients were assigned to the two treatment groups according to a computer-generated list of randomisation"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	High	Only the echocardiographer was blinded to treatment allocation.
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	No funding received. No conflicts of interest.

BEAUTIFUL 2008 (Fox 2008)

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "the random-allocation schedule was computer-generated by non-adaptive balanced randomisation"
Allocation concealment	Low	Quote: "central interactive voice-response system and an interactive web-response system."
Blinding of participants and personnel	Low	Quote: "double-blind" and "randomised to ivabradine or matched placebo"
Blinding of outcome assessment	Low	Quote: "prespecified events were adjudicated by a central endpoint validation committee blinded to the allocation of randomized study medication"
Incomplete outcome data	Low	Intention-to-treat data presented.
Selective reporting	Low High for serious adverse events and hospitalisations	Protocol registered retrospectively. However, serious adverse events and all-cause mortality was reported. All-cause hospitalisation was not reported and this raises serious concerns of selective outcome reporting related to hospitalisations and serious adverse events.
Other bias	Low	Funded by the company that produced ivabradine (Servier).

Bi 2020

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Cao 2019

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	Funded by Yan 'An Science and Technology Research Project. No conflicts of interest.

Cavosoglu 2015

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Unclear	Reported as placebo-controlled, but no mention of blinding
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	No mention of funding. No conflicts of interest.

Chaudhari 2014

Bias domain	Authors' judgement	Support for judgement

Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Chen 2021		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Chen G 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Chen HX 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information

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Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Cheng 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Chumburidze 2013		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: "double-blind"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Cong 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome	Unclear	No information

assessment		
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

CONSTATHE-DHF 2016 (Lofrano-Alves)		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "randomly assigned via computer-generated sequence into two groups"
Allocation concealment	Low	Quote: "the randomisation sequence was held by an independent pharmacy"
Blinding of participants and personnel	Low	Quote: "Commercially available IVA tablets were encapsulated in hard gelatin capsules. To create a PLA, capsules were filled with starch; they were indistinguishable from the IVA-containing capsules. Patient, caregivers, outcome assessors, and researched remained blinded to the intervention."
Blinding of outcome assessment	Low	Quote: "outcome assessors remained blinded to the intervention."
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Low	Protocol not registered prospectively. All-cause mortality and serious adverse events reported.
Other bias	High	An author (EAB) received consulting fees and travel/hotel/registration fee subsidies from Servier. EAB also performed contracted research from Servier, received honoraria from Servier, and was a member of the steering comittee of Servier.

Deng 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of

		interest

Di 2020

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

EDIFY 2017

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Unclear	Quote: "the randomisation was balanced 1:1 and stratified on centres". No information on the procedure of generating the random sequence
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: "double-blind" and "study investigators and participants were masked to treatment for the duration of the trial
Blinding of outcome assessment	Low	Quote: "The trial was conducted under the supervision of an independent executive committee (Supplementary material online, Appendix S3), the members of which were blinded to study medication. After the study unblinding, this committee was given full access to the data and analyses and was responsible for the interpretation of the results and review of the manuscript"
Incomplete outcome data	High	95 were assigned to ivabradine and 84 to placebo. 87 were analysed for efficacy in the ivabradine group and 84 were analysed for efficacy in the placebo group. Hence, 8 patients are unaccounted for in the ivabradine group. 76 participants in the ivabradine group and 77 in the placebo group completed the 8 months follow-up.

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| Selective reporting | High | Protocol not registered prospectively. Quality of life on the Kansas City Cardiomyopathy Questionnaire not reported. |
| Other bias | High | The trial was funded by the company that developed ivabradine (Servier). Servier was responsible for data management, analysis, interpretation, and writing of the article. |

Fu 2021

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Gou 2017

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest.

Guo 2017

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "computer-generated random number"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"

Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

He 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	High	Unaccounted missing data
Selective reporting	Unclear	No information
Other bias	Low	Funded by Guangdong Traditional Chinese Medicine Supervision Bureau. No conflicts of interest.

Hu 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Hu 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information

Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Huang J 2017

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest.

Kosmala 2013

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "The procedure of randomization to receive either ivabradine 5 mg or placebo twice daily was performed by computerized sequence generation."
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: "The hospital pharmacies were responsible for drug randomization and dispensing, and both the investigators and patients were blinded to the treatment option."
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	Retrospectively registered protocol.
Other bias	Low	Funded by Wroclaw Medical University and Brisbane University. No conflicts of interest.

Li 2018

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"

personnel		
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Li 2020

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Li B 2020

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Liu 2019

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information

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Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Liu 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Liu YY 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: "participants and researchers were unaware of allocation"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Lu 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of

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		interest

Lu 2020

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Luo 2021

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Ma 2016

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: "double-blind, placebo-controlled"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Ma 2020

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	Funded by Scientific Research Project of Anhui Provincial Health and Family Planning Commision

Mansour 2011

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "A computer-driven randomization program was used to allocate"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to no intervention. Therefore, the participant and personnel were probably unblinded.
Blinding of outcome assessment	High	No information. Only echocardiographer mentioned as being blinded to treatment allocation.
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	"This work was supported by the Faculty of Medicine at Ain Shams University, and Ain Shams University Hospitals." No conflicts of interest.

Manz 2003

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "single-blind, placebo-controlled study" and "the investigators were aware of the nature of each patient's treatment"
Blinding of outcome	Low	Quote: "The cross-reading investigator

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assessment		was blinded to the identity of the patient, the treatment administered, the timing of the recording (Echo 0, 1 or 2) and the assessment of the other investigator. Only the results of the blinded cross-readings were used for statistical analysis of efficacy."
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	High	Funded by the company that developed ivabradine (Servier)

Mao 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Masi de Luca 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Unclear	No information
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Moiseev 2011		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and	High	Ivabradine was compared to standard

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personnel		care. Therefore, the participants and personnel were probably not blinded.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Nguyen 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote "computer-generated list"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote "patients and physicians were blinded to the study treatment"
Blinding of outcome assessment	High	Quote "an independent sponsor staff was aware of the allocation groups in order to analyze data and monitor adverse events"
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	An inadequate protocol was registered with the European Clinical Trials Database in 2010 (EUDRACT 2009–018175-14). Only the primary endpoint is mentioned in the protocol.
Other bias	High	Two authors were employed by Servier, the study was funded by Servier, and Servier provided statistical support.

Ordu 2015		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No conflicts of interest. No mention of funding.

Pal 2015		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence	Unclear	No information

generation		
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: "double-blind"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	Trial retrospectively registered on clinicaltrials.gov (NCT02354573)
Other bias	Low	No conflicts of interest. Funding by the Chest, Heart and Stroke Society

Pan 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	Funded by Nantong Scientific Project

Potapenko 2011		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to standard care. Therfore, the participants and personnel were probably unblinded.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Qi 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	Quote: "lottery"
Allocation concealment	Unclear	No information
Blinding of participants and	High	Quote: "open-label"

personnel		
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Raja 2017

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	"Computerized random number generation protocol"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Only echocardiographer blinded
Blinding of outcome assessment	High	Only echocardiographer blinded
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	Funded by the Department of Cardiology, SGPGIMS, Lucknow, India. No conflicts of interest.

Sallam 2016

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Unclear	No information
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	High	The Kansas City Cardiomyopathy Questionnaire was funded by the company that developed ivabradine (Servier)

Sarullo 2010

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "computerized sequence generation"
Allocation concealment	Low	Quote: "ivabradine and placebo were prepared in numbered anonymous

		bottles"
Blinding of participants and personnel	High	Quote: "single-blind"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Low	No funding and no conflicts of interest

Shen 2018

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

SHIFT 2010 (Swedberg)

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "Patients were randomly to treatment groups by computer-generated assignment through a telephone interactive voice response system."
Allocation concealment	Low	Quote: "The allocation sequence was generated at the sponsor level through validated in-house application software; access was restricted to people responsible for study therapeutic units production until database lock."
Blinding of participants and personnel	Low	Quote: "Eligible patients were allocated to receive ivabradine or placebo" and "Patients and investigators were masked to treatment allocation. The study drugs (ivabradine or placebo) were identical in appearance."
Blinding of outcome assessment	Low	Quote: "An endpoint validation committee, masked to study treatment, reviewed and adjudicated all prespecified events according to definitions included in the charter."

Incomplete outcome data	Low	Quote: "Analysis was by intention to treat". "6658 patients were randomly assigned to treatment groups (3268 ivabradine, 3290 placebo)." 3241 was included in the ivabradine group and 3264 was included in the placebo group for the analysis of the primary and secondary outcomes.
Selective reporting	Low	The first patient was randomised in 2006. Prospectively registered with ISRCTN with limited information on methodology. The rationale and design article was published on November the 5th 2009. The trial was first registered on ClinicalTrials.gov in 2015.
Other bias	Low High for serious adverse events.	Most authors have received funding from the company that developed ivabradine (Servier). Servier was the sole sponsor of the study. Quote: "There IS an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed." There was an effect on serious adverse events, primarily due to a decrease in hospitalisations. However, the definition of hospitalisations was not pre-defined and the assessment of hospitalisations was not described.

Sisakian 2015		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	Quote: "empirically allocated"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to standard care. Therefore, the participants and personnel were probably not blinded to treatment allocation.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Song 2021

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	Funded by Beijing Dongcheng District Excellent Talents Training Funding

Su 2020

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	Funded by Guangdong Health Bureau Projects

Su DL 2020

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	Funded by Fund Project of Zhongshan City Health Bureau of Guangdong Province

Sun 2020

Bias domain	Authors' judgement	Support for judgement

Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Sun 2021

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Tang 2018

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Tarlovskaya 2011

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Unclear	Reported as "placebo-controlled", but no information on blinding

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Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Tatarchenko 2008

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open randomised controlled study"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest.

Tsutsui 2016

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: "The patients and investigators were masked to the treatment allocation"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	Outcome data for most participants
Selective reporting	Unclear	No protocol available in English.
Other bias	High	Trial designed and conducted by Ono Pharmaceutical, a partner of the company that developed ivabradine (Servier). The data were collected and analysed and the first draft manuscript was written by the sponsor.

Tsutsui 2019

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "A minimization method for dynamic allocation was used with adjustment for study site, baseline resting HR ($\geq$85 and <85 beats/min), and β-

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BMJ EBM

		blocker dose before study treatment (0, >0–<50, and ≥50% of the target dose of carvedilol 20 mg/day and bisoprolol 5 mg/day) to balance baseline covariates."
Allocation concealment	Unclear	No information
Blinding of participants and personnel	Low	Quote: "Patients and investigators were masked to treatment allocation, and study medications (ivabradine or placebo) were the same size and color."
Blinding of outcome assessment	Low	Quote: ""An endpoint adjudication committee, independent from the sponsor and ivestigators, evaluated all clinical events according to prespecified definitions in a blinded manner"
Incomplete outcome data	Low	Almost data for all participants
Selective reporting	Unclear	No protocol was prospectively registered
Other bias	High	Trial designed and conducted by Ono Pharmaceutical, a partner of the company that developed ivabradine (Servier). The data were collected and analysed and the first draft manuscript was written by the sponsor.

Tumasyan 2009		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to no intervention. Therefore, the participants and personnel were probably not blinded to the treatment allocation.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest.

Tumasyan 2012		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to no intervention. Therefore, the participants

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BMJ EBM

		and personnel were probably not blinded to the treatment allocation.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest.

Tumasyan 2016		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to no intervention. Therefore, the participants and personnel were probably not blinded to the treatment allocation.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest.

Tumasyan 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to no intervention. Therefore, the participants and personnel were probably not blinded to the treatment allocation
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest
Tumasyan 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and	High	Ivabradine was compared to no

personnel		intervention. Therefore, the participants and personnel were probably not blinded to the treatment allocation.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest.

Vatinian 2015		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Ivabradine was compared to no intervention. Therefore, the participants and personnel were probably not blinded to the treatment allocation.
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Unclear	No information
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Wang 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Wang FC 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information

Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Wang JJ 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Wang Q 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Wang RM 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome	Unclear	No information

assessment		
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Wang YH 2018

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Wang GK 2020

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Wang LJ 2020

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information

Other bias	Unclear	No mention of funding or conflicts of interest

Wei 2019

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Xia 2016

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Xing 2018

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Xu 2019

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Xu 2020

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Xue 2020

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Yang WT 2019

Bias domain	Authors' judgement	Support for judgement
Random sequence	Low	Quote: "random-number table"

generation		
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Yang Z 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Yao 2016		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Yi 2017		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and	Low	Quote: "double-blind, placebo-

personnel		controlled"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Yu 2018		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Yu 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Yue 2016		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information

Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Zeng FC 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Zeng XM 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Zhang 2019		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of

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		interest

Zhang J 2019

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Low	Quote: "sequential opaque envelopes"
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	High	Unaccounted missing data.
Selective reporting	Unclear	No information
Other bias	Low	Funded by Tianjin Natural Science Foundation

Zhang XJ 2019

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Zhang 2020

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Zhang Y 2020

Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No mention of funding or conflicts of interest

Zhang 2021		
Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Low	Funded by Hubei Province Science and Technology Plan Project

Zhao 2020		
Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Zhou 2019		
Bias domain	Authors' judgement	Support for judgement
Random sequence generation	Unclear	No information
Allocation concealment	Unclear	No information

Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No information

Zhou 2020		
Bias domain	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low	Quote: "random-number table"
Allocation concealment	Unclear	No information
Blinding of participants and personnel	High	Quote: "open-label"
Blinding of outcome assessment	Unclear	No information
Incomplete outcome data	Low	No loss to follow-up
Selective reporting	Unclear	No information
Other bias	Unclear	No information