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Effects of *CYP3A4*22* polymorphism on trough concentration of tacrolimus in kidney transplantation: a systematic review and meta-analysis

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Purpose: Tacrolimus (Tac) is a widely used immunosuppressive agent in kidney transplantation. Cytochrome P450 (CYP), especially *CYP3A4* enzymes are responsible for the metabolism of drugs. However, the correlation between plasma Tac concentration and *CYP3A4*22* gene variants is controversial. This meta-analysis aims to evaluate the association between *CYP3A4*22* polymorphism and the dose-adjusted trough concentration (C₀/D) of Tac in adult kidney transplant patients.

Methods: We conducted a literature review for qualifying studies using the PubMed, Web of Science, and Embase databases until July 2023. For the continuous variables (C_0/D and daily dose), mean difference (MD) and corresponding 95% confidence intervals (CIs) were calculated to evaluate the association between the *CYP3A4*22* and Tac pharmacokinetics. We performed an additional analysis on the relationship of *CYP3A5*3* with Tac PKs and analyzed the effects of *CYP3A4*22* in CYP3A5 non-expressers.

Results: Overall, eight eligible studies with 2,683 renal transplant recipients were included in this meta-analysis. The *CYP3A4*22* allele was significantly associated with a higher C₀/D (MD 0.57 ng/mL/mg (95% CI: 0.28 to 0.86; p = 0.0001) and lower mean daily dose requirement (MD -2.02 mg/day, 95% CI: -2.55 to -1.50; p < 0.00001). An additional meta-analysis demonstrated that carrying the *CYP3A5*3* polymorphism greatly impacted Tac blood concentration. From the result with CYP3A5 non-expressers, *CYP3A4*22* showed significant effects on the Tac C₀/D and dose requirement even after adjusting the effect of *CYP3A5*3*.

Conclusion: Patients with *CYP3A4*22* allele showed significantly higher plasma C_0/D of Tac and required lower daily dose to achieve the therapeutic trough level after kidney transplantation. These findings of our meta-analysis may provide further evidence for the effects of genetic polymorphism in *CYP3A4* on the PKs of Tac, which will improve individualized treatment in a clinical setting.

KEYWORDS

tacrolimus, CYP3A4*22, polymorphism, trough concentration, kidney transplantation

1 Introduction

Tacrolimus (Tac) is a widely used maintenance immunosuppressive agent to prevent graft rejection in kidney transplantation. Tac suppresses T-cell activation by inhibiting the calcineurin activity and exhibits excellent graft survival with a low incidence of rejection (Shapiro et al., 1999; Hamawy, 2003). However, its narrow therapeutic index requires close monitoring of Tac concentration to maintain the level within an optimal range (Venkataramanan et al., 1995). A supratherapeutic level results in drug toxicity and infection while a subtherapeutic level can lead to allograft rejection (Robles-Piedras and González-López, 2009).

Tac is also characterized by its high inter-individual variability in its pharmacokinetics (PKs) (Venkataramanan et al., 1995). This makes it difficult to predict the trough concentration and determine the optimal dose. Moreover, hepatic dysfunction, age, sex, ethnicity, albumin concentration, and gene polymorphism affect the PKs of Tac (Staatz and Tett, 2004).

As Tac is a dual substrate of P-glycoprotein and cytochrome P450 (CYP) 3A4 and 3A5, genetic polymorphisms related to the expression of these proteins have been studied to explain the between-subject PK variability (Saeki et al., 1993; Dai et al., 2006; de Jonge et al., 2009). Among them, *CYP3A5*3* (rs776746; 6986A>G) is the most significant genetic determinant of Tac PKs (Kuehl et al., 2001; Billing et al., 2017; Khan et al., 2020). This polymorphism is known to decrease the metabolic activity of the CYP3A5 enzyme. Several studies showed that patients

with the *CYP3A5*3/*3* variant exhibited a higher trough concentration and required a lower dose of Tac to achieve the target concentration than those with wild-type allele (Tang et al., 2011; Zong et al., 2017; Khan et al., 2020). According to pharmacogenetic-based dosing guidelines such as Clinical Pharmacogenetic Implementation Consortium (CPIC) and the Dutch Pharmacogenetic Working Group (DPWG), lower doses of Tac are recommended for CYP3A5 non-expressers than CYP3A5 expressers (Birdwell et al., 2015; KNMP, 2020).

CYP3A4 plays a significant role in the drug metabolism of numerous drugs (Wrighton et al., 2000; Danielson, 2002). Due to its wide variation in enzyme activity among the population, CYP3A4 polymorphisms could influence the PKs and efficacy of related drugs (Shiraga et al., 1994; Macphee et al., 2002; Mulder et al., 2021). CYP3A4*22 (rs35599367; g.15389C>T), a novel variant of CYP3A4, has been reported to have low messenger RNA (mRNA) expression and low activity of CYP3A4; accordingly, its relationship with drug response has been widely studied (Wang et al., 2011; Elens et al., 2013). Especially for Tac, several studies also have analyzed the effects of CYP3A4*22 on its PKs (Tavira et al., 2013; De Jonge et al., 2015; Lloberas et al., 2017). However, the results are still controversial, and a meta-analysis on the topic has not been conducted yet. Therefore, this meta-analysis aims to elucidate the correlation between CYP3A4*22 polymorphism and Tac concentration in adult patients with renal transplantation.



2 Methods

2.1 Search strategy of literature

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). A comprehensive search was performed for articles published before 13 July of 2023 in PubMed, Web of Science, and Embase based on PICO elements (Supplementary Table S1). The search strategy by using the following keywords: (Transplantation) AND (Polymorphis* OR SNP* OR mutation* OR variant* OR genotyp* OR allele*) AND (Tacrolimus OR FK506) AND (CYP3A4*) (Supplementary Table S2).

2.2 Study selection

The eligible studies were selected in the analysis if they 1) were cohort studies; 2) involved the adult renal transplantation patients who took tacrolimus; 3) evaluated the association between *CYP3A4*22* genotypes and trough concentrations (C_0) of Tac at steady state; 4) adjusted C_0 by daily dose; and 5) expressed data as the mean with standard deviation (SD) or the median with range.

The studies were excluded if they were 1) not original articles (e.g., conference abstracts, letters, or reviews); 2) *in vitro* or *in vivo* studies; or 3) were conducted on patients with a single dose of Tac. If there was possibility of data overlap among the studies, only the most recent and comprehensive data was included.

2.3 Data extraction

Two authors (JSK and SS) performed the initial screening independently using Endnote to exclude duplicate studies. Next, the list of studies was compared, and consensus was achieved through discussion. Subsequently, both reviewers (JSK and SS) independently assessed the titles and abstracts, excluding studies that did not meet the inclusion and exclusion criteria. Throughout this process, the reviewers ensured methodological consistency and error reduction in the extraction techniques. Then, both authors (JSK and SS) independently evaluated the full text of all relevant studies to determine their eligibility. All studies that did not meet the eligibility criteria during the second screening were documented, along with the reasons for their exclusion. In case of any disagreements on study selection, a consensus was reached through discussion with a third reviewer (JY). For each study, extracted data were as follows: first authors, publication years, study design, country, ethnic background, characteristics of participants (population size, age, and weight), immunosuppressive protocol, alleles studied, genotyping methods, measurement methods for the C0 of Tac, the allele frequency of CYP3A4*22, dose-adjusted trough concentration (C₀/D), and the daily dose of Tac according to posttransplantation period.

 C_0/D was calculated by the plasma trough concentration (ng/ mL) of Tac divided by daily dose (mg), expressed as ng/mL per mg (Schütte-Nütgen et al., 2019). For continuous data, the mean and SD were extracted. For the studies providing data in the median with

range, the method of Hozo et al. (2005) was used to estimate the mean and SD.

2.4 Quality assessment

The Newcastle-Ottawa Scale (NOS) system was adopted to rate the quality of the evidence. The total score of NOS ranges from 0 to 9; 0-4 points were assigned for the selection of the population, 0-2 points for comparability, and 0-3 points for the outcomes. For comparability, 1 point each was awarded if studies matched or adjusted with the age or other known risk factors.

2.5 Statistical analysis

For the continuous variables (C₀/D and daily dose), mean difference (MD) and corresponding 95% confidence intervals (CIs) were calculated to evaluate the association between the *CYP3A4*22* and Tac PKs.

All analyses were conducted using Review Manager (RevMan) version 5.4 (The Cochrane Collaboration, Copenhagen, Denmark) and R software (version 3.6.0). A p < 0.05 was considered statistically significant. Heterogeneity was evaluated via chi-square test and I^2 statistic. An $I^2 < 50\%$ was considered low heterogeneity, whereas an $I^2 \ge 50\%$ high heterogeneity. If a low level of heterogeneity was observed, the fixed-effect model (Mantel-Haenszel method) was used; if not, the random-effect model (DerSimonian-Laird method) was applied (Biondi-Zoccai et al., 2011). Begg's test and Egger's test were used to identify publication bias (Begg and Mazumdar, 1994; Egger et al., 1997).

Sensitivity analyses were conducted to evaluate the robustness of the results by omitting the factor to assess its influence on the overall estimate. The first sensitivity analysis was performed by excluding each post-transplantation period at a time sequentially, and another sensitivity analysis by omitting studies that scored lower than 7 on the NOS system. We performed an additional analysis on the relationship of *CYP3A5*3* with Tac C₀ and daily dose. In order to observe the independent influence of *CYP3A4*22* while controlling for *CYP3A5*3*, we analyzed the effects of *CYP3A4*22* in CYP3A5 non-expressers.

3 Results

A total of 950 studies were retrieved by the literature search and 475 duplicates were removed (Figure 1). After excluding 448 studies based on the titles and abstracts, 27 papers remained. We excluded 19 studies that did not investigate concentration (n = 7), did not adjust concentration by dose (n = 6), did not investigate *CYP3A4*22* (n = 4), could not express data in mean with SD (n = 1), and administered a single dose (n = 1). Finally, eight cohort studies were selected, including data of 2,624 patients in the meta-analysis. The main characteristics of the eligible studies are presented in Table 1. All included studies were performed on European patients. The mean age (years) and weight (kg) ranged from 48.6 to 54.4 and from 70.8 to 87.5, respectively. NOS ranged from 5 to 8.

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TABLE 1 Characteristics of included studies.

| First author (year) | Country | Ethnic background | Sample size (male %) | Age (years) (mean ± SD) | Weight (kg) (mean ± SD) | lmmuno- suppressive protocol | Alleles studied | Genotyping method | Tac measurement method | <i>CYP3A4*22</i> allele frequency (%) | NOS |
|---------------------------------|---------------|----------------------|----------------------------|----------------------------|----------------------------|------------------------------------|------------------------------------|----------------------|------------------------------|---|-----|
| Tavira et al. | Service | Caucasians | 206 (NA) | 48.6 ± 13.6 | NA | Tac, MMF, PD | CYP3A5*3 | TaqMan | CLIA | 4.9 | 7 |
| (2013) | Spain | Gudeusiuns | 200 (111) | 10.0 ± 15.0 | IVII | | CYP3A4*1B | ruquun | CLIM | 1.9 | , |
| Kuypers et al. | Belgium | Caucasians | 246 (59.8) | 53.0 ± 14.2 | 70.8 ± 13.5 | | CYP3A5*3 | | MEIA | NA | 7 |
| (2014) | Beigium | Caucasians | 240 (59.8) | 55.0 ± 14.2 | 70.8 ± 13.5 | Tac, MMF, mPD | POR*28 | TaqMan | MEIA | NA | / |
| | | | | | | | CYP3A5*3 | | СМІА | 4.9 | |
| Lunde et al. | Norway | Caucasians | 123 (70.7) | 48.8 ± 9.8 | 87.5 ± 19.1 | Tac, MMF, steroids | POR*28 | PCR equencing | | | 5 |
| (2014) | (2014) (2014) | Culcustans | 125 (76.7) | 10.0 ± 9.0 | 07.5 ± 17.1 | i at, mini, steroius | PPARA (rs4253728, rs4823613) | - I CK equencing | | | |
| De Jonge et al. (2015) | Belgium | Caucasians | 80 (70.0) | 54.6 ± 12.5 | 75.6 ± 14.7 | Tac, MMF, mPD | CYP3A5*3 | TaqMan | LC-MS | NA | 8 |
| Lloberas et al. | | Caucasians | 272 (65.8) | 51.0 ± 15.0 | 69.6 ± 13.7 | Tac, MMF, PD | CYP3A5*3 | Techter | EMIT, | 4.5 | 7 |
| (2017) | Spain | Caucasians | 272 (65.8) | 51.0 ± 15.0 | 69.6 ± 13.7 | Tac, MMF, PD | CIP3A5*3 | TaqMan | LC-MS | 4.5 | |
| | | | | | | | CYP3A5*3 | | Immunoassay | 2.9 | |
| Madsen et al. (2017) Denmark | Denmark | Caucasians | 52 (57.7) | 49.3 ± 12.3 | 77.0 ± 20.0 | Tac, MMF, steroids | POR*28 | TaqMan | | | 6 |
| | Caucasians | 52 (51.7) | | 77.0 ± 20.0 | rae, minir, steroids | PPARA (rs4253728) | | , | 2.7 | 0 | |
| Vanhove et al. (2017) | Belgium | NA | 279 (63.4) | 53.0 ± 13.0 | 73.4 ± 15.2 | Tac, MMF, mPD | CYP3A5*3 | OpenArray | MEIA | 3.4 | 7 |
| Scheibner et al. (2018) | U.S.A | Caucasians | 1,366 (63.3) | 51.3 ± 13.0 | 83.7 ± 19.6 | Tac, MMF | CYP3A5*3 | NA | CLIA | 5.6 | 7 |

CLIA, chemiluminescent immunoassay; CMIA, chemiluminescent microparticle immunoassay; EMIT, enzyme multiplied immunoassay technique; LC-MS, liquid chromatography-mass spectrometry; MEIA, microparticulate enzyme immunoassay; MMF, mycophenolate mofetil; mPD, methylprednisolone; NA, not available; NOS, Newcastle–Ottawa score; PCR, polymerase chain reaction; PD, prednisolone; SD, standard deviation; Tac, tacrolimus.

| | СУРЗА | 4'22 carri | ier | CYP | 3A4*1 | | | Mean Difference | | Mean Difference |
|---|------------|------------------------|-----------|-----------|-----------------------------|-----------------------|--------|----------------------|------|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | Year | IV, Random, 95% Cl |
| .1.1 1 Week | | | | | | | | | | |
| Favira 2013 | 1.66 | 0.82 | 20 | | 1.13 | 186 | 7.7% | -0.76 [-1.15, -0.37] | | |
| /anhove 2017 | 1.82 | 0.7 | 19 | 1.67 | 1.06 | 218 | 8.0% | 0.15 [-0.19, 0.49] | 2017 | + |
| loberas 2017 | 2.07 | 1.18 | 23 | 1.12 | 0.68 | 232 | 7.2% | 0.95 [0.46, 1.44] | 2017 | |
| Subtotal (95% CI) | | | 62 | | | 636 | 22.8% | 0.10 [-0.79, 1.00] | | - |
| Heterogeneity: Tau ² = | | | df = 2 | (P < 0.0 | 00001) | ; l ² = 93 | 3% | | | |
| est for overall effect: | Z = 0.23 (| P = 0.82) | | | | | | | | |
| .1.2 2 Weeks | | | | | | | | | | |
| unde 2014 | 2.54 | 1.02 | 6 | 2.54 | 0.81 | 117 | 5.2% | 0.00 [-0.83, 0.83] | 2014 | |
| Joberas 2017 | 2.48 | 1.17 | 23 | | 0.77 | 237 | 7.2% | 1.15 [0.66, 1.64] | | |
| anhove 2017 | 1.32 | 0.68 | 11 | | 0.71 | 147 | 7.6% | 0.12 [-0.30, 0.54] | | + |
| Subtotal (95% CI) | 1.02 | 0.00 | 40 | | v., , , | 501 | 19.9% | 0.45 [-0.31, 1.21] | 2011 | |
| leterogeneity: Tau ² = | 0.36° Chi | ² = 11.37 | | (P = 0.0) | 003) [,] P | | | | | - |
| est for overall effect. | | | | | | | | | | |
| .1.3 4-6 Weeks | | | | | | | | | | |
| | 0.70 | 2.47 | 22 | 1.00 | 4.40 | 224 | 4.70 | 0.001.0.004.70 | 2014 | |
| Kuypers 2014 | 2.78 | 2.17 | 22 | | 1.19 | 224 | 4.7% | 0.86 [-0.06, 1.78] | | |
| Joberas 2017 | 2.13 | 1.02 | 24 | | 0.94 | 233 | 7.5% | 0.69 [0.26, 1.12] | | |
| ladsen 2017 | 6.42 | 2.93 | 3 | 5.15 | 3.33 | 49 | 0.7% | 1.27 [-2.17, 4.71] | 2017 | |
| Subtotal (95% CI) | 0.00.00 | | 49 | | · · · · · | 506 | 12.9% | 0.73 [0.34, 1.11] | | ▼ |
| Heterogeneity: Tau ² = | | | | -= 0.90 | u); i*= | 0% | | | | |
| est for overall effect: | Z = 3.71 (| P = 0.000 | (2) | | | | | | | |
| .1.4 3 Months | | | | | | | | | | |
| (uypers 2014 | 5.1 | 4.03 | 22 | | 2.59 | 224 | 2.2% | 1.45 [-0.27, 3.17] | | |
| de Jonge 2015 | 2.47 | 0.8 | 5 | 1.76 | 1.08 | 44 | 5.5% | 0.71 [-0.06, 1.48] | 2015 | |
| loberas 2017 | 2.55 | 1.63 | 22 | 1.71 | 1.01 | 221 | 5.9% | 0.84 [0.15, 1.53] | 2017 | |
| Subtotal (95% CI) | | | 49 | | | 489 | 13.6% | 0.84 [0.34, 1.33] | | • |
| Heterogeneity: Tau ² = | 0.00; Chi | ² = 0.59, d | df = 2 (F | P = 0.74 | 4); ² = | 0% | | | | |
| lest for overall effect: | Z = 3.32 (| P = 0.000 | 9) | | | | | | | |
| 2.1.5 6 Months | | | | | | | | | | |
| avira 2013 | 4.35 | 3.07 | 20 | 4.16 | 1.97 | 186 | 3.0% | 0.19 [-1.18, 1.56] | 2013 | |
| Joberas 2017 | 3.02 | 1.95 | 20 | | 1.11 | 200 | 5.0% | 1.30 [0.43, 2.17] | | · · · · · |
| Scheibner 2018 | 2.25 | 1.36 | 150 | | | 1216 | 8.5% | 0.67 [0.45, 0.89] | | - |
| Subtotal (95% CI) | | | 190 | | | 1602 | 16.5% | 0.74 [0.37, 1.10] | 2010 | ◆ |
| Heterogeneity: Tau ² = | | | df = 2 (F | P = 0.30 | 0); l² = | | | | | |
| fest for overall effect: | Z = 3.91 (| P < 0.000 | 11) | | | | | | | |
| .1.6 1 Year | | | | | | | | | | |
| (uypers 2014 | 4.98 | 2.37 | 22 | 4.53 | 2.9 | 224 | 4.1% | 0.45 [-0.61, 1.51] | 2014 | - + |
| de Jonge 2015 | 3.62 | 1.43 | 9 | | 1.06 | 49 | 4.5% | 1.49 [0.51, 2.47] | | |
| Joberas 2017 | 2.21 | 1.56 | 17 | | 1.12 | | 5.6% | 0.37 [-0.39, 1.13] | | |
| Subtotal (95% CI) | | | 48 | | | 451 | 14.1% | 0.74 [0.04, 1.44] | | ◆ |
| Heterogeneity: Tau ² = | 0.16: Chi | ² = 3.43. d | | P = 0.18 | 3); I ² = | | | | | |
| Test for overall effect: | | | | 0.11 | | | | | | |
| fotal (95% CI) | | | 438 | | | 4185 | 100.0% | 0.57 [0.28, 0.86] | | • |
| | 0.25 Chi | 2 = 71 22 | | 7 (P < 0 | 0000 | | | 5.57 [0.20, 0.00] | _ | · · _ · _ · _ · |
| -SucT vienenate | | | | (- = 0 | | 1, 1 = 1 | 5.0 | | | -4 -2 0 2 4 |
| Heterogeneity: Tau ² = | | | | 5 (P = (| 0.78). I | ²=0% | | | | Higher in CYP3A4*1/*1 Higher in CYP3A4*22 carrier |
| Heterogeneity: Tau² = Fest for overall effect: Fest for subgroup diff | | | | | | | | | | |
| fest for overall effect. Fest for subaroup diff | | | | | | | | | | |
| Fest for overall effect: | | | | | 0.755 | | | | | |

The effects of the CYP3A4*22 genetic polymorphism on C₀/ D were evaluated by meta-analysis (Figure 2) (Tavira et al., 2013; Kuypers et al., 2014; Lunde et al., 2014; De Jonge et al., 2015; Lloberas et al., 2017; Madsen et al., 2017; Vanhove et al., 2017; Scheibner et al., 2018) Data from each study were analyzed by classifying post-transplant periods into 1 week, 2 weeks, 4-6 weeks, 3 months, 6 months, and 1 year. When data were combined in all study periods, the CYP3A4*22 carriers exhibited 0.57 ng/mL/mg higher C₀/D than $CYP3A4^{*1/*1}$ recipients (95% CI 0.28 to 0.86; p = 0.0001). Except for the first 2 weeks post-transplantation, statistically notable differences in the C₀/D of Tac were detected according to CYP3A4*22 genotypes. Although substantial heterogeneity across the studies was found ($I^2 = 76\%$, p < 0.00001), no subgroup difference was reported among the six different time periods (p = 0.78). Begg's and Egger's tests indicated no evidence of publication bias (p = 0.733 and p = 0.453, respectively).

Six studies (Tavira et al., 2013; Kuypers et al., 2014; De Jonge et al., 2015; Lloberas et al., 2017; Vanhove et al., 2017; Scheibner et al., 2018) were analyzed to investigate the influence of the *CYP3A4*22* variant on the daily dose of Tac (Figure 3). When data in all study periods were combined, *CYP3A4*22* carriers required a 2.02 mg/day less dose to attain the optimal trough level than non-carriers (95% CI -2.55 to -1.50; p < 0.00001). Except for 1-year post-transplantation, significant differences in the daily dose were observed between *CYP3A4*22* carriers and *CYP3A4*1/*1* carriers. Similar to C₀/D, there were substantial heterogeneity ($I^2 = 75\%$, p < 0.00001) but no subgroup significant difference (p = 0.49). Results from Begg's and Egger's tests indicated no statistical evidence of publication bias (p = 0.177 and p = 0.568, respectively).

| 2.2.11 Week wira 2013 16.8 5.13 20 13 4.67 186 3.2% $-1.37[3.72, 0.98]$ 2013 Jobers 2017 6 3.16 23 8 2.98 232 5.7% $-2.04[3.35, 0.65]$ 2017 Jabora 2017 7.32 2.39 19 3.3 4.32 26 6.2% $-1.98[3, P=0.%]$ Hetrogenety. Tau ² = 0.00, Ch ² = 0.25, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.00, Ch ² = 0.25, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.00, Ch ² = 0.25, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.00, Ch ² = 0.25, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.00, Ch ² = 0.25, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.00, Ch ² = 0.25, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.00, Ch ² = 0.25, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.00, Ch ² = 0.25, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.00; Ch ² = 0.25, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.00; Ch ² = 0.25, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.00; Ch ² = 0.25, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.00; Ch ² = 0.25, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.00; Ch ² = 0.25, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.00; Ch ² = 0.25, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.00; Ch ² = 0.31, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.00; Ch ² = 0.31, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.00; Ch ² = 0.31, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.00; Ch ² = 0.31, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.00; Ch ² = 0.31, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.02; Ch ² = 0.33, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.02; Ch ² = 0.33, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.02; Ch ² = 0.33, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.02; Ch ² = 0.33, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.02; Ch ² = 0.33, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.02; Ch ² = 0.33, df = 2 (P = 0.80); P = 0.% Hetrogenety. Tau ² = 0.72; Ch ² = 0.33, df = 2 (P = 0.40); P = 0.% Hetrogenety. Tau ² | Study or Subgroup | Сүрза | 4*22 carrie | | | BA4*1/ | | | Mean Difference | | Mean Difference |
|--|--|--|---|--|---|--|---|--|---|------------------------------|--------------------|
| wink 2013 1163 513 20 12 467 166 32% -1.371372.088 2013 wink 2017 7.32 2.39 19 33 434 226 62% -1.9813.19.077 2017 wink 2017 7.32 2.39 19 33 434 226 62% -1.9813.19.077 2017 wink 2017 7.32 2.39 19 33 434 226 62% -1.9813.19.077 2017 wink 2017 5 365 3.37 19 11.7 4.7 226 4.9% -2.0413.67.0.41 2017 wink 2017 5 385 23 7.33 7.37 237 4.7% -2.331.40.10.651 2017 wink 2017 5 385 23 7.33 7.37 237 4.7% -2.331.40.10.651 2017 wink 2017 5 385 ($\theta = 0.003$) wink 2016 205% ($\theta = 0.00$, Ch ² = 0.06 df = 1 ($\theta = 0.80$), $\mu = 0.8$ wind 205% ($\theta = 0.00$, Ch ² = 0.06 df = 1 ($\theta = 0.80$), $\mu = 0.8$ wind 205% ($\theta = 0.00$, Ch ² = 0.06 df = 1 ($\theta = 0.80$), $\mu = 0.8$ wind 205% ($\theta = 0.00$, Ch ² = 0.00 df = 1 ($\theta = 0.80$), $\mu = 0.8$ wind 205% ($\theta = 0.00$, Ch ² = 0.00 df = 1 ($\theta = 0.80$), $\mu = 0.8$ wind 2017 4.33 1.97 24 6 2.98 2.33 7.38 -1.80 [2.56, -0.79] 2017 wind 2016 5.6 1.5 5 10.09 407 531 4.7% -2.30 [4.10, -0.40] 2014 wind 205% ($\theta = 0.00$, Ch ² = 0.00 0001) 2.24 Weeks wind 2015 5.6 1.5 5 10.09 407 531 4.7% -2.30 [4.18, -0.47] wind 2013 5.6 1.5 5 10.09 407 531 4.7% -2.30 [3.18, -1.41] 2014 wind 2015 5.6 1.5 5 10.09 407 531 4.7% -2.30 [3.18, -1.41] 2014 wind 2015 5.6 1.5 5 10.09 407 531 4.7% -2.30 [3.18, -1.41] 2014 wind 2015 5.6 1.5 5 10.09 407 531 4.7% -2.30 [3.18, -1.41] 2014 wind 2015 5.6 1.5 5 10.09 407 531 4.7% -2.30 [3.18, -1.41] 2014 wind 2013 5.25 2.75 20 6.5 2.5 186 6.0% -1.25 [2.51, 0.01] 2013 wind 2013 5.25 2.75 20 6.5 2.5 186 6.0% -1.25 [2.51, 0.01] 2013 wind 2016 5.01 19 106 1133 1216 8.44 1.71 [2.22, 12.20] 2016 wind 2013 5.25 2.75 2.0 6.5 2.5 186 6.0% -1.25 [2.51, 0.01] 2013 wind 2013 5.25 2.75 2.0 7.0 9 9.741 2.96 71 7.2% -2.71 [5.52, -3.30] 2017 wind 2016 5.01 19 106 1163 22.44 9.43 22.4 115 [3.43, 0.0.00] 2014 wind 2016 (55% Ch) 4.43 4.43 4.43 4.43 2.47 7.433 10.00\% -2.02 [2.55, -1.50] wind 2016 (55% Ch) 4.43 4.43 4.43 2.47 7.433 10.00\% -2.02 [2.55, -1.50] wind 2016 (55% Ch) 4.43 4.43 4.43 2.47 7.433 10.00\% -2.02 [2.55, -1.50] wind 2016 (55% Ch) 4.43 4.43 4.43 2.47 7.433 10.00\% | | Mean | SD T | otal | Mean | SD | Total | Weight | IV, Random, 95% CI | Year | IV, Random, 95% Cl |
| Jobers 2017 6 316 23 8 2.98 22 57% -2.00 $[3.35, 0.65]$ 2017 authors 2017 7 32 230 19 33 442 26 62% -198 [3.19, 0.77] 2017 authors 2017 7 32 230 df = 2 (P = 0.89); P = 0% estfor overall effect Z = 4.44 (P < 0.00001) 2.22 Weeks anhore 2017 5 3 395 23 7.33 373 237 4.7% -2.33 [4.01, 0.65] 2017 Jobers 2017 5 3 395 23 7.33 3.73 237 4.7% -2.33 [4.01, 0.65] 2017 Jobers 2017 5 3 395 23 7.33 3.73 237 4.7% -2.33 [4.01, 0.65] 2017 Jobers 2017 5 3 395 23 7.33 3.73 237 4.7% -2.33 [4.01, 0.65] 2017 Jobers 2017 4 3.3 1.97 24 6 2.98 233 7.3% -1.90 [3.40, 0.40] 2014 Jobers 2017 4 3.3 1.97 24 6 2.98 233 7.3% -1.90 [3.40, 0.40] 2014 Jobers 2017 4 3.3 1.97 24 6 2.98 233 7.3% -1.90 [3.40, 0.40] 2014 Jobers 2017 4 3.3 1.97 24 6 5 .98 233 7.3% -2.30 [3.19, -1.41] 2014 de Jonge 2015 5.6 1.5 5 10.09 4.07 53 4.7% -2.40 [3.41, -1.42] 2017 Jubtotal (95% Cf) 46 2.2 5 2.9 212 7.5% -2.40 [3.41, -1.42] 2017 Jubtotal (95% Cf) 1.8 22 5 2.9 217 7.5% -2.40 [3.41, -1.42] 2017 Jubtotal (95% Cf) -8.40; P = 0.80; P = 0.80; estfor overall effect Z = 4.78 (P < 0.0001) 2.2.5 Months wintra 2013 5.25 2.75 20 6.5 2.5 186 6.0% -1.25 [2.51, 0.01] 2013 Jobers 2017 3 1.6 2.0 4.33 1216 8.4% -17 [3.22, 1.20] 2018 Jubtotal (95% Cf) 1.90 (2.71 = 20 = 0.64); P = 0.8 estfor overall effect Z = 7.54 (P < 0.00001) 2.2.5 Months wintra 2013 5.25 2.75 20 6.5 2.5 186 6.0% -1.25 [2.51, 0.01] 2013 Jobers 2017 3 1.6 2.0 4.33 1216 8.4% -17 [3.22, 1.20] 2018 Jubtotal (95% Cf) 41 2.0 2 0.64); P = 0.8 estfor overall effect Z = 7.54 (P < 0.00001); P = 7.5% estfor overall effect Z = 7.54 (P < 0.00001); P = 7.5% estfor overall effect Z = 7.54 (P < 0.00001); P = 7.5% estfor overall effect Z = 7.57 (P < 0.00001); P = 7.5% estfor subtorou differences: ChP = 4.43, df = 5 (P = 0.49); P = 0%. URE 3 | .2.1 1 Week | | | | | | | | | | |
| Tanhoe 2017 7. 23 2. 2. 9 19 9.3.4.34 226 6.2% $-1.98 [3.19, 0.27]$ 2017 telerogenety: Tar ² = 0.0; Ch ² = 0.23, df = 2 (P = 0.89); P = 0% telerogenety: Tar ² = 0.0; Ch ² = 0.23, df = 2 (P = 0.89); P = 0% telerogenety: Tar ² = 0.0; Ch ² = 0.23, df = 2 (P = 0.89); P = 0% telerogenety: Tar ² = 0.0; Ch ² = 0.66, df = 1 (P = 0.81); P = 0% telerogenety: Tar ² = 0.0; Ch ² = 0.66, df = 1 (P = 0.81); P = 0% telerogenety: Tar ² = 0.0; Ch ² = 0.0003) 1.2.2 Weeks wypers 2014 6.4 3.4 22 8.3 3.7 224 5.3% -1.90 [3.40, -0.40] 2014 toberas 2017 4.33 1.97 24 6 2.38 233 7.3% -1.67 [2.55, -0.79] 2017 1.2.4 Weeks wypers 2014 6.4 3.4 22 8.3 3.7 224 5.3% -1.90 [3.40, -0.40] 2014 toberas 2017 4.33 1.97 24 6 2.38 233 7.3% -1.67 [2.55, -0.79] 2017 1.2.4 Weeks wypers 2014 6.4 3.4 22 8.3 3.7 224 5.3% -1.90 [3.40, -0.40] 2014 toberas 2017 4.33 1.97 24 6 2.38 223 7.3% -1.67 [2.55, -0.79] 2017 1.2.4 Weeks wypers 2014 6.4 3 1.9 22 6.6 3 224 7.3% -2.30 [-3.19, -1.41] 2014 1.2.6 Months windroat 05% (Ch) 1.2.7 (B = 0.00, P = 0.04) ; P = 0% telerogenety: Tar ² = 0.00; Ch ² = 0.00001) 1.2.4 3 Months windra 2013 5.25 7.75 20 6.5 2.5 186 6.0% -1.25 [-2.51, 0.01] 2013 telerogenety: Tar ² = 0.00; Ch ² = 0.00001) 1.2.4 5 Went windra 2013 5.25 7.75 20 6.5 2.5 186 6.0% -1.25 [-2.51, 0.01] 2013 toberas 2017 3 1.6 20 4.33 2.24 2.01 7.7% -1.33 [-2.10, -0.56] 2017 toberas 2017 3 1.6 20 4.33 2.24 2.01 7.7% -1.33 [-2.10, -0.56] 2017 toberas 2017 3 1.6 20 4.33 2.24 2.01 7.7% -1.33 [-2.10, -0.56] 2017 toberas 2017 3 1.6 20 4.33 2.24 2.01 7.7% -0.38 [-2.16, -0.50] 2015 toberas 2017 3 1.6 20 4.33 2.24 2.01 7.7% -0.38 [-2.16, -0.50] 2015 toberas 2017 3 1.6 20 4.73 2.25 2.5 2.24 7.2% -0.90 [+1.80, -0.00] 2014 telerogenety: Tar ² = 0.00; Ch ² = 0.00; Ch ² = 0.000; P = 0.64; P = 0.% telfor overall effect Z = 7.54 (P = 0.00001); P = 55% telfor overall effect Z = 7.53 (P = 0.00001); P = 55% telfor overall effect Z = 1.84 (P = 0.10) val (0.56% Ch) val 43 437 4318 100.0 43 420 473 2.1 | Favira 2013 | 11.63 | 5.13 | 20 | 13 | 4.67 | 186 | 3.2% | -1.37 [-3.72, 0.98] | 2013 | |
| $\frac{1}{22.5} \frac{1}{24.5} \frac{1}{24.5} \frac{1}{2.5} \frac$ | loberas 2017 | 6 | 3.16 | 23 | 8 | 2.98 | 232 | 5.7% | -2.00 [-3.35, -0.65] | 2017 | |
| $\frac{1}{6} \log_2 \log_1 (1 + 1) \log_2 $ | /anhove 2017 | 7.32 | 2.39 | 19 | 9.3 | 4.34 | 226 | 6.2% | -1.98 [-3.19, -0.77] | 2017 | |
| The field of the | Subtotal (95% CI) | | | 62 | | | 644 | 15.1% | -1.91 [-2.75, -1.07] | | ◆ |
| 2.2 2 Weeks Tarhore 2017 9.66 3.37 19 11.7 47 226 4.9% -2.04 [3.67, -0.41] 2017 Jobers 2017 5 3.87 129 11.7 47 226 4.9% -2.04 [3.67, -0.41] 2017 Jobers 2017 5 3.87 129 14.2 4.63 9.6% -2.18 [.3.35, -1.01] Heterogeneity Taru ² = 0.00; Ch ² = 0.003) 2.3 4 Weeks Typers 2014 6.4 3.4 22 8.3 3.7 224 5.3% -1.90 [3.40, -0.40] 2014 Jobers 2017 4.33 1.97 24 6 2.98 2.33 7.3% -1.67 [2.55, 0.79] 2017 Jobers 2017 4.33 1.97 24 6 2.98 2.33 7.3% -1.67 [2.55, 0.79] 2017 Heterogeneity Taru ² = 0.00; Ch ² = 0.07, d= 1 (P = 0.80); P = 0% 'soft overall effect Z = 4.48 (P < 0.0001) 2.23 4 Weeks Typers 2014 4.3 1.9 22 6.6 3 2.24 7.3% -2.01 [3.19, -1.41] 2014 Heterogeneity Taru ² = 0.04; Ch ² = 6.55, d= 2 (P = 0.04); P = 69% 'soft overall effect Z = 4.78 (P < 0.0001) 2.23 5 Months Moreal 2017 2.95 1.68 22 5 2.96 2.21 7.5% -2.04 [2.84, -1.24] 2017 Jobers 2017 2.95 1.68 22 5 2.96 2.21 7.5% -2.04 [2.84, -1.24] 2017 Jobers 2017 2.95 1.68 2.2 5 2.96 1.00 407 53 47% -4.44 [8.20, 2.78] 2017 Jobers 2017 2.95 1.68 2.2 5 2.96 1.00 407 53 47% -4.44 [8.20, 2.78] 2017 Jobers 2017 2.95 1.68 2.2 5 2.96 1.00 407 53 47% -4.44 [5.20, 2.78] 2017 Jobers 2017 2.95 1.68 2.2 5 2.96 1.00 49 498 1.95% -2.70 [.3.80, -1.59] Heterogeneity Taru ² = 0.00; Ch ² = 0.91, J = 20 (2.77) 4.13 [2.10, 0.65] 2017 Jobers 2017 3 1.6 2.0 4.3 2.24 2.01 7.7% -1.35 [.1.00, 65] 2017 Heterogeneity Taru ² = 0.00; Ch ² = 0.91, J = 2 (P = 0.64); P = 0% Heterogeneity Taru ² = 0.00; Ch ² = 0.91, J = 2 (P = 0.64); P = 0% Heterogeneity Taru ² = 0.00; Ch ² = 0.91, J = 2 (P = 0.64); P = 0% Heterogeneity Taru ² = 0.00; Ch ² = 0.93, J = 2 (P = 0.04); P = 0% Heterogeneity Taru ² = 0.76, Ch ² = 5.76, d = 15 (P < 0.00001); P = 75% Heterogeneity Taru ² = 0.76, Ch ² = 5.76, d = 15 (P < 0.00001); P = 75% Higher in CYP3A4 ⁴ 1P ⁴ Higher in CYP3A4 ⁴ 22 carrier | leterogeneity: Tau ² = | 0.00; Chi | ² = 0.23, df | = 2 (P | 9 = 0.89 |); ² = | 0% | | | | |
| anhore 2017 9.66 3.37 19 11.7 47 226 4.9% $-2.04[3.67, -0.41]$ 2017 Johens 2017 5 3.95 23 7.33 3.73 237 47% $-2.33[4.01, 0.65]$ 2017 whited 195% (C) 42 463 9.6% $-2.18[3.35, -1.01]$ telerogeneity: Tau ² = 0.00; Ch ² = 0.66 d = 1 (P = 0.81); P = 0% set for overall effect Z = 3.56 (P = 0.003) 2.2.3 Weeks Suppers 2014 6.4 3.4 22 8.3 3.7 224 5.3% $-1.90[3.40, -0.40]$ 2014 Johens 2017 4.33 1.9 24 6 2.98 233 7.3% $-1.67[2.55, 0.79]$ 2017 whited 195% (C) 446 4.57 12.6% $-1.73[2.49, -0.97]$ telerogeneity: Tau ² = 0.00; Ch ² = 0.00; P = 0.80; P | est for overall effect. | Z= 4.44 (| P < 0.0000 | 1) | | | | | | | |
| Jobers 2017 $1 - 5 - 3.95 - 23 - 7.33 - 3.73 - 237 - 4.78 - 2.33 [+ 0.1], 0.65] 2017 463 9.6% -2.18[-3.35, -1.01] 464 -2.18[-3.35, -1.01] 465 9.6% -2.18[-3.35, -1.01] 467 9.6% -2.18[-3.35, -1.01] 468 9.6% -2.18[-3.35, -1.01] 468 9.6% -2.18[-3.35, -1.01] 468 9.6% -2.18[-3.35, -1.01] 469 9.6% -2.18[-3.35, -1.01] 469 9.6% -2.18[-3.35, -1.01] 469 9.6% -2.18[-3.35, -1.01] 469 9.6% -2.18[-3.35, -1.01] 469 9.6% -1.25[-2.5, -0.79] 2017 469 9.6% -1.25[-2.5, -0.79] 2017 469 9.6% -1.25[-2.5, -0.79] 2017 469 9.6% -1.25[-2.5, -0.79] 2017 469 9.6% -1.25[-2.5] 9.07] 469 9.6% -1.25[-2.5] 9.07] 469 9.6% -1.25[-2.5] 9.07] 469 9.6% -1.25[-2.5] 9.07] 469 9.6% -1.25[-2.5] 9.01] 9.01 469 9.6% -1.25[-2.5] 9.01] 9.01 460 9.2017 9.96 1.88 22 5 2.98 221 7.5% -2.04[-2.84, -1.24] 2017 469 9.6% -1.25[-2.5], 0.01] 2013 469 9.6% -1.25[-2.5], 0.01] 2013 460 9.6% -1.25[-2.5], 0.01] 2013 460 9.2017 3 1.6 20 4.33 2.24 201 7.7% -1.33[-2.10, -0.56] 2017 560 60mths 461 9.9 150 6.17 33 1216 8.4% -1.71[-2.22, -1.20] 2018 461 9.00 2017 3 1.6 20 4.33 2.24 201 7.7% -1.35[-1.00, -0.66] 2017 561 60 worall effect Z = 7.54 (P < 0.0001) 52.56 Months 461 9.9 150 6.17 33 1216 8.4% -1.71[-2.22, -1.20] 2018 461 9.9 150 6.17 33 1216 8.4% -1.71[-2.22, -1.20] 2018 461 9.9 150 6.17 33 1216 8.4% -1.71[-2.22, -1.20] 2018 461 9.9 150 6.17 33 1216 8.4% -1.71[-2.22, -1.20] 2018 461 9.9 150 6.17 33 1216 0.9 19 0.9 1603 2.2.1% -1.56[-1.96, -1.15] 461 9.9 150 6.17 33 1216 0.9 19 0.9 1603 2.2.1% -1.56[-1.96, -1.15] 461 9.9 150 6.17 3.38 1216 0.9 13 0.01 2014 4.1 2 2 2 5 2.5 2.5 2.27 7.2% -0.9 150 6.17 2.2% -0.9 150 6.17 2.2% -0.9 150 6.17 2.2% -0.9 150 6.17 2.2% -0.9 150 6.27 0.9 9 7.41 2.96 77 7.7% -0.9 164 6.29 2.9 150 6.17 1.26% -0.9 2017 4.1 2 2 0 2 4 4.1 2 2 0 2 4 4.3 4.1 2 2 2 5 2.5 2.5 2.24 7.2% -0.9 0.1 1.8 0.000 1.2014 4.1 2 2 0 2 4 1.26 4.7% -0.9 0.1001 4.1 2 0 0 2.14 0.20 1.20 1.20 1.20 1.20 1.20 1.20 1.20$ | 2.2.2 2 Weeks | | | | | | | | | | |
| Jobers 2017 $1 - 5 - 3.95 - 23 - 7.33 - 3.73 - 237 - 4.78 - 2.33 [+ 0.1], 0.65] 2017 463 - 9.6% -2.18[-3.35, -1.01] 464 - 2.38[-3.35, -1.01] 463 - 9.6% -2.18[-3.35, -1.01] 464 - 2.38[-3.36, -1.03] 464 - 2.38[-3.36, -1.03] 464 - 2.38[-3.36, -1.25] 464 - 2.38[-3.36, -1.25] 475 - 2.38[-3.36, -1.25] 485 - 2.39[-3.36, -1.25] 485 - 2.39[-3.36, -1.25] 485 - 2.39[-3.36, -1.25] 485 - 2.39[-3.36, -1.25] 485 - 2.39[-3.36, -1.25] 485 - 2.39[-3.36, -1.25] 485 - 2.39[-3.36, -1.25] 485 - 2.39[-3.36, -1.25] 485 - 2.39[-3.36, -1.25] 485 - 2.39[-3.36, -1.25] 485 - 2.39[-3.36, -1.25] 485 - 2.39[-3.36, -1.25] 485 - 2.39[-3.36, -1.25] 485 - 2.39[-3.36, -1.25] 485 - 2.39[-3.36, -1.25] 485 - 2.39[-3.36, -1.25] 485 - 2.39[-3.36, -1.25] 485 - 2.49[-3.40, -0.00$ | /anhove 2017 | 9.66 | 3.37 | 19 | 11.7 | 4.7 | 226 | 4.9% | -2.04 [-3.67, -0.41] | 2017 | |
| hibitotal (95% C) 42 42 463 9.6% -2.18 [3.35, -1.01] Hereogeneity. Tau ² = 0.06, df = 1 ($P = 0.81$); $P = 0$ % est for overall effect Z = 3.66 ($P = 0.003$) 2.23 Weeks Suppris 2014 6.4 3.4 22 8.3 3.7 224 5.3% -1.90 [-3.40, -0.40] 2014 Joberas 2017 4.33 1.97 24 6 2.98 233 7.3% -1.67 [2.25, -0.79] 2017 Hereorgeneity. Tau ² = 0.00; Ch ² = 0.07, df = 1 ($P = 0.80$); $P = 0$ % Hereorgeneity. Tau ² = 0.00; Ch ² = 0.07, df = 1 ($P = 0.80$); $P = 0$ % Hereorgeneity. Tau ² = 0.00; Ch ² = 0.00001) 2.2.4 3 Months Worpers 2014 4.3 1.9 22 6.6 3 224 7.3% -2.30 [-3.19, -1.41] 2014 Hereorgeneity. Tau ² = 0.00; Ch ² = 0.65, df = 2 ($P = 0.04$); $P = 0$ % Hereorgeneity. Tau ² = 0.64; Ch ² = 6.55, df = 2 ($P = 0.04$); $P = 60$ % Hereorgeneity. Tau ² = 0.60; Ch ² = 0.7 2, 0 6.5 2.5 196 6.0% Hereorgeneity. Tau ² = 0.00; Ch ² = 0.91, df = 2 ($P = 0.64$); $P = 0$ % Hereorgeneity. Tau ² = 0.00; Ch ² = 0.91, df = 2 ($P = 0.64$); $P = 0$ % Hereorgeneity. Tau ² = 0.00; Ch ² = 0.91, df = 2 ($P = 0.64$); $P = 0$ % Hereorgeneity. Tau ² = 0.00; Ch ² = 0.91, df = 2 ($P = 0.64$); $P = 0$ % Hereorgeneity. Tau ² = 0.00; Ch ² = 0.91, df = 2 ($P = 0.64$); $P = 0$ % Hereorgeneity. Tau ² = 0.20; Ch ² = 4.39, df = 2 ($P = 0.64$); $P = 0$ % Hereorgeneity. Tau ² = 0.37; Ch ² = 4.39, df = 2 ($P = 0.64$); $P = 0$ % Hereorgeneity. Tau ² = 0.73; Ch ² = 4.39, df = 2 ($P = 0.64$); $P = 0$ % Hereorgeneity. Tau ² = 0.73; Ch ² = 4.39, df = 2 ($P = 0.64$); $P = 0$ % Hereorgeneity. Tau ² = 0.73; Ch ² = 4.39, df = 2 ($P = 0.64$); $P = 0$ % Higher in CVP3A4 ^{+1/21} Higher in | | | | | | | | | | | |
| $\frac{1}{23} \frac{1}{4} \frac{1}{2} 1$ | | | 0.00 | | 1.00 | 0.10 | | | | 2011 | |
| iset for overall effect. Z = 3.65 (P = 0.0003) 2.23 Weeks Gypers 2014 6.4 3.4 2.2 8.3 3.7 224 5.3% -1.90 [-3.40, -0.40] 2014 Ubberas 2017 4.33 1.97 24 6 2.88 2.33 7.3% -1.67 [-2.55, -0.79] 2017 ubtotal (95% C) 4.6 4.57 12.6% -1.73 [-2.48, 0.97] 2017 ubtotal (95% C) 4.6 3.224 7.3% -2.30 [-3.19, -1.41] 2014 leonge 2015 5.6 1.5 5 10.09 4.07 53 4.7% -4.49 [-6.20, -2.78] 2015 jobersa 2017 2.96 1.88 2.2 5.288 221 7.5% -2.20 [-3.19, -1.41] 2017 ubtotal (95% C) 4.9 1.25 2.51, 0.01] 2013 2017 2016 ubtotal (95% C) 4.16 2.99 150 6.17 3.38 1216 8.4% -1.25 [-2.51, 0.01] 2013 joberas 2017 3.1 1.6 20 4.33 2.24 7.3% -1.35 [-2.10, 6.0] 2017 <tr< td=""><td></td><td>0.00[.] Chi</td><td>²=0.06 df</td><td></td><td>= 0.81</td><td>$^{2} = 1$</td><td></td><td></td><td>2.1.0 [0.000, 1.001]</td><td></td><td></td></tr<> | | 0.00 [.] Chi | ² =0.06 df | | = 0.81 | $ ^{2} = 1$ | | | 2.1.0 [0.000, 1.001] | | |
| Supports 2014 6.4 3.4 22 8.3 3.7 224 6.3% -1.90 [-3.40, -0.40] 2014 Joberas 2017 4.33 1.97 24 6 2.98 233 7.3% -1.67 [-2.55, -0.79] 2017 Jeterogeneity, Tau" = 0.00; Ch" = 0.07, df = 1 ($P = 0.80$); $P = 0\%$ Set for verall effect $Z = 4.48$ ($P < 0.00001$) 2.2.4 3 Months Supports 2014 4.3 1.9 22 6.6 3 224 7.3% -2.30 [-3.19, -1.41] 2014 Le Jonge 2015 5.6 1.5 5 10.09 4.07 63 4.7% -4.49 [-6.20, -2.78] 2015 Joberas 2017 2.36 1.68 22 5 2.98 221 7.5% -2.04 [-3.81, -1.24] 2017 Jubtotal (95% C) 49 49 498 19.5% -2.70 [-3.80, -1.59] Jeterogeneity, Tau" = 0.64; Ch" = 6.55, df = 2 ($P = 0.04$); $P = 69\%$ Set for overall effect $Z = 4.78$ ($P < 0.00001$) 2.2.5 Months Warra 2013 5.25 2.75 20 6.5 2.5 186 6.0% -1.25 [-2.51, 0.01] 2013 Joberas 2017 3 1.6 20 4.33 2.24 201 7.7% -1.33 [-2.10, -0.56] 2017 Joberas 2017 3 1.6 20 4.33 2.24 201 7.7% -1.33 [-2.10, -0.56] 2017 Joberas 2017 3 1.6 20 4.33 2.24 201 7.7% -1.33 [-2.10, -0.56] 2017 Joberas 2017 3 1.6 20 4.33 2.24 201 7.7% -1.35 [-1.50] Joberas 2017 3 1.6 20 4.33 2.24 7.2% -0.90 [-1.80, -0.00] 2014 Jeterogeneity, Tau" = 0.07; Ch" = 0.91, df = 2 ($P = 0.64$); $P = 0\%$ Set for overall effect $Z = 7.54$ ($P < 0.00001$) 2.2.6 Hyear Jubtotal (95% C) 48 473 21.1% -2.15 [-1.76, 0.42] Jeterogeneity, Tau" = 0.37; Ch" = 4.39.9; df = 2 ($P < 0.00001$); $P = 95\%$ Set for overall effect $Z = 7.54$ ($P < 0.00001$) Joberas 2017 3.17 20 17 4 2.99 71 7.2% -4.71; [5.62, -3.80] 2017 Jubtotal (95% C) 48 473 21.1% -2.15 [-1.73, 0.42] Jeterogeneity, Tau" = 0.79; Ch" = 4.39.9; df = 2 ($P < 0.00001$); $P = 95\%$ Set for overall effect $Z = 7.54$ ($P < 0.00001$); $P = 95\%$ Set for overall effect $Z = 7.54$ ($P < 0.00001$); $P = 95\%$ Set for overall effect $Z = 7.54$ ($P < 0.00001$); $P = 75\%$ Set for overall effect $Z = 7.54$ ($P < 0.00001$); $P = 75\%$ Set for overall effect $Z = 7.54$ ($P < 0.00001$); $P = 75\%$ Set for overall effect $Z = 7.54$ ($P < 0.00001$); $P = 75\%$ Set for overall effect $Z = 7.64$ ($P < 0.00001$); $P = 75\%$ Set for overall effect $Z = 7.64$ | | | | | - 0.01 | / | 0.10 | | | | |
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| $ \begin{array}{c} \text{Jobers 2017} & 4.33 & 1.97 & 24 & 6 & 2.98 & 233 & 7.3\% & -1.67 [-2.55, -0.79] & 2017 \\ \text{instrotal (95% CI)} & 46 & 457 & 12.6\% & -1.73 [-2.49, -0.97] \\ \text{istor overall effect Z = 4.48 (P < 0.00001)} \\ \hline \\ \begin{array}{c} \text{Let orgenetic, Tat' = 0.00, Chi^{2} = 0.07, df = 1 (P = 0.80), (P = 0\%) \\ \text{est for overall effect Z = 4.48 (P < 0.00001)} \\ \hline \\ \begin{array}{c} \text{Let orgenetic, Tat' = 0.01, Chi^{2} = 0.07, df = 1 (P = 0.80), (P = 0\%) \\ \text{est for overall effect Z = 4.48 (P < 0.00001)} \\ \hline \\ \begin{array}{c} \text{Let orgenetic, Tat' = 0.44, Chi^{2} = 6.55, df = 2 (P = 0.04), (P = 69\%) \\ \text{isotro overall effect Z = 4.78 (P < 0.00001) \\ \text{leterogenetic, Tat' = 0.44, Chi^{2} = 6.55, df = 2 (P = 0.04), (P = 69\%) \\ \text{isotro overall effect Z = 4.78 (P < 0.00001) \\ \text{leterogenetic, Tat' = 0.00, Chi^{2} = 0.91, df = 2 (P = 0.64), (P = 0\%) \\ \text{isotro overall effect Z = -7.54 (P < 0.00001) \\ \text{leterogenetic, Tat' = 0.00, Chi^{2} = 0.91, df = 2 (P = 0.64), (P = 0\%) \\ \text{est for overall effect Z = -7.54 (P < 0.00001) \\ \text{leterogenetic, Tat'' = 0.75, Chi^{2} = 3.99, df = 2 (P < 0.00001), (P = 75\%) \\ \text{isotro overall effect Z = -1.54 (P < 0.00001) \\ \text{leterogenetic, Tat'' = 0.79, Chi^{2} = 59.76, df = 15 (P < 0.00001), (P = 75\%) \\ \text{isotro overall effect Z = -1.54 (P < 0.00001), (P = 75\%) \\ \text{isotro overall effect Z = -1.54 (P < 0.00001), (P = 10\%) \\ \text{leterogenetic, Tat'' = 0.79, Chi^{2} = 59.76, df = 15 (P < 0.00001), (P = 75\%) \\ \text{isotro overall effect Z = -1.54 (P < 0.00001), (P = 10\%) \\ \text{isotro overall effect Z = -1.54 (P < 0.00001), (P = 10\%) \\ \text{leterogenetic, Tat'' = 0.79, Chi^{2} = 59.76, df = 15 (P < 0.00001), (P = 17\%) \\ \text{isotro overall effect Z = -1.54 (P < 0.00001), (P = 10\%) \\ \text{isotro overall effect Z = -1.54 (P < 0.00001), (P = 10\%) \\ \text{leterogenetic, Tat'' = 0.79, Chi^{2} = 59.76, df = 15 (P < 0.00001), (P = 10\%) \\ \text{isotro overall effect Z = -1.54 (P < 0.00001)} \\ isotro overall effect Z = -1.54 (P < 0.00001) \\ \text{isotro overall effect Z = -1.54 (P < 0.00001) \\ \text{isotro overall effect Z = -1.54 (P < 0.00001) \\ \text{isotro overal$ | | 6.4 | 3.4 | 22 | 83 | 37 | 224 | 5 3% | -1 90 63 40 -0 401 | 2014 | |
| biblicit (95% C) 46 457 12.6% $\cdot 1.73$ (2.49, 0.07) leferogeneity, Tav ² = 0.00; Chi ² = 0.07, df = 1 (P = 0.80); P = 0% esitor overall effect Z = 4.48 (P < 0.00001) 2.2.4 3 Months (appers 2014 4.3 1.9 22 6.6 3 224 7.3% -2.30 [-3.19, -1.41] 2014 Longe 2015 5.6 1.5 5 5 10.09 4.07 53 4.7% -4.49 [6.20, -2.78] 2015 loberas 2017 2.96 1.68 22 5 2.98 221 7.5% -2.04 [-2.84, -1.24] 2017 ubtotal (95% C) 49 49 498 19.5% -2.70 [-3.80, -1.59] teterogeneity, Tav ² = 0.64, Chi ² = 6.55, df = 2 (P = 0.04); P = 6% esitor overall effect Z = -5, 25 27.5 20 6.5 2.5 186 6.0% -1.25 [-2.51, 0.01] 2013 loberas 2017 3 1.6 20 4.33 2.24 201 7.7% -1.33 [-2.10, -0.56] 2017 chichelane 2018 4.46 2.99 150 6.17 3.38 1216 8.4% -1.71 [-2.22, 1.20] 2018 ubtotal (95% C) 10 10 1603 22.1% -1.56 [-1.96, -1.15] teterogeneity, Tav ² = 0.00; Chi ² = 0.51, df = 2 (P = 0.64); P = 0% esitor overall effect Z = 7.54 (P < 0.00001) 2.2.6 1 Year Suppers 2014 4.1 2 22 5 2.5 224 7.2% -0.90 [-1.80, -0.00] 2014 telerogeneity, Tav ² = 0.00; Chi ² = 0.91, df = 2 (P < 0.00001); P = 0% esitor overall effect Z = -1.64 (P = 0.10) otal (95% C) 48 473 2.1.% -2.15 [-4.73, 0.42] telerogeneity, Tav ² = 0.79; Chi ² = 5.9.6, df = 15 (P < 0.00001); P = 75% esitor overall effect Z = -1.64 (P = 0.10) otal (95% C) 437 4138 100.0% -2.02 [-2.55, -1.50] telerogeneity, Tav ² = 0.79; Chi ² = 5.9.76, df = 15 (P < 0.00001); P = 75% esitor overall effect Z = -1.64 (P = 0.10) otal (95% C) 437 4138 100.0% -2.02 [-2.55, -1.50] telerogeneity, Tav ² = 0.79; Chi ² = 5.9.76, df = 15 (P < 0.00001); P = 75% esitor overall effect Z = -7.59; Chi ² = 5.9.76, df = 15 (P < 0.00001); P = 57% esitor overall effect Z = -7.59; Chi ² = 5.9.76, df = 15 (P < 0.00001) esitor overall effect Z = -7.59; Chi ² = 5.9.76, df = 15 (P < 0.00001) esitor overall effect Z = -7.59; Chi ² = 5.9.76, df = 15 (P < 0.00001) esitor overall effect Z = -7.59; Chi ² = 5.9.76, df = 15 (P < 0.00001) esitor overall effect Z = -7.59; Chi ² = 5.9.76, df = 15 (P < 0.00001) esitor ov | | | | | | | | | | | |
| $\frac{1}{2} \frac{1}{2} \frac{1}$ | | 4.33 | 1.97 | - | 0 | 2.90 | | | | 2017 | • |
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| Suppers 2014 4.3 1.9 22 6.6 3 224 7.3% -2.30 [-3.19, -1.41] 2014 le Jonge 2015 5.6 1.5 5 10.09 4.07 53 4.7% -4.49 [-5.20, -2.78] 2015 Joberas 2017 2.96 1.88 22 5 2.98 221 7.5% -2.04 [-2.84, -1.24] 2017 set for overall effect $Z = 4.78$ ($P < 0.00001$) 22.5 6 Months avira 2013 5.25 2.75 20 6.5 2.5 186 6.0% -1.25 [-2.51, 0.01] 2013 Joberas 2017 3 1.6 20 4.33 2.24 201 7.7% -1.33 [-2.10, -0.56] 2017 Sthelber 2018 4.46 2.99 150 6.17 3.38 1216 8.4% -1.71 [-2.2, -1.20] 2018 Subtotal (95% C) 190 1603 22.1% -1.56 [-1.96, -1.15] Heterogeneity: Tau ² = 0.00; Ch ² = 0.91, df = 2 ($P = 0.64$); $P = 0$ % The set for overall effect $Z = 7.54$ ($P < 0.00001$) 22.6 1 Year Wypers 2014 4.1 2 22 5 2.5 24 7.2% -0.90 [-1.80, -0.00] 2014 Le Jonge 2015 2.7 0.9 9 7.41 2.96 71 7.2% -4.71 [-5.22, -3.80] 2015 Joberas 2017 3.17 2.02 17 4 2.99 178 6.7% -0.83 [-1.89, 0.23] 2017 Joberas 2017 3.17 2.02 17 4 2.99 178 6.7% -0.83 [-1.89, 0.23] 2017 Joberas 2017 3.17 2.02 17 4 1.99 718 6.7% -0.83 [-1.89, 0.23] 2017 Joberas 2017 3.17 2.02 17 4 1.99 718 6.7% -0.83 [-1.89, 0.23] 2017 Joberas 2017 3.17 2.02 17 4 1.99 718 6.7% -0.83 [-1.89, 0.23] 2017 Joberas 2017 3.17 2.02 17 4 1.99 718 6.7% -0.83 [-1.89, 0.23] 2017 Joberas 2017 3.17 2.02 17 4 1.99 718 6.7% -0.83 [-1.89, 0.23] 2017 Joberas 2017 3.17 2.02 17 4 1.99 718 6.7% -0.83 [-1.89, 0.23] 2017 Joberas 2017 3.17 2.02 17 4 1.99 718 6.7% -0.83 [-1.89, 0.23] 2017 Joberas 2017 3.17 2.02 17 4 1.99 718 6.7% -0.83 [-1.89, 0.23] 2017 Joberas 2017 3.17 2.02 17 4 1.99 718 6.7% -0.83 [-1.89, 0.23] 2017 Joberas 2017 3.17 2.02 17 4 1.99 718 6.7% -0.202 [-2.55, -1.50] Heterogeneity: Tau ² = 0.79; Ch ² = 59.76; df = 15 ($P < 0.00001$); $P = 75\%$ Test for overall effect $Z = 7.53$ ($P < 0.00001$); $P = 75\%$ Test for overall effect $Z = 7.53$ ($P < 0.00001$); $P = 0\%$ JURE 3 | | | | | - 0.00 | 0, I" = 1 | 0.70 | | | | |
| Suppers 2014 4.3 1.9 22 6.6 3 224 7.3% -2.30 [-3.19, -1.41] 2014 le Jonge 2015 5.6 1.5 5 10.09 4.07 53 4.7% -4.49 [-5.20, -2.78] 2015 Joberas 2017 2.96 1.88 22 5 2.98 221 7.5% -2.04 [-2.84, -1.24] 2017 set for overall effect $Z = 4.78$ ($P < 0.00001$) 22.5 6 Months avira 2013 5.25 2.75 20 6.5 2.5 186 6.0% -1.25 [-2.51, 0.01] 2013 Joberas 2017 3 1.6 20 4.33 2.24 201 7.7% -1.33 [-2.10, -0.56] 2017 Sthelber 2018 4.46 2.99 150 6.17 3.38 1216 8.4% -1.71 [-2.2, -1.20] 2018 Sthelber 2018 4.46 2.99 150 6.17 3.38 1216 8.4% -1.71 [-2.2, -1.20] 2018 Sthelber 2018 4.46 2.99 150 6.17 3.38 1216 8.4% -1.71 [-2.2, -1.20] 2018 Sthelber 2018 4.46 2.99 150 6.17 3.38 1216 8.4% -1.71 [-2.2, -1.20] 2018 Sthelber 2018 4.46 2.99 170 6103 22.1% -1.56 [-1.96, -1.15] Heterogeneily: Tau ² = 0.00; Ch ² = 0.91, df = 2 ($P = 0.64$); $P = 0\%$ The stor overall effect $Z = 7.54$ ($P < 0.00001$) 2.2.6 1 Year Wypers 2014 4.1 2 22 5 2.5 224 7.2% -0.90 [-1.80, -0.00] 2014 te Jonge 2015 2.7 0.9 9 7.41 2.96 71 7.2% -4.71 [-5.62, -3.80] 2015 Joberas 2017 3.17 2.02 17 4 2.99 178 6.7% -0.83 [-1.89, 0.23] 2017 Joberas 2017 3.17 2.02 17 4 2.99 178 6.7% -0.83 [-1.89, 0.23] 2017 Joberas 2017 3.17 2.02 17 4 1.99 5% Test for overall effect $Z = 7.54$ ($P < 0.00001$); $P = 95\%$ Test for overall effect $Z = 7.57$ ($P < 0.00001$); $P = 25\%$ Test for overall effect $Z = 7.57$ ($P < 0.00001$); $P = 0\%$ JURE 3 URE 3 | 2.4.2 Months | | | | | | | | | | |
| le Jonge 2015 5.6 1.5 5 10.09 4.07 53 4.7% -4.49 [6.20, -2.79] 2015 Joberas 2017 2.96 1.68 22 5 2.98 221 7.5% -2.04 [2.84, -1.24] 2017 Jettorageneity. Tau ² = 0.64; Ch ² = 6.55, df = 2 ($P = 0.04$); $P = 69\%$ leterogeneity. Tau ² = 0.64; Ch ² = 6.55, df = 2 ($P = 0.04$); $P = 69\%$ leterogeneity. Tau ² = 0.64; Ch ² = 6.55, df = 2 ($P = 0.04$); $P = 69\%$ leterogeneity. Tau ² = 0.64; Ch ² = 6.55, df = 2 ($P = 0.04$); $P = 69\%$ leterogeneity. Tau ² = 0.064; Ch ² = 6.55, df = 2 ($P = 0.04$); $P = 0\%$ leterogeneity. Tau ² = 0.00; Ch ² = 0.91, df = 2 ($P = 0.64$); $P = 0\%$ leterogeneity. Tau ² = 0.00; Ch ² = 0.91, df = 2 ($P = 0.64$); $P = 0\%$ leterogeneity. Tau ² = 0.00; Ch ² = 0.91, df = 2 ($P = 0.64$); $P = 0\%$ leterogeneity. Tau ² = 0.00; Ch ² = 0.91, df = 2 ($P = 0.64$); $P = 0\%$ leterogeneity. Tau ² = 0.00; Ch ² = 0.91, df = 2 ($P = 0.64$); $P = 0\%$ leterogeneity. Tau ² = 0.00; Ch ² = 4.39, df = 2 ($P = 0.00001$); $P = 95\%$ leterogeneity. Tau ² = 0.079; Ch ² = 4.39, df = 2 ($P = 0.49$). $P = 0\%$ leterogeneity. Tau ² = 0.79; Ch ² = 4.43, df = 5 ($P = 0.49$). $P = 0\%$ leterogeneity. Tau ² = 0.79; Ch ² = 4.43, df = 5 ($P = 0.49$). $P = 0\%$ leterogeneity. Tau ² = 0.79; Ch ² = 4.43, df = 5 ($P = 0.49$). $P = 0\%$ leterogeneity. Tau ² = 0.79; Ch ² = 4.43, df = 5 ($P = 0.49$). $P = 0\%$ leterogeneity. Tau ² = 0.79; Ch ² = 4.43, df = 5 ($P = 0.49$). $P = 0\%$ leterogeneity. Tau ² = 0.79; Ch ² = 4.43, df = 5 ($P = 0.49$). $P = 0\%$ leterogeneity. Tau ² = 0.79; Ch ² = 4.43, df = 5 ($P = 0.49$). $P = 0\%$ leterogeneity. Tau ² = 0.79; Ch ² = 4.43, df = 5 ($P = 0.49$). $P = 0\%$ | | | | ~~ | ~ ~ | | | | | | |
| $ \begin{array}{c} loberas 2017 & 2.96 & 1.68 & 22 & 5 & 2.98 & 221 & 7.5\% & -2.04 \left[-2.94 \left[-2.94 \left[-1.24 \right] & 2017 \\ 1 \text{ wint out } (95\% \text{ CI}) & 49 & 498 & 19.5\% & -2.70 \left[-3.80, -1.59 \right] \\ \hline \text{ vibrotical} (95\% \text{ CI}) & 49 & 498 & 19.5\% & -2.70 \left[-3.80, -1.59 \right] \\ \hline \text{ vibrotical} (95\% \text{ CI}) & 64 \text{ CP} = 0.04); P = 69\% \\ \hline \text{ vist for overall effect } Z = 4.78 \left(P < 0.00001 \right) \\ \hline \text{ vibrotical} (95\% \text{ CI}) & 5.25 & 2.75 & 20 & 6.5 & 2.5 & 186 & 6.0\% & -1.25 \left[-2.51, 0.01 \right] & 2013 \\ \ \text{ loberas} 2017 & 3 & 1.6 & 20 & 4.33 & 2.24 & 201 & 7.7\% & -1.33 \left[-2.10, -0.56 \right] & 2017 \\ \ \text{ vibrotical} (95\% \text{ CI}) & 190 & 1603 & 22.1\% & -1.56 \left[-1.96, -1.15 \right] \\ \ \text{ vibrotical} (95\% \text{ CI}) & 190 & 1603 & 22.1\% & -1.56 \left[-1.96, -1.15 \right] \\ \ \text{ vibrotical} (95\% \text{ CI}) & 41 & 2 & 22 & 5 & 2.5 & 224 & 7.2\% & -0.90 \left[-1.80, -0.00 \right] & 2014 \\ \ \text{ vibrotical} (95\% \text{ CI}) & 41 & 2 & 22 & 5 & 2.5 & 224 & 7.2\% & -0.90 \left[-1.80, -0.00 \right] & 2014 \\ \ \text{ vibrotical} (95\% \text{ CI}) & 48 & 473 & 21.1\% & -2.15 \left[-4.73, 0.42 \right] \\ \ \text{ vibrotical} (95\% \text{ CI}) & 48 & 473 & 21.1\% & -2.15 \left[-4.37, 0.42 \right] \\ \ \text{ vibrotical} (95\% \text{ CI}) & 437 & 4138 & 100.0\% & -2.02 \left[-2.55, -1.50 \right] \\ \ \text{ vibrotical} (95\% \text{ CI}) & 437 & 4138 & 100.0\% & -2.02 \left[-2.55, -1.50 \right] \\ \ \text{ vibrotical} (95\% \text{ CI}) & 437 & 4138 & 100.0\% & -2.02 \left[-2.55, -1.50 \right] \\ \ \text{ vibrotical} effect Z = 7.53 (P < 0.00001) \\ \ \text{ vibrotical} = 5 (P = 0.49), P = 0\% \\ \ \text{ VURE 3} \\ \end{array}$ | | | | | | | | | | | |
| Subtotal (95% CI) 49 498 19.5% -2.70 [-3.80, -1.59] Heterogeneity, Tau ² = 0.64; Chi ² = 6.55, df = 2 (P = 0.04); P = 69% lest for overall effect Z = 4.78 (P < 0.00001) 1.2.5 6 Months 1.2.5 1.2.5 2.75 20 6.5 2.5 186 6.0% -1.25 [-2.51, 0.01] 2013 Joberas 2017 3 1.6 20 4.33 2.24 201 7.7% -1.33 [-2.10, 0.56] 2017 Schelbner 2018 4.46 2.99 150 6.17 3.38 1216 8.4% -1.71 [-2.22, -1.20] 2018 Heterogeneity, Tau ² = 0.00; Chi ² = 0.91, df = 2 (P = 0.64); I ² = 0% Test for overall effect Z = 7.54 (P < 0.00001) 1.2.6 1 Year (Mypers 2014 4.1 2 22 5 2.5 224 7.2% -0.90 [-1.80, -0.00] 2014 Le Jonge 2015 2.7 0.9 9 7.41 2.96 71 7.2% -4.71 [-5.62, -3.80] 2015 Joberas 2017 3.17 2.02 17 4 2.99 178 6.7% -0.33 [-1.89, 0.23] 2017 1.15 [-4.73, 0.42] Heterogeneity, Tau ² = 4.93; Chi ² = 4.93, gh df = 2 (P < 0.00001); I ² = 95% Test for overall effect Z = 1.64 (P = 0.10) Total (95% CI) 437 4138 100.0% -2.02 [-2.55, -1.50] Heterogeneity, Tau ² = 0.79; Chi ² = 59.76, df = 15 (P < 0.00001); I ² = 75% Test for overall effect Z = 7.53 (P < 0.00001) Test for subarous differences: Chi ² = 4.43, df = 5 (P = 0.49), P = 0% Higher in CYP3A4*1/*1 Higher in CYP3A4*22 carrier HIgher in CYP3A4*1/*1 Higher in CYP3A4*22 carrier | - | | | - | | | | | | | |
| Iderogeneity: Tau ² = 0.64; Ch ² = 6.55, df = 2 (P = 0.04); P = 69% iest for overall effect Z = 4.78 (P < 0.00001) 1.2.5 6 Months Tavina 2013 5.25 2.75 20 6.5 2.5 186 6.0% -1.25 [2.51, 0.01] 2013 Joberas 2017 3 1.6 20 4.33 2.24 201 7.7% -1.33 [2.10, 0.56] 2017 ichelbner 2018 4.46 2.99 150 6.17 3.38 1216 8.4% -1.71 [2.22, -1.20] 2018 Subtotal (95% CI) 190 1603 22.1% -1.56 [-1.96, -1.15] iderogeneity: Tau ² = 0.00; Ch ² = 0.91, df = 2 (P = 0.64); P = 0% iest for overall effect Z = 7.54 (P < 0.00001) 1.2.6 1Year Kuypers 2014 4.1 2 22 5 2.5 224 7.2% -0.90 [-1.80, -0.00] 2014 Ideorgeneity: Tau ² = 0.00; Ch ² = 0.91, df = 2 (P = 0.64); P = 0% iest for overall effect Z = 7.54 (P < 0.00001) 1.2.6 1Year Kuypers 2014 4.1 2 22 5 2.5 224 7.2% -0.90 [-1.80, -0.00] 2014 Ideorgeneity: Tau ² = 4.93; Ch ² = 4.39; df = 2 (P < 0.00001); P = 95% iest for overall effect Z = 1.64 (P = 0.10) otal (95% CI) 437 4138 100.0% -2.02 [-2.55, -1.50] ieterogeneity: Tau ² = 0.79; Ch ² = 59.76, df = 15 (P < 0.00001); P = 95% iest for overall effect Z = 7.53 (P < 0.00001) iest for overall effect Z = 7.53 (P < 0.00001) iest for subaroup differences: Ch ² = 4.43, df = 5 (P = 0.49), P = 0% UURE 3 | | 2.96 | 1.68 | | 5 | 2.98 | | | | 2017 | |
| The stor overall effect $Z = 4.78 (P < 0.0001)$ 1.2.5 6 Months Tavira 2013 5.25 2.75 20 6.5 2.5 186 6.0% -1.25 [-2.51, 0.01] 2013 1.0beras 2017 3 1.6 20 4.33 2.24 201 7.7% -1.33 [-2.10, -0.56] 2017 1.0beras 2017 3 1.6 20 4.33 2.24 201 7.7% -1.33 [-2.10, -0.56] 2017 1.0beras 2018 4.46 2.99 150 6.17 3.38 1216 8.4% -1.71 [-2.22, -1.20] 2018 1.0beras 2018 4.46 2.99 150 6.17 3.38 1216 8.4% -1.71 [-2.22, -1.20] 2018 1.0beras 2017 3.16 2.2 5 2.5 2.24 7.2% -0.90 [-1.80, -0.00] 2014 1.0eerogeneity. Tau ² = 0.00; Ch ² = 0.91, df = 2 (P = 0.64); P = 0% Test for overall effect $Z = 7.54 (P < 0.00001)$ 1.2.6 1 Year 1.2.6 1 Year 1.2.6 1 Year 1.2.5 2.5 2.5 2.4 7.2% -0.90 [-1.80, -0.00] 2014 1.2.6 1 Year 1.2.6 1 Year 1.2.7 1 Year | | | | | | | | 19.5% | -2.70 [-3.80, -1.59] | | |
| $\begin{array}{c} \textbf{1.2.5 6 Months} \\ \hline \textbf{2.2.5 6 Months} \\ \hline \textbf{3wira 2013} & 5.25 & 2.75 & 20 & 6.5 & 2.5 & 186 & 6.0\% & -1.25 [-2.51, 0.01] & 2013 \\ \hline \textbf{10beras 2017} & 3 & 1.6 & 20 & 4.33 & 2.24 & 201 & 7.7\% & -1.33 [-2.10, -0.56] & 2017 \\ \hline \textbf{3cheibner 2018} & 4.46 & 2.99 & 150 & 6.17 & 3.38 & 1216 & 8.4\% & -1.71 [-2.22, -1.20] & 2018 \\ \hline \textbf{abutotal (95% CI)} & 190 & 1603 & 22.1\% & -1.56 [-1.96, -1.15] \\ \hline \textbf{1eterogeneity. Tau2 = 0.00; Chi2 = 0.91, df = 2 (P = 0.64); P = 0\% \\ \hline \textbf{est for overall effect: Z = 7.54 (P < 0.00001) \\ \hline \textbf{22.6 1 Year} \\ \hline \textbf{suppose 2015} & 2.7 & 0.9 & 9 & 7.41 & 2.96 & 71 & 7.2\% & -4.71 [-5.62, -3.80] & 2015 \\ \hline \textbf{1oberas 2017} & 3.17 & 2.02 & 17 & 4 & 2.99 & 178 & 6.7\% & -0.83 [-1.89, 0.23] & 2017 \\ \hline \textbf{subtotal (95\% CI)} & 48 & 473 & 21.1\% & -2.15 [-4.73, 0.42] \\ \hline \textbf{teterogeneity. Tau2 = 4.93; Chi2 = 43.99, df = 2 (P < 0.00001); P = 95\% \\ \hline \textbf{rest for overall effect: Z = 7.53 (P < 0.00001) \\ \hline \textbf{teterogeneity. Tau2 = 0.79; Chi2 = 59.76, df = 15 (P < 0.00001); P = 95\% \\ \hline \textbf{rest for overall effect: Z = 7.53 (P < 0.00001) \\ \hline \textbf{rest for overall effect: Z = 7.53 (P < 0.00001) \\ \hline \textbf{rest for subaroub differences: Chi2 = 4.43. df = 5 (P = 0.49). P = 0\% \\ \hline \textbf{URE 3} \\ \end{array}$ | | | | | '= 0.04 |); * = | 69% | | | | |
| Tavira 2013 5.25 2.75 20 6.5 2.5 186 6.0% -1.25 [-2.51, 0.01] 2013 Joberas 2017 3 1.6 20 4.33 2.24 201 7.7% -1.33 [-2.10, -0.56] 2017 Scheibner 2018 4.46 2.99 150 6.17 3.38 1216 8.4% -1.71 [-2.22, -1.20] 2018 Jubtotal (95% CI) 190 1603 22.1% -1.56 [-1.96, -1.15] Heterogeneity: Tau ² = 0.00; Chi ² = 0.91, df = 2 (P = 0.64); i ² = 0% Test for overall effect: $Z = 7.54$ (P < 0.00001) 12.2.6 1 Year Kuypers 2014 4.1 2 22 5 2.5 224 7.2% -0.90 [-1.80, -0.00] 2014 Le Jonge 2015 2.7 0.9 9 7.41 2.96 71 7.2% -4.71 [-5.62, -3.80] 2015 Joberas 2017 3.17 2.02 17 4 2.99 178 6.7% -0.83 [-1.89, 0.23] 2017 14tetarogeneity: Tau ² = 4.93; Chi ² = 4.3.99, df = 2 (P < 0.00001); i ² = 95% Test for overall effect: $Z = 7.53$ (P < 0.00001); i ² = 95% Test for overall effect: $Z = 1.64$ (P = 0.10) 15tal (95% CI) 437 4138 100.0% -2.02 [-2.55, -1.50] Heterogeneity: Tau ² = 0.79; Chi ² = 59.76, df = 15 (P < 0.00001); i ² = 95% Test for overall effect: $Z = 7.53$ (P < 0.00001) Test for suboroup differences: Chi ² = 4.43. df = 5 (P = 0.49). i ² = 0% 15tal (95% CI) 437 4138 100.0% -2.02 [-2.55, -1.50] Higher in CYP3A4*1/*1 Higher in CYP3A4*22 carrier 15tal (95% CI) 437 4138 100.0% -2.02 [-2.55, -1.50] 15tal (95% CI) 438 40.44 40.5 (-2.00001) 15tal (95% CI) 437 4138 100.0% -2.02 [-2.55, -1.50] 15tal (95% CI) 438 40.44 40.5 (-2.00001) 15tal (95% CI) 438 40.44 40.5 (-2.00001) 15tal (95% CI) 438 40.44 40.5 (-2.000001) 15tal (95% CI) 40.5 (-2.00001) | est for overall effect: | Z = 4.78 (| P < 0.0000 | 1) | | | | | | | |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$ | | | | | | | | | | | |
| Scheibner 2018 4.46 2.99 150 6.17 3.38 1216 8.4% -1.71 [-2.22, -1.20] 2018 Subtotal (95% CI) 190 1603 22.1% -1.56 [-1.96, -1.15] Heterogeneily: Tau ² = 0.00; Chi ² = 0.91, df = 2 (P = 0.64); l ² = 0% rest for overall effect: Z = 7.54 (P < 0.00001) 2.2.6 1Year Support 2014 4.1 2 22 5 2.5 224 7.2% -0.90 [-1.80, -0.00] 2014 le Jonge 2015 2.7 0.9 9 7.41 2.96 71 7.2% -4.71 [-5.62, -3.80] 2015 Subtotal (95% CI) 48 473 21.1% -2.15 [-4.73, 0.42] Heterogeneily: Tau ² = 4.93; Chi ² = 43.99, df = 2 (P < 0.00001); l ² = 95% rest for overall effect: Z = 7.53 (P < 0.00001); l ² = 95% rest for overall effect: Z = 7.53 (P < 0.00001) rest for subaroup differences: Chi ² = 4.43, df = 5 (P = 0.49). l ² = 0% HURE 3 | 2.2.5 6 Months | | | | | | | | | | |
| habitotal (95% Cl) 190 1603 22.1% -1.56 [-1.96, -1.15] Heterogeneity: Tau ² = 0.00; Chi ² = 0.91, df = 2 (P = 0.64); I ² = 0% -0.64); I ² = 0% -1.56 [-1.96, -1.15] Heterogeneity: Tau ² = 0.00; Chi ² = 0.91, df = 2 (P = 0.64); I ² = 0% -0.90 [-1.80, -0.00] 2014 Les of year -0.90 [-1.80, -0.00] 2014 Les of year -4.1 2 22 5 2.5 224 7.2% -4.71 [-5.62, -3.80] 2015 Joberas 2017 3.17 2.02 17 4 2.99 178 6.7% -0.83 [-1.489, 0.23] 2017 Subtotal (95% Cl) 48 473 21.1% -2.15 [-4.73, 0.42] -2.15 [-4.73, 0.42] Heterogeneity: Tau ² = 4.93; Chi ² = 43.99, df = 2 (P < 0.00001); I ² = 95% -2.02 [-2.55, -1.50] -4 -2 0 2 4 Heterogeneity: Tau ² = 0.79; Chi ² = 59.76, df = 15 (P < 0.00001); I ² = 75% -2.02 [-2.55, -1.50] -4 -2 0 2 4 Higher in CYP3A4*1/*1 Higher in CYP3A4*1/*1 Higher in CYP3A4*22 carrier Higher in CYP3A4*1/*1 Higher in CYP3A4*1/*1 Higher in CYP3A4*1/*1 | 2.2.5 6 Months Favira 2013 | 5.25 | 2.75 | 20 | 6.5 | 2.5 | 186 | 6.0% | -1.25 [-2.51, 0.01] | 2013 | |
| teterogeneity: Tau ² = 0.00; Chi ² = 0.91, df = 2 (P = 0.64); l ² = 0% est for overall effect: Z = 7.54 (P < 0.00001) 1.2.6 1 Year (auppers 2014 4.1 2 22 5 2.5 224 7.2% -0.90 [-1.80, -0.00] 2014 le Jonge 2015 2.7 0.9 9 7.41 2.96 71 7.2% -4.71 [-5.62, -3.80] 2015 Joberas 2017 3.17 2.02 17 4 2.99 178 6.7% -0.03 [-1.89, 0.23] 2017 Jubtotal (95% Cl) 48 473 21.1% -2.15 [-4.73, 0.42] teterogeneity: Tau ² = 4.93; Chi ² = 43.99, df = 2 (P < 0.00001); l ² = 95% rest for overall effect: Z = 7.53 (P < 0.00001) teterogeneity: Tau ² = 0.79; Chi ² = 59.76, df = 15 (P < 0.00001); l ² = 75% rest for overall effect: Z = 7.53 (P < 0.00001) rest for subaroup differences: Chi ² = 4.43. df = 5 (P = 0.49). l ² = 0% URE 3 | | | | | | | | | | | |
| The state of the set | Favira 2013 | 3 | 1.6 | 20 | 4.33 | 2.24 | 201 | 7.7% | -1.33 [-2.10, -0.56] | 2017 | = |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | Tavira 2013 Lloberas 2017 | 3 | 1.6 2.99 | 20 150 | 4.33 | 2.24 | 201 1216 | 7.7% 8.4% | -1.33 [-2.10, -0.56] -1.71 [-2.22, -1.20] | 2017 | |
| $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | Favira 2013 Lloberas 2017 Scheibner 2018 Subtotal (95% CI) | 3 4.46 | 1.6 2.99 | 20 150 190 | 4.33 6.17 | 2.24 3.38 | 201 1216 1603 | 7.7% 8.4% | -1.33 [-2.10, -0.56] -1.71 [-2.22, -1.20] | 2017 | |
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The first sensitivity analysis was performed by excluding each post-transplantation period at a time (Supplementary Table S3). In the sensitivity analysis of C₀/D, heterogeneity was mitigated when data measured in the first week after transplantation (Biondi-Zoccai et al., 2011; Tavira et al., 2013; Lloberas et al., 2017) were excluded ($I^2 = 30\%$, p = 0.13). The results of the dose requirement showed an MD range of -2.19 to -1.85 mg/day with an I^2 range of 15%-80%. For dose requirements, heterogeneity was greatly reduced when data measured 1 year after transplantation (Moher et al., 2009; De Jonge et al., 2015; Lloberas et al., 2017) were omitted ($I^2 = 15\%$, p = 0.30). Another sensitivity analysis was performed with the studies that scored 7 or higher on the NOS system (Supplementary Table S4). The MD of C₀/D was 0.60 ng/mL/mg, which was comparable to the main result.

As Tac is a substrate of CYP3A5, we performed an additional meta-analysis of the relationship between *CYP3A5*3* and Tac PKs in the same cohorts. The *CYP3A5*3/*3* carriers exhibited 1.23 ng/ mL/mg higher C_0/D than *CYP3A5*1* carriers (95% CI 1.06 to 1.41,

p < 0.00001; Supplementary Figure S1A). In order to attain the optimal trough level, *CYP3A5*3/*3* carriers required 4.96 mg/day less dose than patients with *CYP3A5*1* allele (95% CI -5.91 to -4.00, p < 0.00001; Supplementary Figure S1B).

To further investigate the independent effect of *CYP3A4*22* while adjusting for *CYP3A5*3*, we analyzed the effects of *CYP3A4*22* in CYP3A5 non-expressers. Four studies (Egger et al., 1997; Moher et al., 2009; Tavira et al., 2013; De Jonge et al., 2015) elucidated the impact of the *CYP3A4*22* genotype on C₀/D and the dose requirement of Tac in CYP3A5 non-expressers. The evaluation of outcomes occurred within 3 to 6 months after kidney transplantation. When the effect of CYP3A5 was adjusted, the C₀/D of *CYP3A4*22* carriers was 0.67 ng/mL/mg higher (95% CI 0.44 to 0.89, p < 0.00001; Figure 4A) and dose requirement was 1.83 mg/day lower (95% CI – 2.59 to –1.06, p < 0.00001; Figure 4B) than patients with *CYP3A4*1/*1*. Therefore, the significant effect of *CYP3A4*22* on C₀/D and the dose requirement of Tac remained evident even after adjusting for *CYP3A5*3*.



4 Discussion

This is the first meta-analysis to evaluate the effects of the *CYP3A4*22* variants on C_0/D and the dose of Tac in adult renal transplant patients. Compared to patients with *CYP3A4*1/*1*, *CYP3A4*22* carriers tend to exhibit increased C_0/D and require a lower dose of Tac. Considering that C_0/D is considered as a surrogate marker to determine the Tac metabolism rate (Thölking et al., 2014), this finding implies that *CYP3A4*22* carriers may have lower CYP3A4 activity than *CYP3A4*1/*1* carriers, thereby leading to overexposure to Tac, especially from first 4 weeks to 1 year after transplantation.

*CYP3A4*22*, an intronic variant of *CYP3A4*, occurs when C is substituted with T in intron 6 (Wang et al., 2011). In both *in vitro* and *in vivo* studies, this variant was associated with increased production of a non-functional *CYP3A4* alternative splice variant with partial intron 6 retention (Wang and Sadee, 2016). This resulted in decreased functional mRNA and protein production compared to the wild-type (Wang et al., 2011; Klein et al., 2012). Hence, it can be speculated that those with *CYP3A4*22* may have lower CYP3A4 enzymatic activity and exhibit higher plasma concentration, which can lead to drug-induced toxicities.

In line with our results, several clinical studies showed that CYP3A4*22 was related to decreased metabolism and increased exposure to CYP3A substrate drugs. For example, CYP3A4*22 carriers showed 20% higher simvastatin plasma concentrations and 58% higher plasma concentration of simvastatin acid (Tsamandouras et al., 2014; Luzum et al., 2015). Similarly, CYP3A4*22 carriers showed a 2.5-fold concentration and 1.7-fold higher C₀/D of quetiapine (van der Weide and van der Weide, 2014). For cyclosporine, another immunosuppressive agent, CYP3A4*22 was associated with increased concentration by 50% and decreased clearance by 15% (Lunde et al., 2014; Moes et al., 2014).

*CYP3A5*3* is one of the most significant genetic determinants of Tac PKs (Kuehl et al., 2001; Billing et al., 2017; Khan et al., 2020). An additional meta-analysis demonstrated that carrying the *CYP3A5*3*

polymorphism greatly impacted Tac blood concentration. From the result with CYP3A5 non-expressers, *CYP3A4*22* showed significant effects on the Tac trough concentration and dose requirement. Furthermore, there was no linkage disequilibrium between *CYP3A5*3* and *CYP3A4*22* reported in the included studies (Moher et al., 2009; De Jonge et al., 2015) and GBR/FIN populations of the 1000 Genomes Project ($r^2 = 0.004$). This finding indicates that the *CYP3A4*22* and *CYP3A5*3* polymorphisms are independently associated with Tac exposure.

This meta-analysis revealed a significant degree of heterogeneity among the included studies. Statistical heterogeneity can be attributed to the small number of included studies and the wide range of sample sizes, varying from 52 to 1,366 patients. Also, some factors that can potentially contribute to clinical heterogeneity, including variances in analytic methods and target trough concentration. In the sensitivity analysis of C_0/D , the heterogeneity was reduced when data collected within the first week after transplantation was excluded. This suggests that the observed heterogeneity may be attributed to the early posttransplant period, which is characterized by the insufficient function of the transplanted graft.

This study has several limitations. First, all included studies were conducted in European populations. This was because *CYP3A4*22* is rarely found in African or Asian descent, whereas the allele frequency of *CYP34*22* is approximately 8% in Caucasians (Okubo et al., 2013). Second, there is considerable heterogeneity in the clinical setting, such as immunosuppressive protocol, target trough level, and comorbidities. Lastly, confounding factors that could affect the PKs of Tac, including age, body weight, and comedication were not adjusted.

5 Conclusion

CYP3A4*22 allele carriers showed significantly higher plasma C_0/D of Tac and required a lower daily dose to

achieve the therapeutic trough level after kidney transplantation. These findings of our meta-analysis may provide further evidence for the effects of genetic polymorphism in *CYP3A4* on the PKs of Tac, which will improve individualized treatment in a clinical setting.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

Conceptualization: JSK, JY, and HSG; methodology: JSK, SS, JY, KHC, and HSG; formal analysis: JSK and SS; writing—original draft preparation: JSK, JY, and HSG; writing—review and editing: JY and HSG; supervision: HSG. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1201083/ full#supplementary-material

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