Appendix Table F2. Assessment of risk of bias in studies of CYP2C19 genetic testing assessing treatment effect modification

| **Author** **Year****Country****PMID****Study name (if available)** | **Q1** | **Q2** | **Q3** | **Q4** | **Q5** | **Q6** | **Q7** | **Q8** | **Q9** | **Q10** | **Q11** | **Q12** | **Q13** | **Q14** | **Q15** | **Q16** | **Q17** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Pare\*2010Multinational20979470CURE | High(selected patients from an RCT) | Low | High(included patients ~40% of the CURE trial population) | Unclear | Low(genotype grouping based on prior literature) | Low | Unclear | Unclear | Low | Low | Low(central, 24h, computerized randomization service) | Low (centralized computer generated randomization) | Low | Low(independent blind ascertainment) | Low | Low | Low |
| Pare†2010Multinational20979470ACTIVE-A | High(selected patients from an RCT) | Low | High(included patients ~15% of the ACTIVE-A population) | Unclear | Low(genotype grouping based on prior literature) | Low | Unclear | Unclear | Low | Low | Low(interactive phone system, varying blocks sizes) | Low(centralized, phone-based randomization) | Low | Low(independent blind ascertainment) | Low | Low | Low |
| Mega‡2009Multinational19106084§ 19414633 TRITON TIMI – 38  | High(selected patients from an RCT) | Low | High(included patients ~22% of the TRITON TIMI – 38 population) | Unclear | Low(genotype grouping based on prior literature) | Low | Unclear | Low | Low | Low | Unclear | Unclear | Low | Low(independent blind ascertainment) | Low | Low | Low |
| Mega\*\*2010Multinational20801494TRITON TIMI – 38  | High(selected patients from an RCT) | Low | High(included patients ~22% of the TRITON TIMI – 38 population) | Unclear | Low(genotype grouping based on prior literature) | Low | Unclear | Low | Low | Low | Unclear | Unclear | Low | Low(independent blind ascertainment) | High(incomplete reporting in analyses relevant to this KQ) | High(missing numerical results for this KQ) | Low |
| Varenhorst††2009Sweden19429918TABR | Unclear | Low | High (included ~90% of eligible patients) | Unclear | Low(genotype grouping based on prior literature) | High(no clinical outcomes) | Unclear | High(30 d) | Unclear | Low | Low(Interactive voice-response system; random permuted block randomization) | Low(centralized randomization) | Low | Unclear | High(inadequate data reported) | Low | Low |
| Tantry‡‡2010USA and UK21079055ONSET/OFFSET and RESPOND Genotype Studies | Unclear | Low | High(included ~79% of the patients in the parent trial were included) | Unclear | High(multiple groupings of genotypes were evaluated) | High(no clinical outcomes) | Unclear | High(2-4 w) | Low | Low | Low(centralized, balanced block randomization) | Low(random allocation was performed as patients were entered in the study) | Low | Unclear | High (data only in graphical form) | High (incomplete reporting) | Low |
| Kim§§2011S. Korea21511217ACCELAMI2C19 | Unclear | Low | High(included ~90% of patients in the parent trial) | Unclear | Unclear (rationale for genotype grouping NR) | Low | Unclear | High(30d) | Low | Low | Low(computer-generated randomization sequence) | Unclear | Unclear | Unclear(study personnel assessed reactivity “blinded to the study protocol”) | Low | Low | Low |
| Hwang\*\*\*2010S. Korea20823393ACCEL-RESISTANCE, DM, and COMPLEX trials (ACEL-POLYMORPHISM) | Unclear | Low | High(included ~89% of patients in the parent trial) | Unclear | Unclear(the authors cited a previous publication from their team) | High(no clinical outcomes) | Unclear | High(30 d) | Low | Low | Low(computer-generated randomization sequence) | High(randomization sequence was provided in envelopes) | Unclear | Low(study personnel assessed reactivity “blinded to group assignment”) | Low | Low | Low |
| Gladding†††2008New Zealand19463375PRINC | Unclear | Low | Low (included 100% of patients in the parent trial) | Unclear | High(no rationale reported; data on some genotypes not presented) | High(no clinical outcomes) | Unclear | High (7 d) | Low | Low | Low(computer-generated randomized sequence) | Unclear | Low | Low | High(some data only in graphical form) | Low | High(results not reported for all genotypes observed) |
| Wallentin2010Multinational20801498PLATO | Unclear | Low | High(included ~55% of patients in the parent trial) | Unclear | Low(genotype grouping based on prior literature) | Low | Unclear | Low | Low | Low | Unclear | Unclear | Low | Low | Low | Low | High(results not reported for all genotypes observed) |
| Park2011S. Korea21345843CILON-T | Unclear | Low | High(included ~85% of patients in the parent trial) | Unclear | Low(genotype and phenotypic grouping based on prior literature) | High(no clinical outcomes) | Unclear | High (until discharge) | Low | Low | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Low |
| Bhatt‡‡‡2012Multinational22450429CHARISMA | High(selected patients from an RCT) | Low | High(included ~45% of patients in the parent trial) | Unclear | Unclear | Low | Unclear | Low | Low | Low | Low (preestablished randomization scheme, stratified according to site) | Low (central; interactive voice-response system) | Low | Low | Low | Low | High (significant differences between patients enrolled in the parent trial and the genetic substudy) |
| Collet2011France21511218CLOVIS-2 | Unclear | Low | Low (reported results on 96% of the enrolled patients) | Unclear | Low (enrollment in trial was stratified by baseline genotype status) | High(no clinical outcomes) | Low (reactivity measurement was blinded to genotype) | High (2 periods of 21 d) | Low | Low | Low (web-based, centralized randomization procedure) | Low (web-based, centralized randomization procedure) | High (open-label) | High (open-label) | Low | Low | Low |

\*Some information extracted from Yusuf et al. 2001 [PMID = 11519503].
†Some information extracted from Connolly et al. 2009 [PMID = 19336502].
‡Some information extracted from Wiviott et al. 2007 [PMID = 17982182]
§Detailed information on the clopidogrel treated arm of the TRITON TIMI 38 trial was provided in Mega et al. 2009 [PMID = 19106084]; detailed information on the prasugrel treated arm was provided in Mega et al. 2009 [PMID = 19414633]. Additional information was extracted from Wiviott et al. 2006 [PMID = 16996826] and Wiviott et al. 2007 [PMID = 17982182].
\*\*Some information on the patient selection criteria and the treatments compared in the parent trial were extracted from Wiviott et al. 2007 [PMID = 17982182] and Wiviott et al. 2006 [PMID = 16996826].
††Some information extracted from Wallentin et al. 2008 [PMID = 18055486].
‡‡Some information extracted from Gurbel et al. 2008 [PMID = 19923168] and Gurbel et al. 2010 [PMID = 20194878].
§§Some information extracted from Jeong et al. 2010 [PMID = 20118150].
\*\*\*Some information extracted from Jeong et al. 2009 [PMID = 19324253].
†††Some information extracted from Gladding et al. 2008 [PMID = 19463374].
‡‡‡Some information extracted from Bhatt et al. 2006 [PMID = 16531616].
**Abbreviation:** RCT = randomized controlled trial.

**Quality items**

Q1: Consecutive sample of patients enrolled

Q2: Case-control design avoided

Q3: Study avoided inappropriate exclusions and post-hoc exclusions were <5%

Q4: Index test results interpreted without knowledge of outcomes?

Q5: If a test threshold was used, was it prespecified?

Q6: Reference standard likely to correctly classify the target condition (low if at least one clinical outcome assessed)?

Q7: Reference standard results interpreted without knowledge of index test results?

Q8: Appropriate interval between index test and reference standard (at least 12 mo of followup)?

Q9: All patients received a reference standard (outcome data for >90% of patients)?

Q10: All patients received the same reference standard?

Q11: Random sequence generation

Q12: Allocation concealment

Q13: Blinding of participants and personnel

Q14: Blinding of outcome assessment

Q15: Incomplete outcome data (do they report enough data to estimate uncertainty for the primary outcome)

Q16: Selective reporting bias (do they report numerical results on the primary and secondary outcome; and are these identified in the methods)

Q17: Other bias (e.g., extreme numerical errors and inconsistencies)