Figure S1. Flowchart for the literature search and selection.


Figure S2. Forest plot showing the comparison of allele C vs. allele T for all studies. The squares and horizontal lines correspond to the study-specific OR and $95 \%$ CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and $95 \%$ CI. OR, odds ratio; df, degrees of freedom; CVE, cardio-cerebrovascular events.


Figure S3. Forest plot showing the comparison of CC vs. TT for all studies. The squares and horizontal lines correspond to the study-specific OR and $95 \%$ CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and $95 \%$ CI. OR, odds ratio; df, degrees of freedom; CVE, cardio-cerebrovascular events.


Figure S4. Forest plot showing the comparison of CT vs. TT for all studies. The squares and horizontal lines correspond to the study-specific OR and $95 \%$ CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and $95 \%$ CI. OR, odds ratio; df, degrees of freedom; CVE, cardio-cerebrovascular events.


Figure S5. Forest plot showing the comparison of (CC + CT) vs. TT for all studies. The squares and horizontal lines correspond to the study-specific OR and $95 \%$ CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and $95 \%$ CI. OR, odds ratio; df, degrees of freedom; CVE, cardio-cerebrovascular events.


Figure S6. Forest plot showing the comparison of CC vs. (CT + TT) for all studies. The squares and horizontal lines correspond to the study-specific OR and $95 \%$ CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and $95 \%$ CI. OR, odds ratio; df, degrees of freedom; CVE, cardio-cerebrovascular events.


Figure S7. Forest plot showing the comparison of CT vs. (TT + CC) for all studies. The squares and horizontal lines correspond to the study-specific OR and $95 \%$ CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and $95 \%$ CI. OR, odds ratio; df, degrees of freedom; CVE, cardio-cerebrovascular events.


Figure S8. Forest plot showing the comparison of C vs. T for studies with Hardy-Weinberg equilibrium. The squares and horizontal lines correspond to the study-specific OR and $95 \%$ CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and $95 \%$ CI. OR, odds ratio; df, degrees of freedom; CVE, cardio-cerebrovascular events.


Figure S9. Forest plot showing the comparison of CC vs. TT for studies with Hardy-Weinberg equilibrium. The squares and horizontal lines correspond to the study-specific OR and $95 \%$ CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and $95 \%$ CI. OR, odds ratio; df, degrees of freedom; CVE, cardio-cerebrovascular events.


Figure S10. Forest plot showing the comparison of CT vs. TT for studies with Hardy-Weinberg equilibrium. The squares and horizontal lines correspond to the study-specific OR and $95 \%$ CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and $95 \%$ CI. OR, odds ratio; df, degrees of freedom; CVE, cardio-cerebrovascular events.


Figure S11. Forest plot showing the comparison of $(C C+C T)$ vs. TT for studies with Hardy-Weinberg equilibrium. The squares and horizontal lines correspond to the study-specific OR and $95 \%$ CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and $95 \%$ CI. OR, odds ratio; df, degrees of freedom; CVE, cardiocerebrovascular events.

| Exposed group Control group |  |  |  |  |  | Odds ratio |  | OR | 95\%-CI | Weight |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| All CVE |  |  |  |  |  |  |  |  |  |  |
| Rubattu 2004 | 65 | 130 | 141 | 312 |  |  |  | 1.21 | [0.81; 1.83] | 2214.6\% |
| Barbato 2012 | 321 | 430 | 683 | 967 |  |  | $\pm$ | 1.22 | [0.95; 1.58] | 5342.0\% |
| Francia 2013 | 47 | 92 | 121 | 244 |  |  |  | 1.06 | [0.66; 1.72] | 1630.3\% |
| Rubattu 2016 | 65 | 103 | 193 | 276 |  |  |  | 0.74 | [0.46; 1.18] | 1656.3\% |
| Pastori 2021 | 19 | 128 | 78 | 429 |  |  |  | 0.78 | [0.45; 1.35] | 1267.1\% |
| Common effect model |  | 883 |  | 2228 |  |  | - | 1.07 | [0.90; 1.27] | -- |
| Heterogeneity: $I^{2}=21 \%, \tau^{2}=0.0131, p=0.28$ |  |  |  |  |  |  |  |  |  |  |
| Atrial fibrillation |  |  |  |  |  |  |  |  |  |  |
| Francia 2013 | 47 | 92 | 121 | 244 |  |  |  | 1.06 | [0.66; 1.72] | 1630.3\% |
| Cerebrovascular event |  |  |  |  |  |  |  |  |  |  |
| Rubattu 2004 | 65 | 130 | 141 | 312 |  |  | 1 | 1.21 | [0.81; 1.83] | 2214.6\% |
| Coronary heart disease |  |  |  |  |  |  |  |  |  |  |
| Barbato 2012 | 321 | 430 | 683 | 967 |  |  | 1 | 1.22 | [0.95; 1.58] | 5342.0\% |
| Myocardial infarction |  |  |  |  |  |  |  |  |  |  |
| Rubattu 2016 | 65 | 103 | 193 | 276 |  | 1 |  | 0.74 | [0.46; 1.18] | 1656.3\% |
| Heterogeneity: $J^{2}=9 \%, \tau^{2}=0.0014, p=0.36$ |  |  |  |  |  |  |  |  |  |  |
| Test for subgroup differenc | es: $\chi_{4}^{2}=$ | 72, df | $=4(p=0$ | .45) | 0.5 |  |  |  |  |  |

Figure S12. Forest plot showing the comparison of CC vs. $(\mathrm{CT}+\mathrm{TT})$ for studies with Hardy-Weinberg equilibrium. The squares and horizontal lines correspond to the study-specific OR and $95 \%$ CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and $95 \%$ CI. OR, odds ratio; df, degrees of freedom; CVE, cardiocerebrovascular events.


Figure S13. Forest plot showing the comparison of CT vs. (CT + TT) for studies with Hardy-Weinberg equilibrium. The squares and horizontal lines correspond to the study-specific OR and $95 \%$ CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and $95 \%$ CI. OR, odds ratio; df, degrees of freedom; CVE, cardiocerebrovascular events.


Figure S14. Egger's publication bias plot and P-value for the comparison of (CC + CT) vs. TT. Each data-point represents a separate study for the indicated association.


Figure S 15 . Sensitivity analysis for testing the stability of the overall estimate in the recessive model for studies. OR, odds ratio.


| OR | 95\%-CI | P-value | Tau2 | Tau | I2 |
| ---: | ---: | ---: | ---: | ---: | ---: |
| 1.56 | $[1.03 ; 2.38]$ | 0.04 | 0.1498 | 0.3871 | $68 \%$ |
| 1.20 | $[0.89 ; 1.62]$ | 0.23 | 0.0619 | 0.2488 | $46 \%$ |
| 1.40 | $[0.96 ; 2.04]$ | 0.08 | 0.1453 | 0.3812 | $64 \%$ |
| 1.58 | $[1.02 ; 2.46]$ | 0.04 | 0.1500 | 0.3873 | $44 \%$ |
| 1.40 | $[0.91 ; 2.16]$ | 0.12 | 0.1834 | 0.4283 | $67 \%$ |
| 1.41 | $[0.94 ; 2.09]$ | 0.09 | 0.1595 | 0.3993 | $69 \%$ |
| 1.40 | $[0.87 ; 2.26]$ | 0.16 | 0.2099 | 0.4582 | $55 \%$ |
| 1.44 | $[0.96 ; 2.16]$ | 0.08 | 0.1675 | 0.4093 | $69 \%$ |
| 1.32 | $[0.90 ; 1.93]$ | 0.16 | 0.1338 | 0.3657 | $63 \%$ |
|  |  |  |  |  |  |
| $\mathbf{1 . 4 0}$ | $[\mathbf{0 . 9 6 ; ~ 2 . 0 4 ]}$ | $\mathbf{0 . 0 8}$ | $\mathbf{0 . 1 4 5 3}$ | $\mathbf{0 . 3 8 1 2}$ | $\mathbf{6 4 \%}$ |

Figure S16. Sensitivity analysis for testing the stability of the overall estimate in the homozygote model for studies with Hardy-Weinberg equilibrium. OR, odds ratio.


Figure S17. Sensitivity analysis for testing the stability of the overall estimate in the recessive model for studies with Hardy-Weinberg equilibrium. OR, odds ratio.


Figure S18. Forest plot for the subgroup analysis for NOS score in the recessive model regarding composite cardio-cerebrovascular event outcome. The squares and horizontal lines correspond to the study-specific OR and $95 \%$ CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and $95 \%$ CI. OR, odds ratio; df, degrees of freedom; NOS, Newcastle-Ottawa scale.


Figure S19. Forest plot for the subgroup analysis for year of publication in the recessive model regarding composite cardio-cerebrovascular event outcome. The squares and horizontal lines correspond to the study-specific OR and $95 \%$ CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and $95 \%$ CI. OR, odds ratio; df, degrees of freedom.


Figure S20. Forest plot for the subgroup analysis for year in the recessive model regarding study region. The squares and horizontal lines correspond to the study-specific OR and $95 \% \mathrm{CI}$. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and $95 \%$ CI. OR, odds ratio; df, degrees of freedom.


Figure S21. Forest plot for the subgroup analysis for sample size in the recessive model regarding composite cardio-cerebrovascular event outcome. The squares and horizontal lines correspond to the study-specific OR and $95 \%$ CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and $95 \%$ CI. OR, odds ratio; df, degrees of freedom.


Figure S22. Forest plot for the subgroup analysis for underlying disease in the recessive model regarding composite cardio-cerebrovascular event outcome. The squares and horizontal lines correspond to the study-specific OR and $95 \%$ CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and $95 \%$ CI. OR, odds ratio; df, degrees of freedom.


