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| **Additional file 4** Criteria used for assessment of risk of bias of individual studies |
| **Blinding of participants and personnel** *Was knowledge of the allocated interventions adequately prevented during the study?* |
| Low risk  | * Blinding of participants and key study personnel; unlikely the blinding could have been broken
 |
| Unclear risk | * Insufficient information provided
 |
| High risk | * No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding
* Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken
 |
| **Blinding of outcome assessors** *Were study personnel who performed or interpreted ECGs blinded?*  |
| Low risk  | * Blinding of study personnel who performed or interpreted ECGs; unlikely the blinding could have been broken
 |
| Unclear risk | * Insufficient information provided
 |
| High risk | * No blinding or incomplete blinding, and the outcome measurement is likely to be influenced by lack of blinding
 |
| **Incomplete outcome data** *Were incomplete outcome data, specifically cardiovascular outcomes, adequately addressed?* |
| Low risk  | * No missing outcome data
* Reasons for missing outcome data unlikely to be related to true outcome
* Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
 |
| Unclear risk | * Insufficient reporting of attrition or exclusions (e.g. number randomised not stated, no reasons for missing data provided)
 |
| High risk | * Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups
* ‘As-treated’ analysis done with substantial departure of the intervention received from that assigned at randomisation
 |
| **Selective outcome reporting** *Are reports of the study free of suggestion of selective outcome reporting?* |
| Low risk  | * The study protocol is available and the study’s pre-specified outcomes, with regards to cardiovascular safety, have been reported in the pre-specified way
* The study protocol is not available but the published reports include all expected outcomes, including those that were pre-specified
 |
| Unclear risk | * Insufficient information provided
 |
| High risk | * Incomplete reporting of the study’s pre-specified outcomes with regards to cardiovascular safety
* One or more reported outcomes, with regards to cardiovascular safety, were not pre-specified
 |
| **Other potential threats to validity** *Was the study apparently free of other problems that could put it at a risk of bias?* |
| Low risk  | * Instrument sensitivity: a 12-lead electrocardiogram was used to record cardiovascular parameters, recorded at 50mm/s
* At least 2 ECGs were recorded within 12 hours from initial drug administration
* Manually interpreted ECGs
 |
| Unclear risk | * Insufficient information
 |
| High risk | * 1 or 3 lead ECG used to record cardiovascular parameters, recorded at 25mm/s
* < 2 ECGs were recorded within 12 hours from initial drug administration
* Automatically interpreted ECGs
 |
| ECGs, electrocardiograms |