Critical Care Medicine

Society of Critical Care Medicine
The Intensive Care Professionals

REVIEW ARTICLE

Fixed- Versus Variable-Dose Prothrombin Complex Concentrate for the Emergent Reversal of Vitamin K Antagonists: A Systematic Review and Meta-Analysis

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•Introduction

- **VKAs and Hemorrhage Risk**: VKAs are commonly used anticoagulants but pose a significant risk of bleeding, including intracerebral hemorrhage, especially in the elderly.
- **4-PCC for VKA Reversal**: Four-factor prothrombin complex concentrate (4-PCC) is the preferred treatment for reversing VKAs in emergencies due to its higher safety and efficacy compared to fresh frozen plasma.
- **Fixed vs. Variable Dosing**: Different dosing strategies for 4-PCC have been proposed, with fixed-dose regimens ranging from 1000–2500 IU and variable-dose regimens based on patient weight and INR.
- **Study Focus**: This study aims to compare the effectiveness and safety of fixed- and variable-dose regimens for 4-PCC in reversing VKAs during emergencies.

Materials and methods

1/ systematic review:

was Conducted according to Cochrane and PRISMA Guidelines to Compare 4-PCC Dosing Regimens

2/search strategy:

Comprehensive Search of PubMed, Embase, and Ovid MEDLINE Databases (january2000–august 2023)

Keywords:

Focused on Studies of Vitamin K Reversal Using 4-PCC

No Restrictions , No limitations on language, date, or article type during the search

Materials and methods

3/studyselection and inclusion criteria

Study Selection Process:
Conducted by Two Independent Reviewers
Initial Screening: Title Screening for Duplicates
Relevance Screening: Based on Title and Abstract

Final Inclusion Criteria:
1/ written in or translated into english language
2/ Unique Patient Population on VKAs
3/ Intervention using Fixed-Dose 4-PCC for VKA Reversal
4/ Comparator of VKA reversal using Variable-Dose 4-PCC

4/data collection and outcomes

- **Data Collection**: Detailed Baseline and Treatment Characteristics
  - **Patient Characteristics**: Age, sex, weight, BMI, reason for reversal, baseline INR levels
  - **Treatment Variables**: 4-PCC dose, time to administration, use of additional 4-PCC or other reversal agents (e.g., vitamin K, fresh frozen plasma, blood products)
- **Definitions of Administration Timing**:
  - **"Door-to-Needle"**: Time from hospital presentation to 4-PCC administration
  - **"Order-to-Needle"**: Time from entry of the treatment order to actual administration of 4-PCC
- **Efficacy Outcomes Assessed by**:
  - **INR Targets**: Overall INR achieved post-4-PCC administration, with pooled target INRs of <2 and <1.5 due to study variability
  - **Clinical Hemostasis**: Evaluated in four studies, defined as the absence of major bleeding per the International Society on Thrombosis and Hemostasis criteria
- **Safety Outcomes Monitored**:
  - **Mortality**: In-hospital mortality rate
  - **Thromboembolic Events (TEEs)**: Occurrence of any TEEs post-treatment
  - **Hospital Stay Duration**: Length of hospital stay as a safety outcome

- **5/heterogeneity**
- **The study assessed heterogeneity using Cochrane's Q test and the I^2 statistic, considering it significant if I^2 was above 50% and p-value below 0.1. Due to few RCTs, separate analyses were done on cohort studies. Evidence quality was rated from "high" to "very low" using the GRADE tool, and subgroup analyses were performed to examine potential biases across various patient and treatment factors.**
- **VKA Reversal Indication**: All indications, non-ICH only, ICH only
- **Baseline INR Levels**: INR ≥ 4 vs. INR < 4
- **Patient Weight**: ≥ 80 kg vs. < 80 kg
- **4-PCC Dose**: Grouped as 1000–1500 IU, 1500–2000 IU, or 2000–2500 IU

Results

Articles Identified

- 1,428 found
- 19 met inclusioncriteria

Study Types and Designs:

- **RCTs**: Three prospective randomized controlled trials
- **Cohort Studies**: Includes prospective and retrospective cohorts, with some studies comparing to historical data

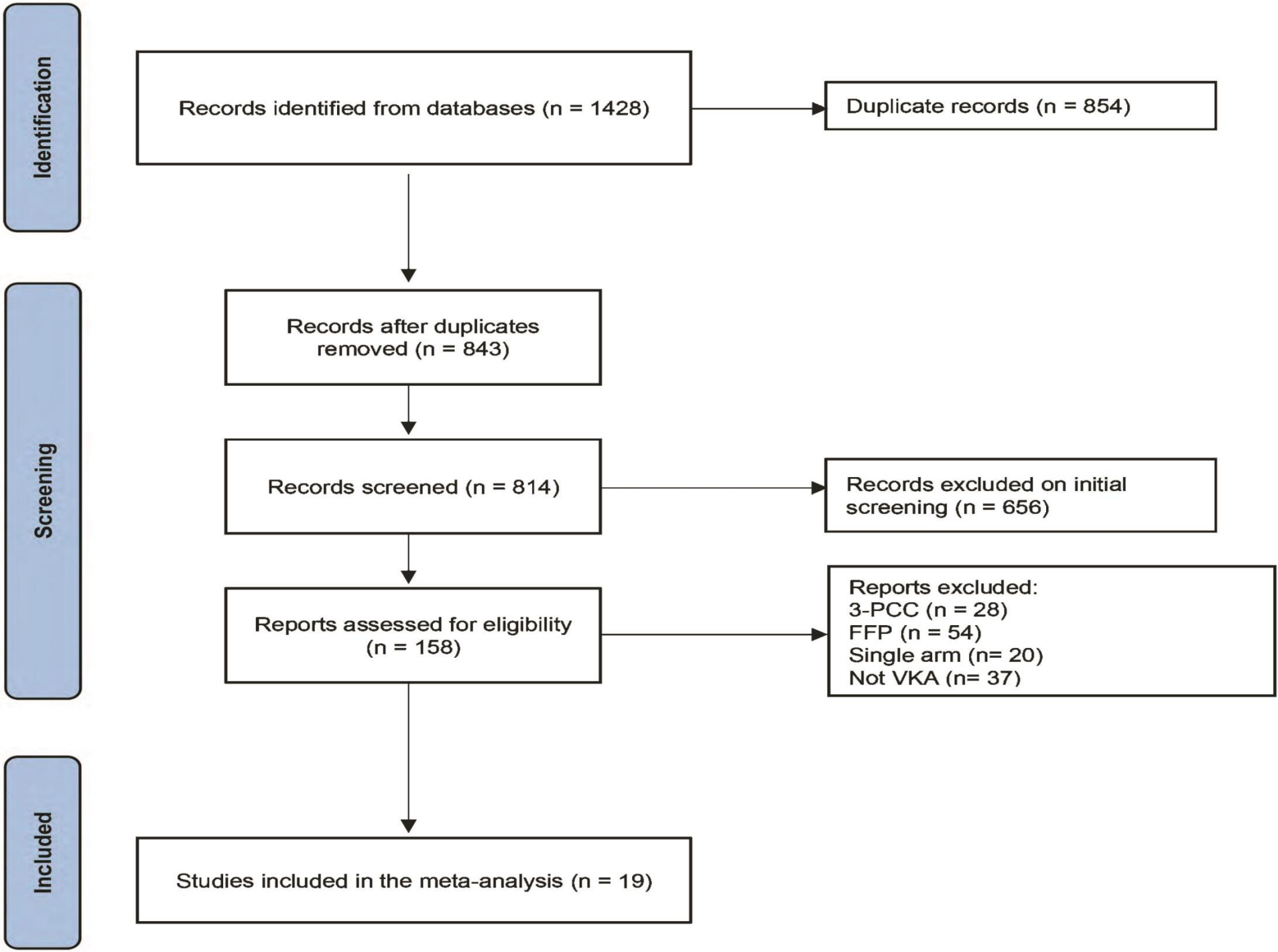
Geographic Locations: Studies conducted in the United States and The Netherlands

4-PCC Products Used

- **U.S.**: Primarily usedKCentra(CSL Behring)
- **Netherlands**:Cofactand occasionallyBeriplexwere used; two studies did not specify the product

Dosing Regimens:

- **Fixed-Dose Range**: 750 to 3000 IU
- **Variable-Dose**: Followed manufacturer guideline


Identification
Screening
Included
Records identified from databases (n = 1428)
Duplicate records (n = 854)
Records after duplicates removed (n = 843)
Records screened (n = 814)
Records excluded on initial screening (n = 656)
Reports assessed for eligibility (n = 158)
Reports excluded:
3-PCC (n = 28)
FFP (n = 54)
Single arm (n= 20)
Not VKA (n= 37)
Studies included in the meta-analysis (n = 19)

ICH Patient Inclusion:

- **ICH Only**: Four studies
- **ICH Subgroup Analysis**: Three studies
- **ICH Exclusion**: Four studies

Quality Assessment

- **Cohort Studies**: High quality with NOS scores of 7–9
- **RCTs**: Low risk of bias according to the ROBINS-I tool

Study Sample Sizes:

- **RCTs**: 323 subjects (161 on fixed dose, 162 on variable dose)
- **Cohort Studies**: 1,912 patients (858 on fixed dose, 1,054 on variable dose

Data Availability::

- **RCTs**: Data available for 11 variables
- **Cohort Studies**: Comprehensive data covering all variables

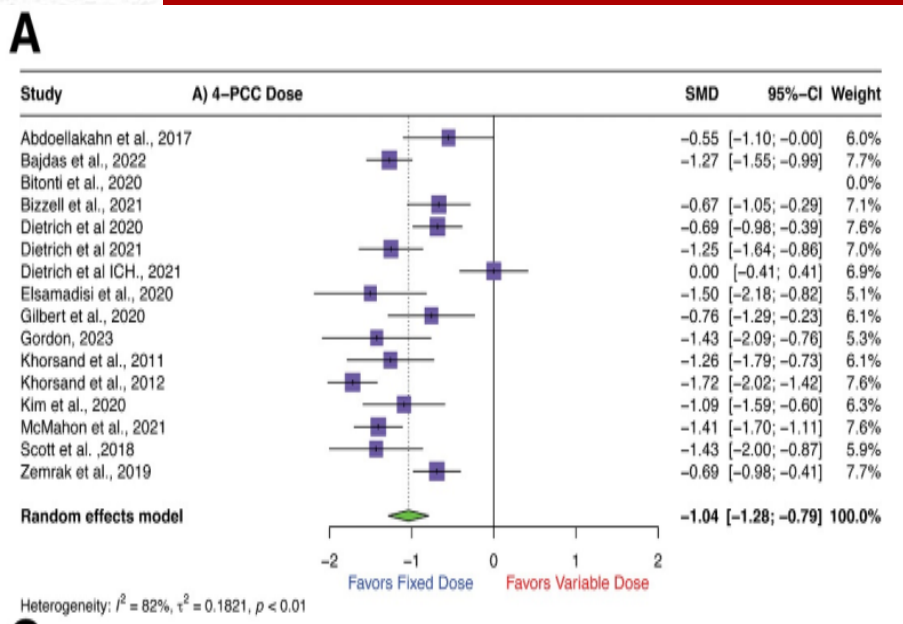
	Fixed dose	Variable dose
Stady populations	No significant demographic differences between fixed- and variable-dose groups.	No significant demographic differences between fixed- and variable-dose groups.
- **Dosing**:	Fixed-dose regimens used a lower 4-PCC dose, possibly improving cost-effectiveness.	
Administration time	Faster administration with fixed-dose regimens, beneficial in emergency settings.	
efficacy	Fixed-dose regimens were effective in clinical hemostasis but slightly less for strict INR targets.	
safety	Fixed-dose regimens showed lower mortality and fewer thromboembolic events.	

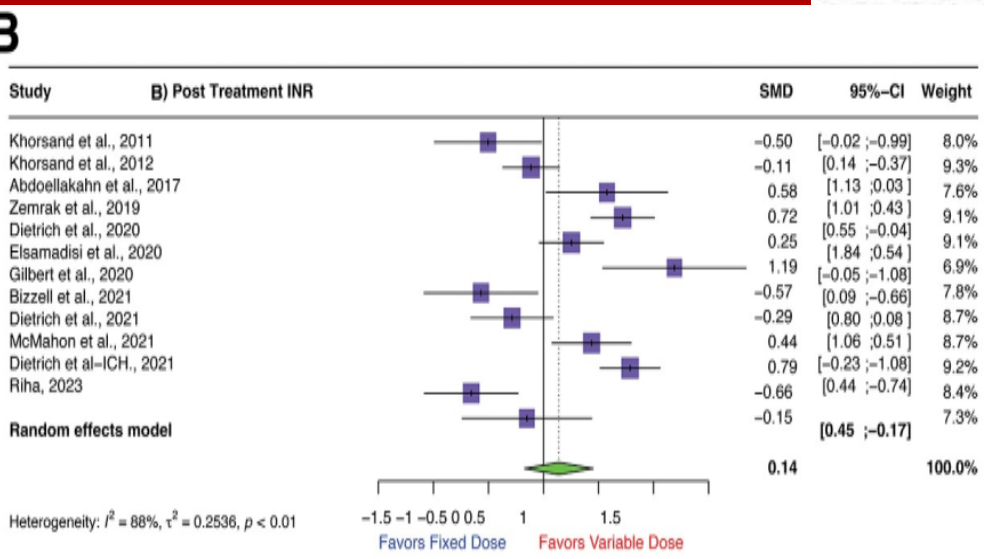
*4-PCC Administration: Fixed-Dose vs. Variable-Dose Regimens**

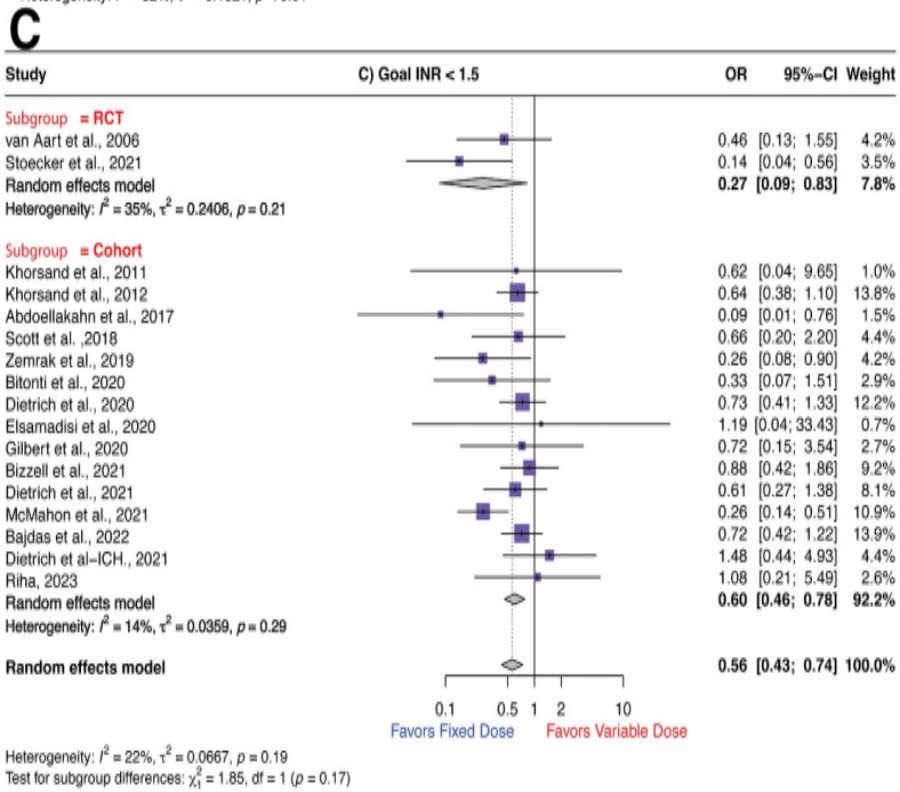
- - **4-PCC Dose**: Fixed-dose used significantly less 4-PCC overall (1537.3 IU vs. 2222.2 IU) and per kg (22.1 IU/kg vs. 27.7 IU/kg).
- - **Order-to-Needle Time**: Fixed-dose reduced time to 39 minutes vs. 72 minutes.
- - **PCC-to-INR Time**: Fixed-dose reduced time to 147.4 minutes vs. 192.5 minutes.
- ==>Summary: Fixed-dose regimen lowers both 4-PCC dose and treatment time compared to variable-dose.

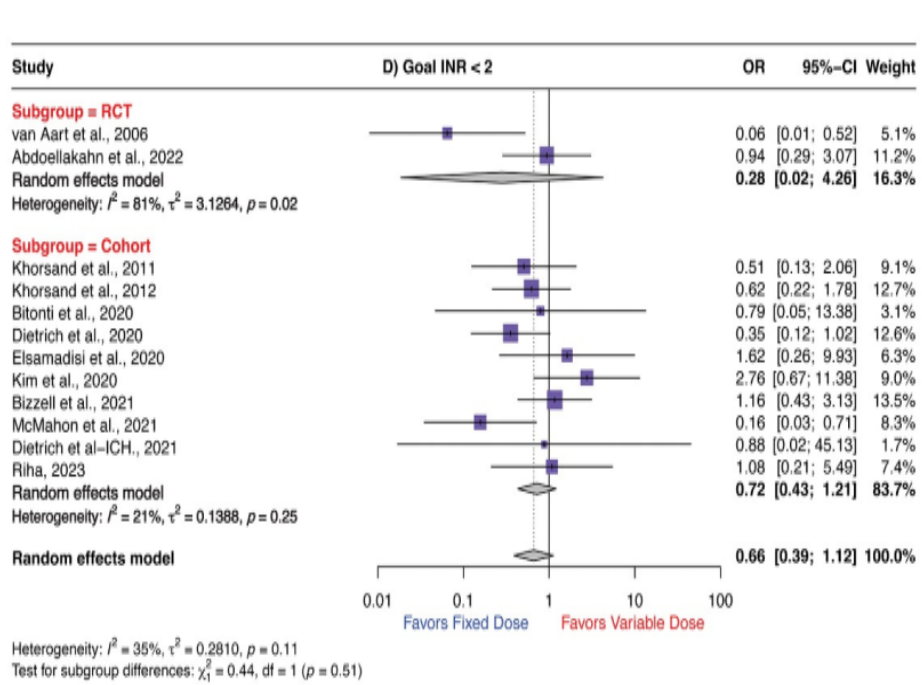
Efficacy Outcomes of Fixed-Dose vs. Variable-Dose 4-PCC Regimens**

- 1- **Clinical Hemostasis**: Fixed-dose likely improves clinical hemostasis compared to variable-dose (74.1% vs. 61.6%; moderate certainty).
- 2- **Goal INR < 2**:
- - **Cohort Studies**: Fixed-dose is slightly less effective than variable-dose (88.8% vs. 92.4%; moderate certainty).
- - **RCTs**: Evidence is uncertain for achieving INR < 2.
- 3- **Goal INR < 1.5**:
- - **Cohort Studies**: Fixed-dose is less effective than variable-dose (64.6% vs. 74.3%; moderate certainty).
- - **RCTs**: Fixed-dose shows a lower likelihood of achieving INR < 1.5 (66.7% vs. 88.6%; high certainty).


A
Study
A) 4–PCC Dose
SMD
95%–CI
Weight
Abdoellakahn et al., 2017 −0.55 [−1.10; −0.00] 6.0%
Bajdas et al., 2022 −1.27 [−1.55; −0.99] 7.7%
Bitonti et al., 2020 0.0%
Bizzell et al., 2021 −0.67 [−1.05; −0.29] 7.1%
Dietrich et al 2020 −0.69 [−0.98; −0.39] 7.6%
Dietrich et al 2021 −1.25 [−1.64; −0.86] 7.0%
Dietrich et al ICH., 2021 0.00 [−0.41; 0.41] 6.9%
Elsamadisi et al., 2020 −1.50 [−2.18; −0.82] 5.1%
Gilbert et al., 2020 −0.76 [−1.29; −0.23] 6.1%
Gordon, 2023 −1.43 [−2.09; −0.76] 5.3%
Khorsand et al., 2011 −1.26 [−1.79; −0.73] 6.1%
Khorsand et al., 2012 −1.72 [−2.02; −1.42] 7.6%
Kim et al., 2020 −1.09 [−1.59; −0.60] 6.3%
McMahon et al., 2021 −1.41 [−1.70; −1.11] 7.6%
Scott et al. ,2018 −1.43 [−2.00; −0.87] 5.9%
Zemrak et al., 2019 −0.69 [−0.98; −0.41] 7.7%
Random effects model −1.04 [−1.28; −0.79] 100.0%
−2 −1 0 1 2
Favors Fixed Dose
Favors Variable Dose
Heterogeneity: I^2 = 82%, τ^2 = 0.1821, p < 0.01

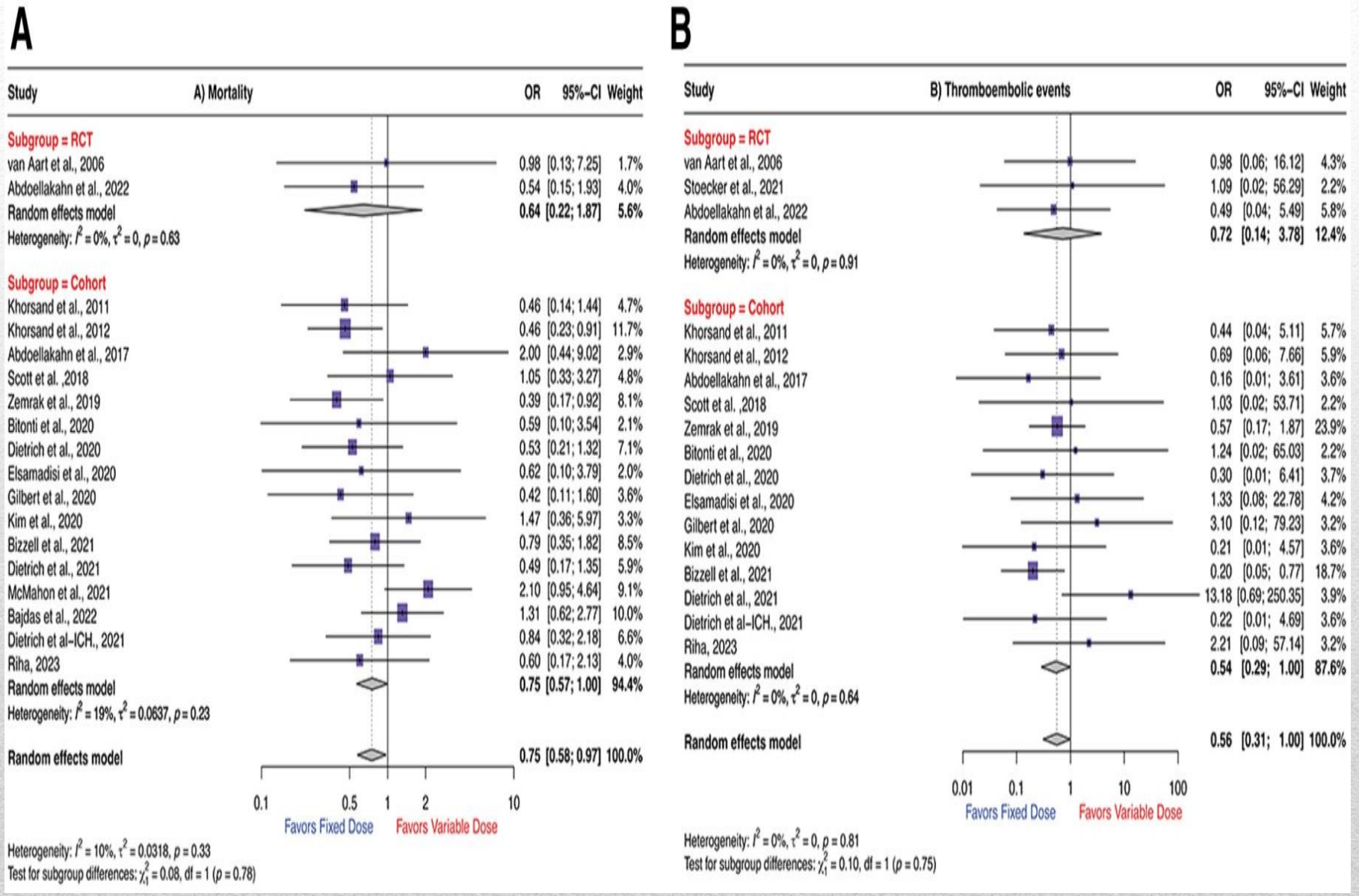

B
Study
B) Post Treatment INR
SMD
95%–CI
Weight
Khorsand et al., 2011 −0.50 [−0.02 ;−0.99] 8.0%
Khorsand et al., 2012 −0.11 [0.14 ;−0.37] 9.3%
Abdoellakahn et al., 2017 0.58 [1.13 ;0.03] 7.6%
Zemrak et al., 2019 0.72 [1.01 ;0.43] 9.1%
Dietrich et al., 2020 0.25 [0.55 ;−0.04] 9.1%
Elsamadisi et al., 2020 1.19 [1.84 ;0.54] 6.9%
Gilbert et al., 2020 −0.57 [−0.05 ;−1.08] 7.8%
Bizzell et al., 2021 −0.29 [0.09 ;−0.66] 8.7%
Dietrich et al., 2021 0.44 [0.80 ;0.08] 8.7%
McMahon et al., 2021 0.79 [1.06 ;0.51] 9.2%
Dietrich et al–ICH., 2021 −0.66 [−0.23 ;−1.08] 8.4%
Riha, 2023 −0.15 [0.44 ;−0.74] 7.3%
Random effects model 0.14 [0.45 ;−0.17] 100.0%
−1.5 −1 −0.5 0 0.5 1 1.5
Favors Fixed Dose
Favors Variable Dose
Heterogeneity: I^2 = 88%, τ^2 = 0.2536, p < 0.01


C
Study
C) Goal INR < 1.5
OR
95%–CI
Weight
Subgroup = RCT
van Aart et al., 2006 0.46 [0.13; 1.55] 4.2%
Stoecker et al., 2021 0.14 [0.04; 0.56] 3.5%
Random effects model 0.27 [0.09; 0.83] 7.8%
Heterogeneity: I^2 = 35%, τ^2 = 0.2406, p = 0.21
Subgroup = Cohort
Khorsand et al., 2011 0.62 [0.04; 9.65] 1.0%
Khorsand et al., 2012 0.64 [0.38; 1.10] 13.8%
Abdoellakahn et al., 2017 0.09 [0.01; 0.76] 1.5%
Scott et al. ,2018 0.66 [0.20; 2.20] 4.4%
Zemrak et al., 2019 0.26 [0.08; 0.90] 4.2%
Bitonti et al., 2020 0.33 [0.07; 1.51] 2.9%
Dietrich et al., 2020 0.73 [0.41; 1.33] 12.2%
Elsamadisi et al., 2020 1.19 [0.04; 33.43] 0.7%
Gilbert et al., 2020 0.72 [0.15; 3.54] 2.7%
Bizzell et al., 2021 0.88 [0.42; 1.86] 9.2%
Dietrich et al., 2021 0.61 [0.27; 1.38] 8.1%
McMahon et al., 2021 0.26 [0.14; 0.51] 10.9%
Bajdas et al., 2022 0.72 [0.42; 1.22] 13.9%
Dietrich et al–ICH., 2021 1.48 [0.44; 4.93] 4.4%
Riha, 2023 1.08 [0.21; 5.49] 2.6%
Random effects model 0.60 [0.46; 0.78] 92.2%
Heterogeneity: I^2 = 14%, τ^2 = 0.0359, p = 0.29
Random effects model 0.56 [0.43; 0.74] 100.0%
0.1 0.5 1 2 10
Favors Fixed Dose
Favors Variable Dose
Heterogeneity: I^2 = 22%, τ^2 = 0.0667, p = 0.19
Test for subgroup differences: χ^2_1 = 1.85, df = 1 (p = 0.17)


D
Study
D) Goal INR < 2
OR
95%–CI
Weight
Subgroup = RCT
van Aart et al., 2006 0.06 [0.01; 0.52] 5.1%
Abdoellakahn et al., 2022 0.94 [0.29; 3.07] 11.2%
Random effects model 0.28 [0.02; 4.26] 16.3%
Heterogeneity: I^2 = 81%, τ^2 = 3.1264, p = 0.02
Subgroup = Cohort
Khorsand et al., 2011 0.51 [0.13; 2.06] 9.1%
Khorsand et al., 2012 0.62 [0.22; 1.78] 12.7%
Bitonti et al., 2020 0.79 [0.05; 13.38] 3.1%
Dietrich et al., 2020 0.35 [0.12; 1.02] 12.6%
Elsamadisi et al., 2020 1.62 [0.26; 9.93] 6.3%
Kim et al., 2020 2.76 [0.67; 11.38] 9.0%
Bizzell et al., 2021 1.16 [0.43; 3.13] 13.5%
McMahon et al., 2021 0.16 [0.03; 0.71] 8.3%
Dietrich et al–ICH., 2021 0.88 [0.02; 45.13] 1.7%
Riha, 2023 1.08 [0.21; 5.49] 7.4%
Random effects model 0.72 [0.43; 1.21] 83.7%
Heterogeneity: I^2 = 21%, τ^2 = 0.1388, p = 0.25
Random effects model 0.66 [0.39; 1.12] 100.0%
0.01 0.1 1 10 100
Favors Fixed Dose
Favors Variable Dose
Heterogeneity: I^2 = 35%, τ^2 = 0.2810, p = 0.11
Test for subgroup differences: χ^2_1 = 0.44, df = 1 (p = 0.51)

Safety Outcomes of Fixed-Dose vs. Variable-Dose 4-PCC Regimens**

- -1**Mortality**:
- - **Cohort Studies**: Lower mortality with fixed-dose (15.6% vs. 18.8%; high certainty).
- - **RCTs**: Lower mortality with fixed-dose (4.7% vs. 7.2%; high certainty).
- -2 **Thromboembolic Events (TEEs)**:
- - **Cohort Studies**: Lower TEE rate with fixed-dose (2.4% vs. 4.4%; high certainty).
- - **RCTs**: Likely lower TEE rate with fixed-dose (1.2% vs. 1.8%; moderate certainty).


A
Study
A) Mortality
OR
95%-CI
Weight
Subgroup = RCT
van Aart et al., 2006 0.98 [0.13; 7.25] 1.7%
Abdoellakahn et al., 2022 0.54 [0.15; 1.93] 4.0%
Random effects model 0.64 [0.22; 1.87] 5.6%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.63
Subgroup = Cohort
Khorsand et al., 2011 0.46 [0.14; 1.44] 4.7%
Khorsand et al., 2012 0.46 [0.23; 0.91] 11.7%
Abdoellakahn et al., 2017 2.00 [0.44; 9.02] 2.9%
Scott et al. ,2018 1.05 [0.33; 3.27] 4.8%
Zemrak et al., 2019 0.39 [0.17; 0.92] 8.1%
Bitonti et al., 2020 0.59 [0.10; 3.54] 2.1%
Dietrich et al., 2020 0.53 [0.21; 1.32] 7.1%
Elsamadisi et al., 2020 0.62 [0.10; 3.79] 2.0%
Gilbert et al., 2020 0.42 [0.11; 1.60] 3.6%
Kim et al., 2020 1.47 [0.36; 5.97] 3.3%
Bizzell et al., 2021 0.79 [0.35; 1.82] 8.5%
Dietrich et al., 2021 0.49 [0.17; 1.35] 5.9%
McMahon et al., 2021 2.10 [0.95; 4.64] 9.1%
Bajdas et al., 2022 1.31 [0.62; 2.77] 10.0%
Dietrich et al-ICH., 2021 0.84 [0.32; 2.18] 6.6%
Riha, 2023 0.60 [0.17; 2.13] 4.0%
Random effects model 0.75 [0.57; 1.00] 94.4%
Heterogeneity: I^2 = 19%, τ^2 = 0.0637, p = 0.23
Random effects model 0.75 [0.58; 0.97] 100.0%
0.1
0.5
1
2
10
Favors Fixed Dose
Favors Variable Dose
Heterogeneity: I^2 = 10%, τ^2 = 0.0318, p = 0.33
Test for subgroup differences: χ^2_1 = 0.08, df = 1 (p = 0.78)
B
Study
B) Thromboembolic events
OR
95%-CI
Weight
Subgroup = RCT
van Aart et al., 2006 0.98 [0.06; 16.12] 4.3%
Stoecker et al., 2021 1.09 [0.02; 56.29] 2.2%
Abdoellakahn et al., 2022 0.49 [0.04; 5.49] 5.8%
Random effects model 0.72 [0.14; 3.78] 12.4%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.91
Subgroup = Cohort
Khorsand et al., 2011 0.44 [0.04; 5.11] 5.7%
Khorsand et al., 2012 0.69 [0.06; 7.66] 5.9%
Abdoellakahn et al., 2017 0.16 [0.01; 3.61] 3.6%
Scott et al. ,2018 1.03 [0.02; 53.71] 2.2%
Zemrak et al., 2019 0.57 [0.17; 1.87] 23.9%
Bitonti et al., 2020 1.24 [0.02; 65.03] 2.2%
Dietrich et al., 2020 0.30 [0.01; 6.41] 3.7%
Elsamadisi et al., 2020 1.33 [0.08; 22.78] 4.2%
Gilbert et al., 2020 3.10 [0.12; 79.23] 3.2%
Kim et al., 2020 0.21 [0.01; 4.57] 3.6%
Bizzell et al., 2021 0.20 [0.05; 0.77] 18.7%
Dietrich et al., 2021 13.18 [0.69; 250.35] 3.9%
Dietrich et al-ICH., 2021 0.22 [0.01; 4.69] 3.6%
Riha, 2023 2.21 [0.09; 57.14] 3.2%
Random effects model 0.54 [0.29; 1.00] 87.6%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.64
Random effects model 0.56 [0.31; 1.00] 100.0%
0.01
0.1
1
10
100
Favors Fixed Dose
Favors Variable Dose
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.81
Test for subgroup differences: χ^2_1 = 0.10, df = 1 (p = 0.75)

Additional 4-PCC and Blood Products**

- - **Additional 4-PCC**: Fixed-dose likely requires more additional 4-PCC in both cohort and RCT studies.
- - **FFP Administration**: Minor differences in FFP use between fixed- and variable-dose regimens.

- ICU and Hospital Lengths of Stay
- There is uncertain evidence regarding the effect of a fixed- vs. variable-dose regimen on ICU and hospital length of stays

- **VKA Therapy and Anticoagulation Reversal**
- VKA therapy carries a risk of life-threatening bleeding, necessitating rapid reversal. This meta-analysis compares the fixed-dose and variable-dose regimens for 4-PCC.
- **Key Findings:**
- Fixed-dose regimens use lower 4-PCC doses and result in faster administration.
- The fixed-dose approach may improve clinical hemostasis but is less likely to achieve a strict INR target of less than 1.5.
- The difference in achieving an INR below 2 is uncertain.
- **Conclusion**
- A fixed-dose regimen may be effective for most cases, offering cost and time benefits, but might not be suitable for achieving very low INR targets.

Discussion

Meta-Analysis of Fixed-Dose vs. Variable-Dose 4-PCC Regimens**

- - **Objective**: Compare efficacy and safety of fixed-dose and variable-dose 4-PCC regimens.
- - **Dosing**:
- Fixed-dose uses lower doses, improving cost-effectiveness.
- - **Administration Time**:
- Fixed-dose leads to faster treatment.
- - **Efficacy**:
- Fixed-dose may improve hemostasis but is less likely to achieve strict INR targets.
- - **Safety**:
- Fixed-dose associated with lower mortality and fewer thromboembolic events.
- **- **Conclusion**: Fixed-dose regimens offer better outcomes and safety.**

Fixed-Dose Regimens for VKA Reversal**

- - **Efficacy**: Higher doses (1500–2500 IU) show better outcomes.
- - **Key Studies**:
- - 1000–1500 IU is safe and effective for emergencies.
- - 1500 IU achieved target INR in most cases with no TEEs.
- - **Findings**:
- - 1000–1500 IU: Moderate efficacy, potential higher mortality.
- - 1500–2000 IU: Better efficacy, lower mortality.
- - 2000–2500 IU: Best results, but with low-certainty evidence.
- - **Conclusion**: A dose of at least 2000 IU may be optimal.

VKA Reversal for ICH**

- - **High Mortality**: ICH with VKA use has high mortality rates.
- - **Subgroup Analysis**: Few significant differences between fixed- and variable-dose regimens for ICH patients.
- - **Key Findings**:
- **- Fixed-dose reduces "order-to-needle" time compared to variable-dose.**
- **- Similar rates of achieving goal INR <2 and clinical hemostasis.**
- **- Fixed-dose less effective in achieving INR <1.5 (80% vs. 89%).**
- **- Fixed-dose may reduce thromboembolic events (TEEs).**
- - **Mortality**:
- Evidence on mortality differences is uncertain.

Defining 4-PCC Outcome Endpoints**

- **Unclear INR Goal**:
No definitive INR target for VKA-related hemorrhage.
- **Clinical Hemostasis**:
Fixed-dose better than variable-dose in most cases, except ICH.
- **Safety**:
Fixed-dose shows better safety outcomes.
- **Conclusion**: INR <2 or clinical hemostasis may be sufficient; more studies needed.**

Use of Standardized Initial Fixed Dose**

- **Faster and Effective**:
Fixed-dose 4-PCC works faster and is effective for clinical hemostasis and INR normalization.
- **Optimal Dose**: At least 2000 IU may be ideal.
- **Protocol**: Start with 2000 IU fixed-dose, add variable-dose for specific cases (e.g., ICH, high INR, or heavier patients).**

• Limitations

- **Few RCTs**: Most studies were retrospective.
- **Outcome Variability**: Different primary outcomes and definitions.
- **Limited Data**: Some outcomes had few reports, limiting subgroup analysis.
- **Heterogeneity**: Moderate to high variation in results.
- **GRADE Evaluation**: Mixed quality of evidence.

• Conclusions

- This meta-analysis suggests that a fixed-dose regimen of 4-PCC may be more cost-effective, faster to administer, and offer better efficacy and safety than a variable-dose regimen. Although the quality of evidence varies, these findings pave the way for future research to refine the optimal 4-PCC dosing strategy for emergency VKA reversal.