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REVIEW ARTICLE

Efficacy and Safety of the Fixed-Dose Versus Variable-Dose of 4-PCC for Vitamin K Antagonist Reversal: A Comprehensive Systematic Review and Meta-Analysis

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Abstract

Background The optimal dosing strategy of four-factor prothrombin complex concentrate (4F-PCC) for vitamin K antagonists (VKAs) reversal is unknown.

Methods We conducted systematic search on the PubMed, SCOPUS, and Embase databases from inception to December 2020 for clinical studies that compared the fixed-dose versus variable-dose of 4-PCC for VKAs reversal with at least one reported clinical outcome. The treatment effects were expressed as relative ratios (RR) with 95% confidence intervals (CIs) and pooled by a random-effects model.

Results Ten studies, including 988 patients, were included. Fixed-dose 4-PCC was associated with lower rate of mortality (RR= 0.65, 95% CI 0.47 to 0.9, p= 0.009), comparable rate of thromboembolic event (TEE) (RR= 1.10, 95%CI 0.44 to 2.80, p= 0.826), and lower goal INR reached (RR= 0.87, 95%CI 0.78 to 0.96, p= 0.007). Less 4-PCC cumulative dose, shorter duration of order-to-needle time, similar hospital length of stay, the comparable time required for INR reversal, higher post-4-PCC INR, and a higher need for additional dose were observed in fixed-dose.

Conclusions The use of a fixed-dose of 4-PCC may be considered an effective and safe dosing strategy for VKAs reversal in various clinical situations. However, further well-designed, controlled studies should be conducted focusing on clinical outcomes to determine the optimal dose of 4-PCC for VKAs reversal.

Keywords Reversal · Warfarin · Vitamin K antagonist · Prothrombin complex concentrates · Fixed-dose · Variable-dose

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Introduction

Vitamin K antagonists (VKAs) are widely prescribed effective anticoagulants for the prevention and treatment of various thromboembolic events [1] and mainly act via inhibition of the vitamin K-dependent clotting factors synthesis [2]. Although direct oral anticoagulants have been introduced as alternatives, there are still some conditions in that VKAs remained the agent of choice [3], but the VKAs-related bleeding complications should not be neglected [4], as the rate of warfarin-induced major bleeding was reported to be 10 to 16% [5]. The risk of warfarin-associated intracerebral hemorrhage (ICH) may reach 1 to 2% per year, and this risk increases up to 4.2% in older patients [6, 7] The risk of major bleeding in the patient receiving warfarin who undergo urgent surgery was also as high as 21.6% [8]. Consequently, if indicated, these patients require prompt and effective reversal of VKA associated coagulopathy [9]. Vitamin K is used mainly in combination with other reversal agents, such as prothrombin complex concentrates (PCC) [9, 10] and fresh frozen

plasma (FFP) [11] for VKAs reversal. Generally, 4-factor PCC (4-PCC) is preferred over FFP [12] and 3-factor PCC (3-PCC) [13] for urgent reversal of VKA due to better safety and efficacy.

4-PCC contains the human coagulation factors, including factors II, VII, IX, and X [13]. Although the safety and efficacy of 4-PCC have been well established for VKA reversal [12], optimal dosing strategy remains uncertain. Therefore, several studies have been conducted to determine the optimal dose of 4-PCC for VKAs reversal [14]. The recommended dosing regimen of package insert is a variable-dose regimen based on body weight and pre-treatment INR ranging from 25 to 50 units of factor IX per kg [15]. Based on this dosing, the efficacy of 4-PCC is not optimal, and adequate hemostasis is reported only in up to 71% of patients [16].

The most recent 2020 American College of Cardiology (ACC) Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants recommended reversal of VKAs with 4-PCC using either package insert recommendations or low, fixed-dose strategy [17]. Several advantages of fixed-dose strategy have been proposed, including faster 4-PCC administration [18], no need for dose calculation [19], hypothetically decreased risk of thromboembolic event (TEE) [14, 20], and lower cost [21]. Conversely, the variable-dose may be associated with a higher rate of goal INR reached, especially in the patient with a high baseline INR [18]; however, the TEE rate may be increased in concordance with the PCC dose [22]. Therefore, several studies have evaluated the clinical outcomes of the fixed-dose versus variable-dose strategy of 4-PCC; nevertheless, the results were inconsistent [14]. To address these dicrapancies, we did a systematic review and meta-analysis of clinical studies to investigate the efficacy and safety of fixed-dose 4-PCCs compared to the variable, weight/INR-based dosing strategy for VKAs reversal in patients who present with major bleeding or a need for urgent surgery or invasive procedure.

Methods

Search Strategy

This systematic review and meta-analysis were performed in concordance with the PRISMA [Preferred Reporting Items for Systematic Review and Meta-analysis] guidelines [23]. A comprehensive systematic search was carried out in PubMed, SCOPUS, Embase, and Gray literature by two independent reviewers (KM and SY) from inception until December 2020 without any time or language restrictions by using the following keywords: "warfarin OR vitamin K antagonists OR VKA OR VKAs OR coumarin OR coumadin OR phenprocoumon OR acenocoumarol" AND "4-factor prothrombin complex concentrate OR prothrombin complex concentrate OR 4-PCC OR PCC." Relevant studies were handsearched within their references.

Study Selection and Inclusion Criteria

Two reviewers (KM and SY) independently performed study selection using prespecified inclusion and exclusion criteria. Studies were included if they met the following criteria: (1) randomized controlled trials (RCTs) and prospective or retrospective observational studies, (2) publications that were carried out on adult patients who presented with VKAs-related major bleeding, or those who required urgent VKAs reversal for surgery or an invasive procedure, (3) studies which compared fixed-dose (based on indication; regardless of the patient's weight and presenting INR) and variable-dose of 4-PCC (package insert-based recommendation; INR/weight-based dosing) (4) those with at least one reported relevant efficacy and safety outcome. Any disagreements regarding the inclusion of each study were resolved by a third researcher (AH). Reviews, comments, abstracts, letters, conference papers, case reports, duplicates, and unpublished articles were excluded from consideration in this study.

Data Extraction

Two researchers (SY, MA) extracted the data using a standardized data record form, and the whole team resolved any disagreements in this step. The following information was retrieved: name of the first author, publication year, study location, subjects' demographic data (age, sex, weight, etc.), study design, number of participants, VKAs indications, site of bleeding, the administered dose of 4-PCC, reversal-related efficacy and safety outcomes (number or mean ± SD of measured outcomes).

Outcomes

The various efficacy and safety outcomes were extracted and evaluated as outcome measures. The primary outcomes including the mortality rate during a follow-up period of each study, rate of 4-PCC related arterial and venous thrombotic events, and the number of goal INR reached that defined as patients who reached goal INR as specified by each study. The secondary outcomes including the number of patients required administration of the supplemental dose of 4-PCC in addition to the initial dose, the total and weight-based administered dose of the 4-PCC, the mean time required for INR reversal, post 4-PCC administration mean INR (after 15–30 min or other close times as defined by the included studies), order-to-needle time (the time between the ordering of 4-PCC to start of infusion), and the total length of hospital stay.

Assessment of Study Quality

The methodological quality of the included studies was evaluated independently by two reviewers, and any

disagreements were resolved by consensus. The Newcastle-Ottawa Scales (NOS) [24] and Jadad scale [25] were used for quality assessment of cohort and RCTs studies, respectively. The NOS assesses the quality of nonrandomized/observational cohort studies based on eight items that are categorized into three groups: (a) the selection of the study groups (0–4 points), (b) the comparability of the groups (0–2 points), and (c) the and study outcomes (0–3 points). The NOS scores of 7 or higher were considered high-quality studies, and scores of 5 to 6 denoted moderate qualities [26]. In the Jadad scale, papers were evaluated based on randomization, blinding, and inclusion of participants. Based on this scale, studies with a score of 3 or more were considered high-quality trials [25].

Data Synthesis and Statistical Analysis

To evaluate the pooled effects of various dosing strategies (fixed-dose vs. variable-dose of 4-PCCs) on categorical and continuous outcomes, a meta-analysis was carried out using the relative risk (RR), weighted mean differences (WMD), and their 95% confidence intervals (CI), respectively, by random-effects model [27, 28]. Heterogeneity across included studies was determined using Cochrane's Q test and the I^2 statistic. [29]. I^2 above 50% and Cochrane's Q test with $p < 0.1$ was considered the existence of significant heterogeneity. In some instance, we performed a priori subgroup analysis according to indication for VKAs reversal (all indication together, non-ICH patients and only ICH patients), mean baseline INR of the included patient (INR ≥ 4 vs. INR < 4), and weight of the patient (weight ≥ 80 kg vs. weight

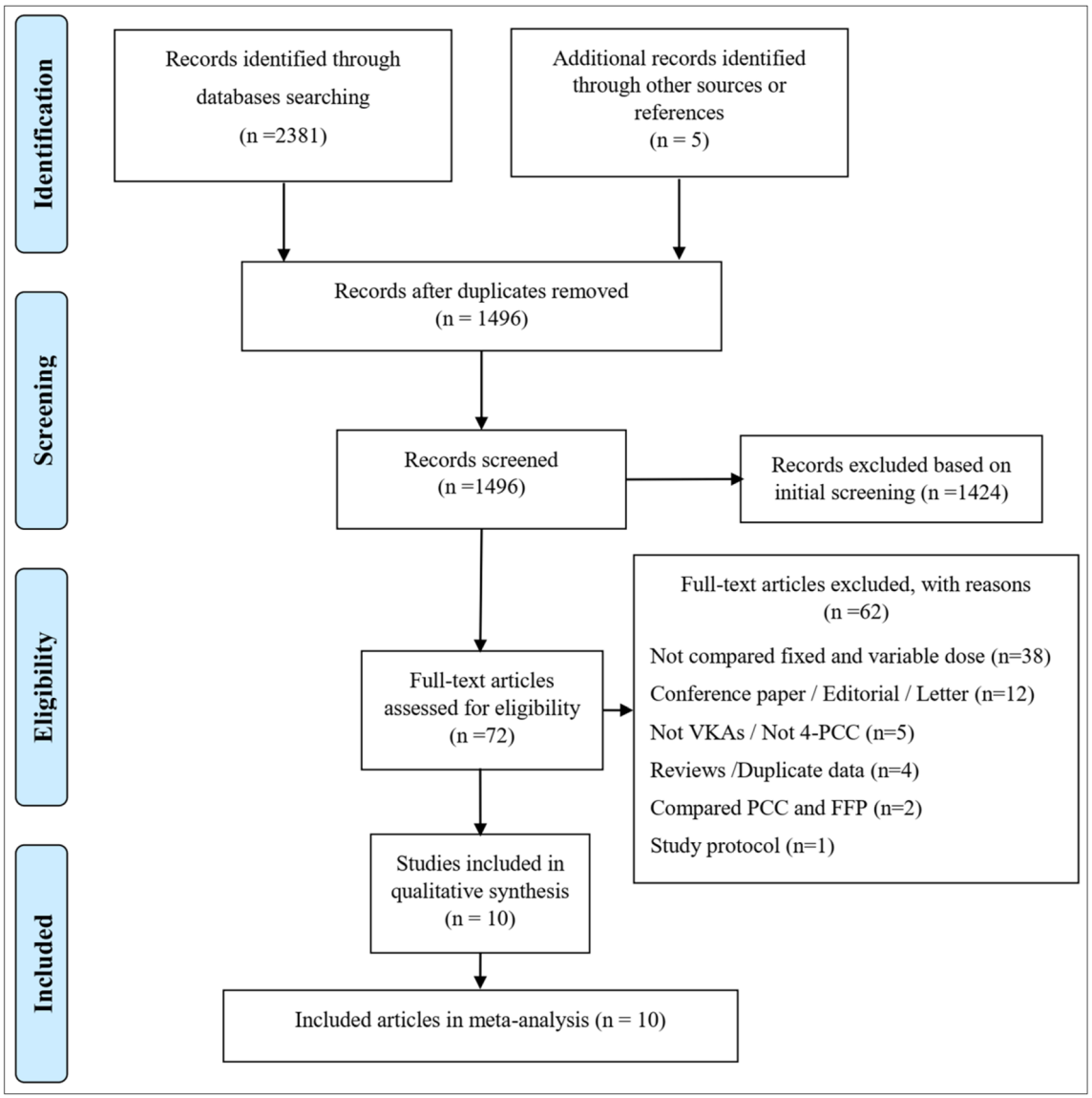

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses diagram indicating method for selection of papers included in the present study

Table 1 Characteristics of included studies

Author/year	Country/design	Study population (*n*)		Age (mean ± SD)		Male; *n* (%)		Reversal indication; *n* (%)		4-PCC dosing strategy		NOS/ score
		Fixed-dose	Variable-dose	Fixed-dose	Variable-dose	Fixed-dose	Variable-dose	Fixed-dose	Variable-dose	Fixed-dose	Variable-dose	
Bitonti et al 2020 [33]	USA/retrospective cohort	24	30	77	74	11 (45)	19 (63)	ECH 14 (58), ICH 9 (38), ES 1 (4)	ECH 10 (33), ICH 19 (63), ES 1 (4)	1500 IU (2000 IU if Wt >100 kg or INR >7.5)	25 IU/kg if INR 1.5–3.9, 35 IU/kg if INR 4-6, 50 IU/kg if INR >6	8
Gilbert et al 2020 [34]	USA/retrospective cohort	30	30	78 ±19	79 ± 21	15 (50)	16 (53)	ECH 9 (30), ICH 15 (50), ES 6 (20)	ECH 8 (26), ICH 11 (37), ES 11 (37)	1000 IU for non-ICH and 1500 for ICH (additional 500 IU if Wt>100 or INR >10)	25 IU/kg if INR 2–<4, 35 IU/kg if INR 4–6, 50 IU/kg if INR >6	8
Khorsand et al 2011 [37]	Netherlands/ prospective cohort	35	32	76 ± 16.25	74 ± 12.5	16 (45)	18 (56)	ECH 18 (51), ES 17 (49)	ECH 19 (59), ES 13 (41)	1040 IU for non-ICH patients and 520 IU prior to invasive procedure	Manufacturer's algorithm based on the initial and the target INR and bodyweight	8
Khorsand et al 2012 [18]	Netherlands/ prospective cohort	101	139	77 ± 14.5	79 ± 18.75	50 (49)	71 (51)	ECH 101 (100)	ECH 139 (100)	1040 IU for non-ICH patients only	Manufacturer's algorithm based on the initial and the target INR and bodyweight	7
Abdoellakhan et al 2017 [24]	Netherlands/ retrospective cohort	28	25	77 ± 10.5	77 ± 10.25	14 (50)	13 (52)	ICH 28 (100)	ICH 25 (100)	1000 IU (additional 500 IU if target INR of <1.5 was not achieved)	Manufacturer's algorithm based on the initial and the target INR and bodyweight	9
Dietrich et al (a) 2020 [23]	USA/prospective cohort	53	72	77 ± 10.37	76 ± 10	28 (52)	41 (56)	ECH 23 (43), ICH 21 (40), ES 9 (17)	ECH 17 (23), ICH 28 (39), ES 27 (38)	1500 IU (2000 IU if Wt>100 or INR >7.5)	25 IU/kg if INR 2–<4, 35 IU/kg if INR 4–6, 50 IU/kg if INR >6	8
Scott et al 2018 [35]	USA/retrospective cohort	30	31	78 ± 11.9	81 ± 11	19 (63)	18 (58)	ICH 30 (100)	ICH 31 (100)	1000 IU fixed in ICH patients	Package labeled dose of 25, 35, and 50 IU/kg as indicated by pretreatment INR	9
van Aart et al 2006 [25]	Netherlands/open, prospective RCT	47	46	75 ± 8.7	71.1 ± 11.8	21 (44)	29 (63)	ECH 13 (28), ICH 2 (4), ES 32 (68)	ECH 14 (30), ICH 8 (18), ES 24 (52)	500 IU fixed	Manufacturer's algorithm based on the initial and the target INR and bodyweight	3*
		75	116		72.1 ± 17.5	37 (49)	59 (50)					7

Table 1 (continued)

Author/year	Country/design	Study population (*n*)		Age (mean ± SD)		Male; *n* (%)		Reversal indication; *n* (%)		4-PCC dosing strategy		NOS/ score
		Fixed-dose	Variable-dose	Fixed-dose	Variable-dose	Fixed-dose	Variable-dose	Fixed-dose	Variable-dose	Fixed-dose	Variable-dose	
Dietrich et al (b) 2020 [21]	USA/retrospective cohort			67.3 ± 17.3				ECH 43 (57), ICH 8 (11), ES 24 (32)	ECH 50 (43), ICH 37 (32), ES 29 (25)	1500 IU (2000 IU if Wt>100 or INR >7.5)	Package labeled dose of 25, 35, and 50 IU/kg as indicated by pretreatment INR	
Elsamadisi et al 2020 [36]	USA/retrospective cohort	19	25	65 ± 8.9	73 ± 7.41	11 (57)	19 (76)	ECH 8 (42), ICH 2 (11), ES 9 (47)	ECH 6 (24), ICH 12 (48), ES 7 (28)	wt > 100 only. 2000 IU in Wt > 100 kg (additional 500–1000 IU if need)	Weight-based dosing of 4F-PCC based on labeling	8

ECH extra-cranial hemorrhage, *ICH* intracerebral hemorrhage, *ES* emergent surgery, *NOS* Newcastle–Ottawa scale, *Wt* weight, *INR* international normalized ratio. *The Jadad score

<80 kg). The potential non-linear effects for the dose of 4-PCC were examined using fractional polynomial modeling. Egger's regression test and visual examination of the funnel plot were applied to measure publication bias. All statistical analyses were performed using STATA 15.0 statistical software (Stata Corporation, College Station, TX, USA).

Results

Study Selection

The flowchart of literature the search and selection process of studies is presented in Fig. 1. From the literature search, we identified 2386 articles. After removing duplicates, 1496 articles were screened by title and abstract. Overall, 72 articles were found potentially relevant for detailed full-text evaluation. Finally, the literature search yielded ten [18, 21, 30–37] eligible articles for the current meta-analysis

Study Characteristics

The characteristics of the included studies are summarized in Table 1. Six and four studies were conducted in the USA [21, 30–34] and the Netherlands [18, 35–37], respectively. Studies were published between 2006 and 2020. Among these, nine studies were prospective or retrospective cohort studies [18, 21, 30–36], and one of them was RCT [37]. All of the studies were performed to compare fixed-dose versus variable-dose of 4-PCC for reversal of VKAs in different clinical settings, including intracranial hemorrhage (ICH), extra-cranial hemorrhage (ECH), and emergent surgical procedures. The Cofact and Kcentra 4-PCC products were used in four [18, 35–37] and five [21, 30–32, 34] studies, respectively. One study did not mention the brand name of the administered 4-PCC [33]. Two studies included only ICH patients [33, 36], while ICH patients were excluded from two studies [18, 35]. The mean ± SD age of the participants was 75.2 ± 3.9 years. Data of 988 patients (442 patients in the fixed-dose and 546 patients in the variable-dose group) were pooled for this analysis. The results of the quality assessment of eligible cohort studies are also presented in Table 1. The cohort studies demonstrated high quality with NOS scores ranging from 7 to 9. The Jadad score of one included RCT was equal to 3 points, considered high quality.

Results of the Meta-Analysis

Primary Outcome: Mortality, TEE, and Goal INR Reached

Mortality was reported in nine studies. As shown in Fig. 2, the risk of mortality was significantly lower in the fixed-dose

Table 2 Overall and subgroup analysis of 4-PCC dosing strategy (fixed-dose versus variable-dose) on categorical outcomes

Outcomes and subgroups				No. of studies	RR (95% CI)	*p* value	p-heterogeneity/I^2 (%)
Mortality	Overall analysis			9	0.65 (0.47, 0.9)	0.009	0.802 /0.0
	Sub.g analysis (on 895 patients)	Based on weight	Wt ≥ 80 kg	4	0.75 (0.42, 1.33)	0.319	0.761 /0.0
			Wt < 80 kg	4	0.61 (0.41, 0.90)	0.013	0.388 /0.0
		Baseline INR	Baseline INR ≥ 4	3	0.55 (0.33, 0.99)	0.026	0.921 /0.0
			Baseline INR < 4	6	0.72 (0.48, 1.08)	0.114	0.578 /0.0
		Based on 4-PCC indication	4-PCC indication: all indications	5	0.56 (0.35, 0.90)	0.019	0.999 /0.0
			4-PCC indication: ICH cases	2	1.22 (0.60, 2.46)	0.580	0.483 /0.0
			4-PCC indication: Non-ICH cases	2	0.55 (0.32, 0.95)	0.032	0.707 /0.0
TEE	Overall analysis			10	1.10 (0.44, 2.80)	0.826	0.881 /0.0
	Sub.g analysis (on 988 patients)	Based on weight	Wt ≥ 80 kg	4	1.56 (0.30, 8.09)	0.972	0.972 /0.0
			Wt < 80 kg	5	1.17 (0.32, 4.22)	0.481	0.481 /0.0
		Baseline INR	Baseline INR ≥ 4	4	0.70 (0.18, 2.69)	0.966	0.9660/0.0
			Baseline INR < 4	6	1.68 (0.46, 6.13)	0.650	0.650/0.0
		Based on 4-PCC indication	4-PCC indication: all indications	6	1.64 (0.48, 5.58)	0.649	0.649/0.0
			4-PCC indication: ICH cases	2	0.96 (0.06, 15.03)	0.960	0.960 /0.0
			4-PCC indication: Non-ICH cases	2	0.56 (0.10, 2.99)	0.811	0.811 /0.0
Goal INR reached	Overall analysis			10	0.87 (0.78, 0.96)	0.007	0.023/53.2
	Sub.g analysis (on 988 patients)	Based on weight	Wt ≥ 80 kg	4	0.95 (0.85, 1.07)	0.385	0.563 /0.0
			Wt < 80 kg	5	0.79 (0.66, 0.96)	0.016	0.003/75.2
		Baseline INR	Baseline INR ≥ 4	4	0.78 (0.61, 1.02)	0.006	0.004/77.7
			Baseline INR < 4	6	0.91 (0.82, 1.00)	0.055	0. 33/13.2
		Based on 4-PCC indication	4-PCC indication: all indications	6	0.85 (0.72, 1.01)	0.064	0. 012/65.9
			4-PCC indication: ICH cases	2	0.80 (0.78, 0.96)	0.076	0. 199/39.4
			4-PCC indication: Non-ICH cases	2	0.94 (0.86, 1.03)	0.196	0.567 /0.0
Additional 4-PCC requirement	Overall analysis			10	2.38 (1.33, 4.24)	0.003	0.478 /0.0
	Sub.g analysis (on 863 patients)	Based on weight	Wt ≥ 80 kg	4	1.06 (0.39, 2.92)	0.910	0.999 /0.0
			Wt < 80 kg	5	3.47 (1.50, 8.04)	0.004	0.276 /22.4
		Baseline INR	Baseline INR ≥ 4	4	2.76 (0.93, 8.22)	0.067	0.263 /24.7
			Baseline INR < 4	6	1.90 (0.86, 4.19)	0.112	0.574/0.0
		Based on 4-PCC indication	4-PCC indication: all indications	6	4.59 (1.82, 11.60)	0.001	0.773/0.0
			4-PCC indication: ICH cases	2	1.89 (0.50, 7.10)	0.345	0.145/52.8
			4-PCC indication: Non-ICH cases	2	1.23 (0.32, 4.68)	0.762	0.582/0.0
Vitamin K administered	Overall analysis			6	0.99 (0.93, 1.06)	0.849	0.301/17.5

RR relative risks, *CI* confidence interval, *Sub.g* sub-group, *ICH* intracerebral hemorrhage, *Wt* weight

group (50 of 395 [12.6%]) than the variable-dose group (98 of 500, [19.6%]; RR= 0.65, 95% CI, 0.47 to 0.9; p= 0.009). Heterogeneity among the studies was negligible (p-heterogeneity= 0.802, I^2= 0.0). Subgroup analysis based on indication of reversal and site of bleeding showed the lower mortality rate in fixed-dose compared to variable-dose in all reversal indications (RR= 0.56, 95% CI 0.35 to 0.9, p= 0.019) and non-ICH patients (RR= 0.55, 95% CI 0.32 to 0.95, p= 0.032); however, in patients with ICH, the difference in mortality rate was not significant (RR= 1.22, 95% CI 0.6 to 2.46, p= 0.580). In subgroup analysis of data based on weight of included population, lower rate of mortality was seen in both groups weight <80 kg (RR= 0.66, 95% CI 0.41 to 0.9, p= 0.013) and weight ≥ 80 kg (RR= 0.75, 95% CI 0.42 to 1.33, p= 0.319), although this was not significant in later group. The mortality rate was significantly lower in the fixed-dose versus the variable-dose strategy among patients with baseline INR > 4 (RR= 0.55, 95% CI 0.33 to 0.99, p= 0.026), but this difference was not significant among patient with baseline INR < 4 (RR= 0.72, 95% CI 0.48 to 1.08, p= 0.114) (Table 2).

TEE rate was reported in 10 studies. Similar TEE rate was seen between the two dosing strategies (fixed-dose 9 of 442 patients [2.03%] vs. variable-dose 8 of 546 patients [1.47%]; RR= 1.10, 95% CI 0.44, 2.80, p= 0.826) in overall analysis, as shown in Fig. 3. No heterogeneity was observed among studies which reported TEE rate (p-heterogeneity= 0.881, I^2= 0.0%). A similar rate of thromboembolic events was also seen in fixed-dose compared to variable-dose in subgroups analysis based on VKA reversal indication, weight, and baseline INR (Table 2).

The number of goal INR reached, or hemostasis reversal, was assessed as an efficacy outcome in all ten included studies. As shown in Fig. 4, the rate of goal INR reached was significantly lower in the fixed-dose group (311 of 442 [70.36%]) than the variable-dose group (444 of 546, [81.32%]; RR= 0.87, 95% CI; 0.78, 0.96, p= 0.007) with substantial heterogeneity (p-heterogeneity= 0.023, I^2= 53.2). In subgroup analysis based on 4-PCC indication, the number of goal INR reached was not statistically significant between the two groups (Table 2). Similar goal INR reached was observed in subgroup analysis of patient with weight ≥ 80 kg (RR= 0.95, 95% CI 0.85, 1.07, p= 0.385), whereas among patient with weight < 80, lower INR reversal was observed in fixed-dose (RR= 0.79, 95% CI 0.66 to 0.96, p= 0.016). The goal INR reached was significantly lower in fixed-dose than variable-dose in patients with baseline INR ≥ 4 (RR= 0.78, 95% CI 0.61 to 1.02, p= 0.006), while this result was not significant for patients with baseline INR < 4 (RR= 0.91, 95% CI 0.82 to 1.00, p= 0.055) (Table 2).

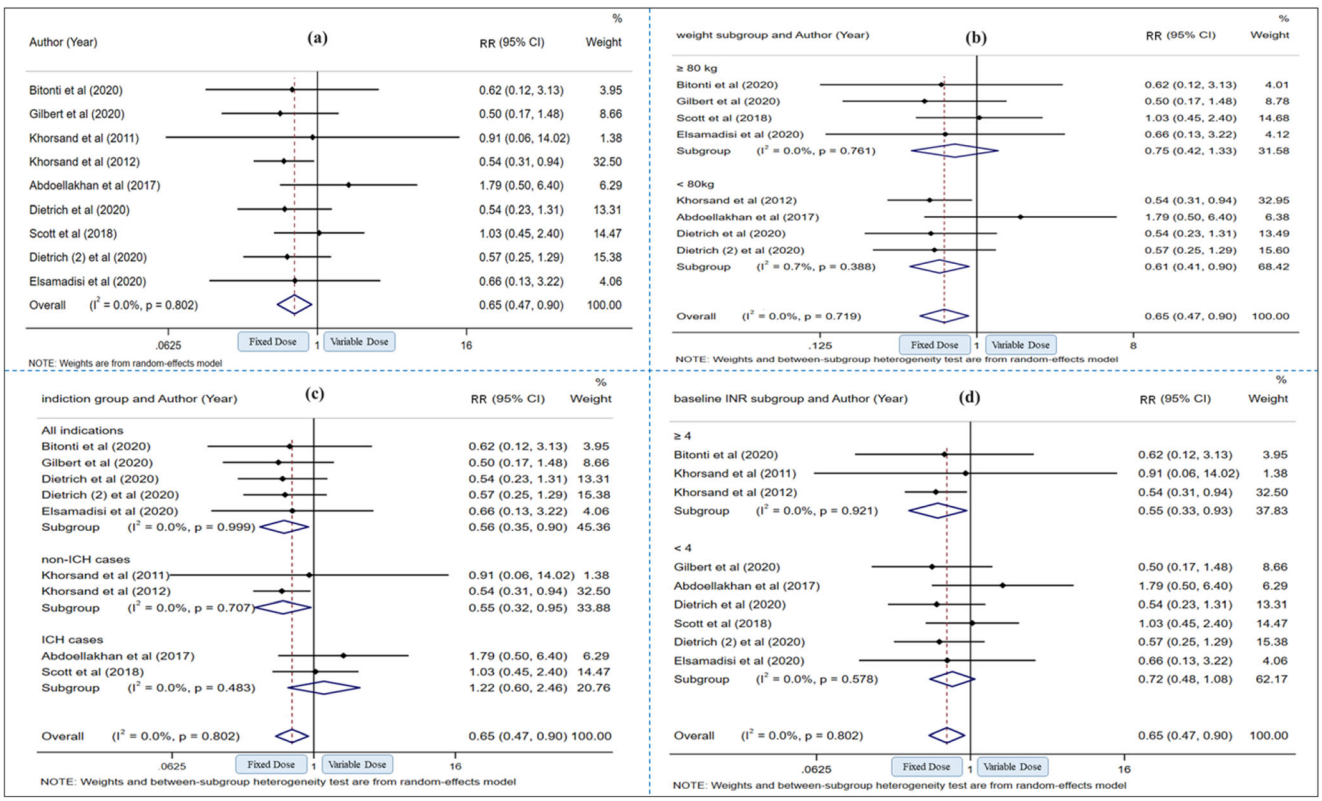

Fig. 2 Forest plot of the mortality in patients receiving fixed-dose 4-PCC comparing with variable-dose strategy, **a** overall analysis, **b** sub-group analysis based on weight, **c** sub-group analysis based on reversal indication, **d** sub-group analysis based on pre-PCC administration INR (total sample size; fixed-dose = 395, variable-dose = 500). ICH: intracerebral hemorrhage, RR; relative risk, CI: confidence intervals

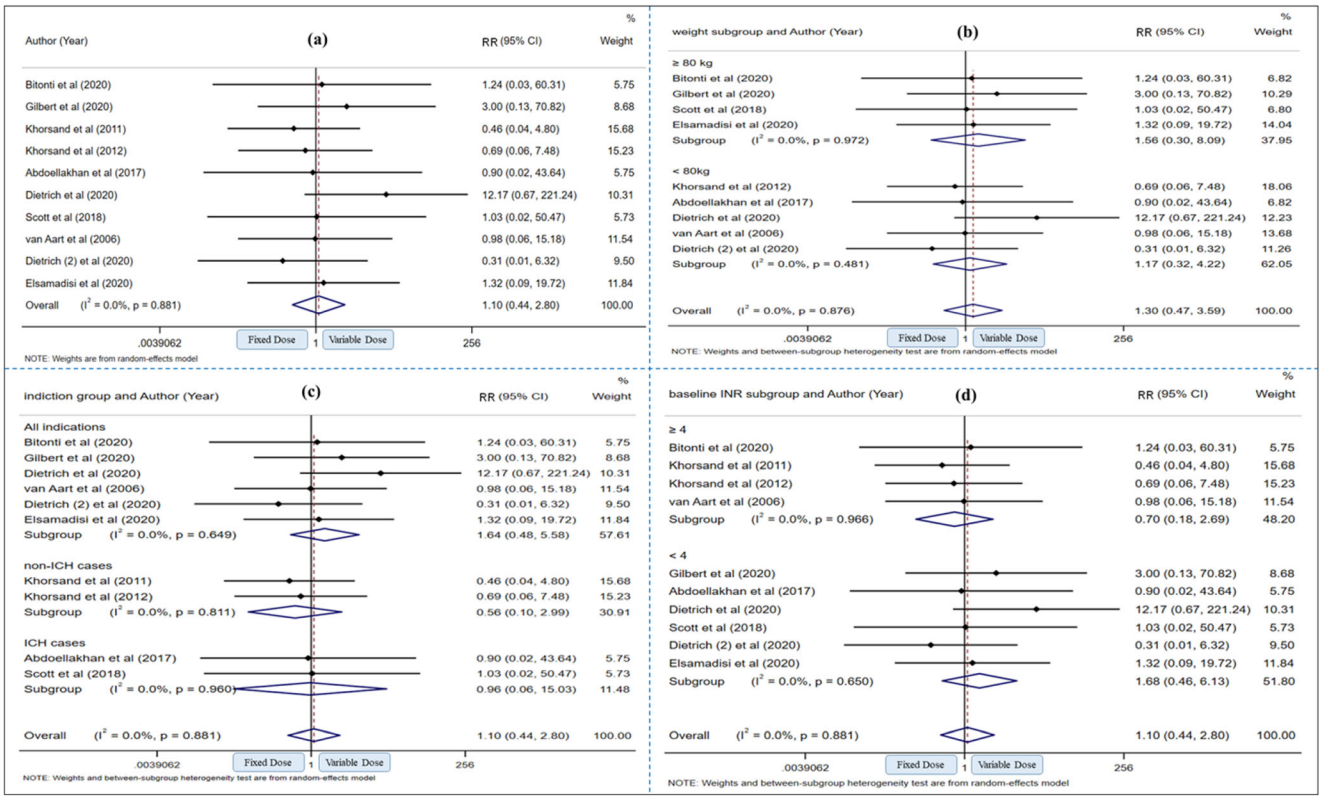

Fig. 3 Forest plot of the thromboembolic events in patients receiving fixed-dose 4-PCC comparing with variable-dose strategy, **a** overall analysis, **b** sub-group analysis based on weight, **c** sub-group analysis based on reversal indication, **d** sub-group analysis based on pre-PCC administration INR (total sample size; fixed-dose = 442, variable-dose = 546). ICH: intracerebral hemorrhage, RR; relative risk, CI: confidence intervals

Secondary Outcomes

Higher number of patients required administration of additional dose of 4-PCC in fixed-dose (41 of 389 [10.5%]) than variable-dose group (15 of 474, [3.2%]; RR= 2.38, 95% CI 1.33 to 4.24, p= 0.003) in nine studies (Supplemental Fig. 1). Non-significant heterogeneity was seen among studies (p-heterogeneity = 0.478, I^2= 0.0%). In subgroup analysis based on reversal indication, requirement for additional doses of 4-PCC was not statically significant in ICH (p= 0.345) and non-ICH patients (p= 0.762). The number of additional 4-PCC dose requirement was similar in subgroup patient with weight ≥ 80 kg (p= 0.910), baseline INR ≥ 4 (p= 0.067), and baseline INR < 4 (p= 0.112) as shown in Table 2. The number of patient who received concurrent vitamin K did not differ between two groups (RR= 0.99, 95% CI 0.93 to 1.06, p= 0.849).

The overall results of all ten studies revealed a significantly lower total administered cumulative dose of 4-PCC in fixed-dose (mean 1360.4 unit) in comparison to variable-dose (mean 2028.9 unit) (WMD= −629.45 unit, 95% CI −790.31 to −468.59 unit, p <0.001) (Supplemental Fig. 2). Considerable heterogeneity was also observed between studies (p-heterogeneity <0.001, I^2= 82.9%). A similar finding was observed in all subgroup analyses (Table 3). Likewise, in overall and subgroup analysis of unit per kilogram of administered 4-PCC dose, total administered unit/kg 4-PCC dose (mean 16.39 unit/kg in fixed and mean 24.7 unit/kg in variable-dose) was significantly lower in fixed-dose (WMD = −7.83 unit/kg, 95% CI −9.71 to −5.96 unit/kg, p <0.001) (p-heterogeneity <0.001, I^2=78.8%) (Supplemental Fig. 3), as shown in Table 3.

Combined results indicated that there was no significant difference in the required time for goal INR achievement between fixed-dose (mean 190.67 min) and variable-dose (mean 205.87 min) of 4-PCC (WMD = −23.22 min, 95% CI −92.19 to 45.75 min, p= 0.509) (Supplemental Fig. 4) in the analysis of three studies. There was substantial heterogeneity among pooled studies (p-heterogeneity= 0.03, I^2= 70.6%). The post 4-PCC administration INR was higher in fixed-dose (mean 1.48) group compared to variable-dose (mean 1.34) among all 10 studies (WMD = 0.15, 95% CI 0.04 to 0.45, p= 0.005) with considerable heterogeneity (p-heterogeneity <0.001, I^2 = 79.0%) (Supplemental Fig. 5). On the other hand, the mean post-PCC INR was not significantly different in the subgroup of patients with baseline INR ≥ 4 (p = 0.069) and weight ≥ 80 (p = 0.068) (Table 3).

The order to needle time was significantly lower in fixed-dose (mean 68 min) compared to variable-dose (mean 87.75 min; WMD= −22.50 min, 95% CI −31.88 to −13.12 min, p <0.001) with negligible heterogeneity (p-heterogeneity= 0.517, I^2= 0.0%) (Supplemental Fig. 6) (Table 3).

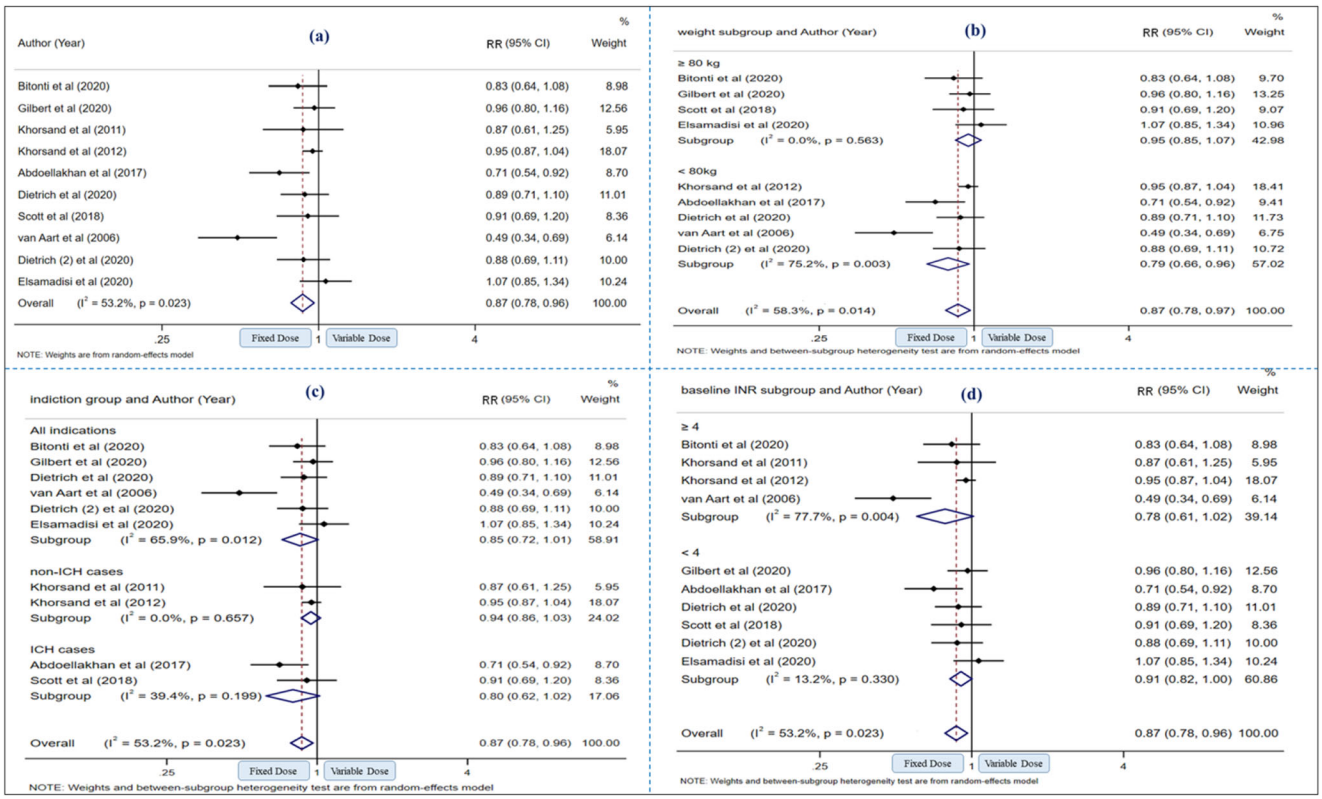

Fig. 4 Forest plot of the number of goal INR reached in patients receiving fixed-dose 4-PCC comparing with variable-dose strategy, **a** overall analysis, **b** sub-group analysis based on weight, **c** sub-group analysis based on reversal indication, **d** sub-group analysis based on pre-PCC administration INR (total sample size; fixed-dose = 442, variable-dose = 546). ICH: intracerebral hemorrhage, RR; relative risk, CI: confidence intervals

The duration of hospital stay between fixed-dose (mean 8.15 days) and variable-dose group (mean 6.71 days) was not significantly different in the analysis of four studies (WMD= 1.64 days, 95% CI −0.38, 3.66 days, p= 0.112) (Supplemental Fig. 7). No heterogeneity was seen (p-heterogeneity= 0.713, I^2=0.0%) (Table 3).

Non-linear Dose-Response Between the Dose of 4-PCC and Primary Outcomes

The non-linear dose-response relationship analysis between 4-PCC administered dose and primary outcomes was conducted, and no specific association was found between 4-PCC administered dose and rate of mortality, rate of a thromboembolic event, and number of goal INR achieved (Fig. 5)

Publication Bias

In this study, we used Egger's weighted regression test and visual examination of the funnel plot to measure publication bias. The Egger's regression test was not significant for measured outcomes, including mortality (p= 0.332), thromboembolic event (p= 0.557), number of goal INR achieved (p= 0.097), number of need for additional 4-PCC dose (p= 0.719), total 4-PCC administered dose (p= 0.066 for total unit dose and p= 0.068 for unit/kg dose), required time for INR reversal (p= 0.516), post 4-PCC administration mean INR (p= 0.095), and the mean door-to-needle time (p= 0.364). Visual inspection of funnel plot illustrated no evidence of publication bias among primary outcomes (Fig. 5).

Discussion

Main Findings

The overarching aim of this systematic review and meta-analysis of eligible studies was to compare the fixed-dose versus variable-dose of 4-PCC in VKAs reversal. We found ten studies in which 988 patients received 4-PCC in two dosing strategies (fixed-dose and variable-dose based on the package insert and INR/weight of the patients) for reversal of VKAs in cases of major hemorrhage or urgent surgery. To the best of our knowledge, this is the first meta-analysis to compare the efficacy and safety outcomes of fixed-dose versus variable-dose strategy of 4-PCC for VKAs reversal.

The lower mortality rate was observed in fixed-dose 4-PCC compared to variable-dose strategy in our meta-analysis. A similar result was noticed in some subgroup analyses, including the patient with baseline INR ≥ 4. The comparable

Table 3 Overall and subgroup analysis of 4-PCC dosing strategy (fixed-dose versus variable-dose) on continuous outcomes

Outcomes and subgroups				No. of studies	WMD (95% CI)	*p* value	p-heterogeneity/I^2 (%)
Administered cumulative 4-PCC dose (unit)	Overall analysis			10	−629.45 IU (−790.31, −468.59)	<0.001	<0.001 /82.9
	Sub.g analysis (on 988 patients)	Based on weight	Wt ≥ 80 kg	4	−770.4 IU (−1273.89, −266.90)	0.003	<0.001 /91.3
			Wt < 80 kg	5	−576.86 IU (−732.38, −421.34)	<0.001	0.001 /77.9
		Baseline INR	Baseline INR ≥ 4	4	−704.07 IU (−939.45, −468.70)	<0.001	0.013 /72.2
			Baseline INR < 4	6	−587.72 IU (−805.96, −369.48)	<0.001	<0.001 /85.3
		Based on 4-PCC indication	4-PCC indication: all indications	6	−595.15 IU (−821.02, −369.28)	<0.001	<0.001 /87.1
			4-PCC indication: ICH cases	2	−879.45 IU (−1191.29, −567.61)	<0.001	0.148 /52.1
			4-PCC indication: Non-ICH cases	2	−520.00 IU (−640.63, −399.37)	<0.001	1.000 /0.0
Administered cumulative 4-PCC dose (unit/kg)	Overall analysis			9	−7.83 IU/kg (−9.71, −5.96)	<0.001	<0.001 /78.8
	Sub.g analysis (on 921 patients)	Based on weight	Wt ≥ 80 kg	4	−8.67 IU/kg (−12.73, −4.60)	<0.001	0.005 /76.8
			Wt < 80 kg	5	−7.46 IU/kg (−9.74, −5.17)	<0.001	<0.001 /83.0
		Baseline INR	Baseline INR ≥ 4	3	−9.12 IU/kg (−12.13, −6.11)	<0.001	0.034 /70.4
			Baseline INR < 4	6	−7.06 IU/kg (−9.24, −4.89)	<0.001	0.001 /75.4
		Based on 4-PCC indication	4-PCC indication: all indications	6	−7.06 IU/kg (−9.29, −4.84)	<0.001	<0.001 /78.2
			4-PCC indication: ICH cases	2	−10.70 IU/kg (−14.96, −6.45)	<0.001	0.120 /58.6
			4-PCC indication: Non-ICH cases	1	−7.49 IU/kg (−9.32, −5.66)	<0.001	NA
Mean post 4-PCC INR	Overall analysis			10	0.15 (0.04, 0.25)	0.005	<0.001 /79.0
	Sub.g analysis (on 921 patients)	Based on weight	Wt ≥ 80 kg	4	0.14 (−0.01, 0.29)	0.068	0.143 /44.7
			Wt < 80 kg	5	0.15 (0.01, 0.29)	0.040	<0.001 /88.0
		Baseline INR	Baseline INR ≥ 4	4	0.21 (−0.02, 0.44)	0.069	<0.001 /79.0
			Baseline INR < 4	6	0.10 (0.01, 0.19)	0.037	0.143 /44.7
		Based on 4-PCC indication	4-PCC indication: all indications	6	0.17 (−0.00, 0.35)	0.051	<0.001 /88.0
			4-PCC indication: ICH cases	2	0.09 (0.01, 0.17)	0.029	0.666 /0.0
			4-PCC indication: Non-ICH cases	2	0.12 (−0.03, 0.26)	0.124	0.466 /0.0
Order-to- needle time	Overall analysis			4	−22.50 min (−31.88, −13.12)	<0.001	0.517 /0.0
Time required reached to target INR	Overall analysis			3	−23.22 min (−92.19, 45.75)	0.509	0.033 /70.6
Total LOS	Overall analysis			4	1.64 days (−0.38, 3.66)	0.112	0.713 /0.0

WMD weighted mean difference, *CI* confidence interval, *Sub.g* sub-group, *ICH* intracerebral hemorrhage, *Wt* weight, *NA* not applicable

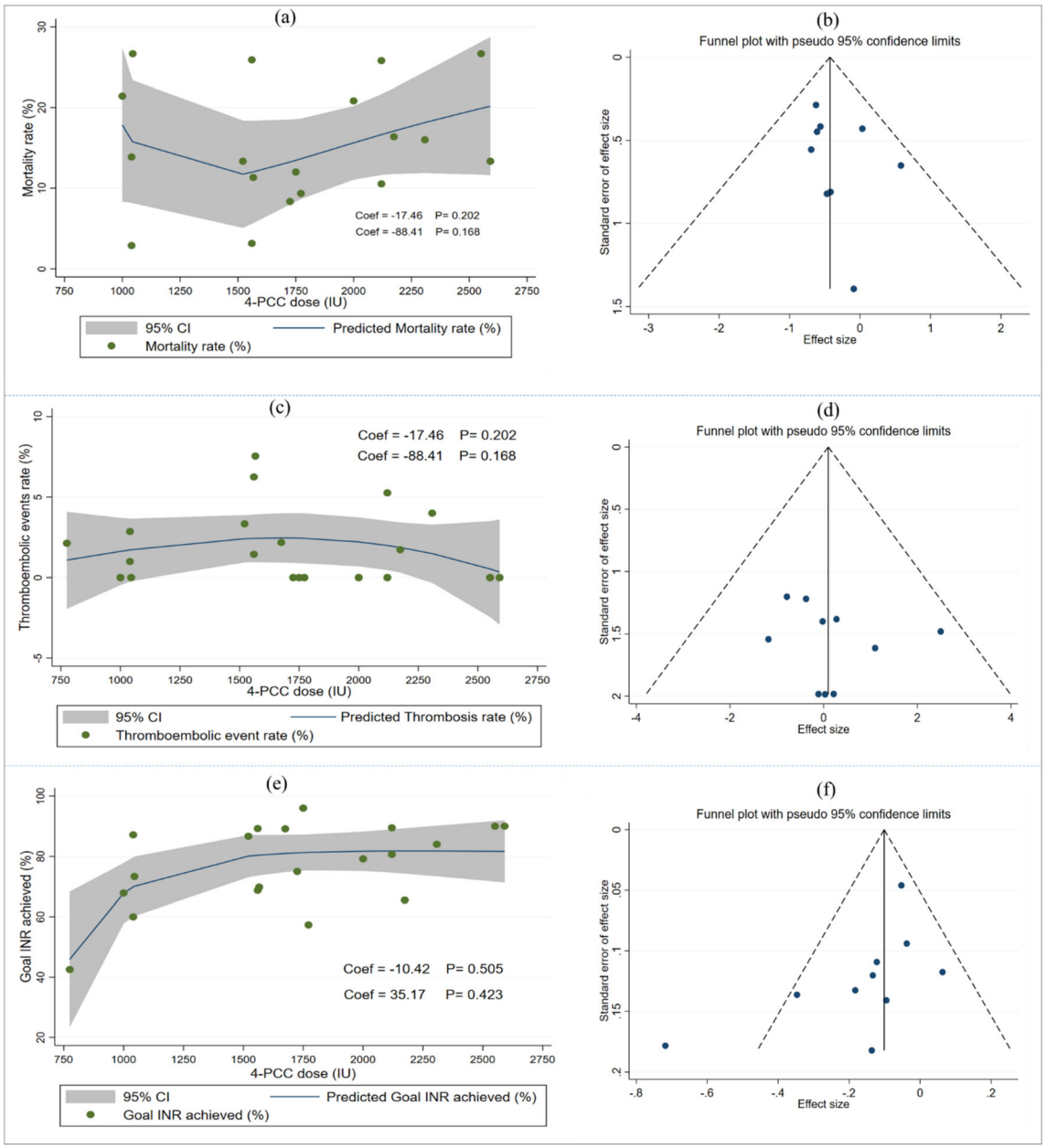

Fig. 5 Non-linear dose response between 4-PCC administered dose and mortality (**a**), thromboembolic events (**c**), and goal INR reached (**e**). Funnel plot analysis for mortality (**b**), thromboembolic events (**d**), and goal INR reached (**f**)

mortality rate was seen in both dosing strategies in the analysis of two studies in which only ICH patients were included. Nonetheless, these findings should be evaluated in further studies. Additionally, the risk of TEE in overall and subgroup analysis of two dosing groups did not differ significantly. Although the use of variable-dose 4-PCC is associated with the lower mean value of post 4-PCC INR and the higher likelihood of achieving hemostasis (reached to goal INR after a defined period time, generally after 15–30 min), the time needed to reach goal INR was similar between two groups.

On the other hand, the need for an additional 4-PCC dose was higher in overall analysis in the fixed-dose strategy group, but this was not statistically significant in the subgroup of the patient with INR ≥ 4 or weight ≥ 80 kg or ICH patients. Despite this finding, it should be kept in mind that the total administered dose of 4-PCC based on total IU, and IU/kg was significantly lower in the fixed-dose versus variable-dose. Furthermore, a lower order-to-needle time in the fixed-dose group was reported. Indeed, the required time for preparation, ordering, and start of infusion of 4-PCC was lower in the fixed-dose group. The overall search strategy, results, and conclusion of our systematic review and meta-analysis are presented in Fig. 6.

The efficacy and safety of fixed-dose strategies have been discussed in various clinical studies and review articles. In

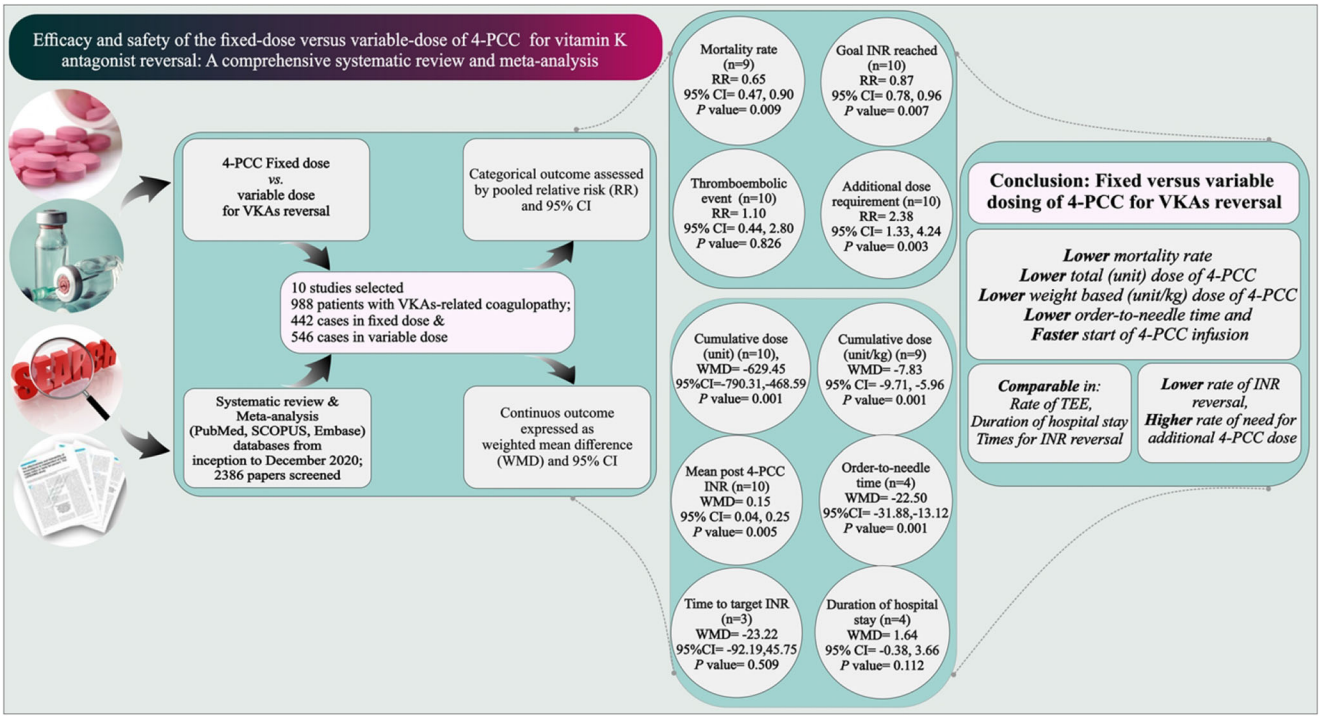

Fig. 6 Overall search strategy, result, and final conclusion of systematic review and meta-analysis

some studies, no difference was reported in the clinical outcomes between the two dosing strategies [21, 32], while in other studies, lower number of goal INR reached with comparable mortality rate was seen in fixed-dose 4-PCC compared to variable-dose [36, 37]. Varga et al. [38] retrospectively reviewed data of 103 patients who received PCCs for warfarin reversal. They found that 1000 IU fixed-dose strategy was associated with satisfactory clinical response (control of bleeding without requiring additional measures) in 84% of patients. In another retrospective study, Klein et al. [39] reported that 1500 IU 4-PCC successfully reversed median INR in 92% (36 participants) of 39 patients who presented with VKA-related bleeding. No associated thromboembolic event was seen in this report. A systematic review was conducted by Khorsand et al. [14] in 2015 to review the efficacy and clinical outcomes of the all used PCC dosing strategies for VKAs reversal. The fixed-dose strategy was used in only seven studies in this systematic review; however, most of them were not a comparative study. Meanwhile, the authorsy concluded that relatively satisfactory results are obtained with the use of various PCC dosing strategies. Furthermore, lower administered PCC doses were used in the fixed-dose strategy.

Altogether, our study revealed that 4-PCC fixed-dose strategy1000–1500 IU of 4-PCC is a safe, effective, and time-saving strategy for the patients with VKAs-related major bleeding or undergoing the procedure. In contrast, the optimal 4-PCC dosing strategy in patients with VKAs-related ICH is more challenging. ACC guidelines recommended using either INR/weight-based variable dosing or fixed-dose 1500 IU in ICH patients [17]. In our pooled data of ICH patients, no significant difference in the major outcomes (e.g., mortality, hemostasis reversal, etc.) was seen in fixed-dose versus variable-dose. Two studies included only ICH patients, and six studies included ICH patients in their participants. As the mean dose of the 4-PCC in the fixed-dose group in the pooled data of the studies in which ICH patients were included was 1440.5 units, it can be concluded that the recommended dose of 1500 IU 4-PCC in ACC guideline may be suitable in ICH patient. However, the use of fixed-dose in ICH patients should be evaluated in further studies. Use of the upper range of dose or adding a re-dose option (e.g., if INR goal not achieved or in patients with obesity or significantly elevated INR > 7.5 or in ICH patients) is the more prudent strategy and may be considered in selected patients. Besides, in dose-response analysis between primary outcomes and administered 4-PCC dose, no significant correlation was seen. The non-significant growing trend in mortality rate in 4-PCC dose above 1500 IU may be due to the fact that the number of death was numerically greater in the variable-dose group in which higher doses were given.

In conclusion, our results suggest that fixed-dose 4-PCC strategy may be considered for VKAs reversal in the different clinical settings; however, this finding should be interpreted with caution. The conduction of more extensive clinical studies focusing on the efficacy and safety outcomes and the optimal dosing strategy of 4-PCC for the VKAs reversal in the different clinical settings, especially ICH patients, is needed. The PROPER3 study [40], RCT trial that evaluating fixed-dose 4-PCC versus variable-dose for VKA reversal, is currently ongoing and will hopefully provide further information on the efficacy and safety of these dosing regimens.

Strengths and Limitations

The current meta-analysis has some strengths. All of the included studies were comparative and have been performed to compare the fixed-dose to variable-dose of 4-PCC. A variety range of patients, including ICH, ECH, and those in need of urgent procedures, were included. Low publication bias and none to moderate risk of heterogeneity among included studies were observed in findings evaluations. Moreover, we assessed both clinically relevant efficacy and safety outcomes. Subgroup analysis based on the particular situations that may act as a confounding factor was also performed. As with all meta-analysis, there are several limitations to be taken into consideration. Most of the included studies in our analysis were retrospective/prospective cohort designs which mostly did not adjust their results for differences among groups. Additionally, for some outcomes, the cohort studies conflicted with one included RCT. The limitation of dose-response analysis due to the risk of potential aggregation bias, especially in weight-based dosing groups, should be considered. Another limitation of our study was related to the unifying definition of some measured outcomes. For example, our included studies had not used a universal and same INR cutoff for goal INR reached in their studies.

Conclusion and Relevance

To summarize, the use of fixed-dose of 4-PCC in VKAs-related coagulopathy may be associated with the lower mortality rate, less total 4-PCC administered, and the faster start of 4-PCC infusion. The thrombotic events rate, duration of hospital stays, and the time needed to reach goal INR were similar between the two groups. In contrast, the variable-dose has been associated with the more hemostatic reversal. Altogether, the fixed-dose strategy of 4-PCC may be considered for urgent reversal of VKAs, but further well-designed, controlled studies should be conducted focusing on clinical outcomes to determine the optimal dose of 4-PCC for VKAs reversal.

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Author Contribution All authors were responsible for the study conception and design. KM, SY, and MA contributed to database searching, data extraction, assessment of study quality, data analysis and interpretation, and drafting of the manuscript. AT and KM critically evaluated and revised the manuscript. All authors approved the final version of the manuscript.

Data Availability All data generated or analyzed during this study were included in the article.

Declarations

Ethics Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to Participate Not applicable.

Competing Interests The authors declare no competing interests.

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