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ORIGINAL ARTICLE

Efficacy and safety of prothrombin complex concentrate for vitamin K antagonist-associated intracranial hemorrhage: a systematic review and meta-analysis

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Abstract

Background Prothrombin complex concentrate (PCC) is the treatment of choice in vitamin K antagonist-associated intracranial hemorrhage (VKA-ICH). However, the efficiency and safety associated with their use remain unclear.

Aims This study aimed to assess the current evidence of the clinical outcomes in patients with VKA-ICH treated with or without PCC.

Summary of review A meta-analysis was conducted. Two randomized controlled trials and 19 observational studies were included. PCC use demonstrated a significant increased likelihood of international normalized ratio (INR) normalization (OR = 3.76; 95% CI 1.74–8.12), shortened time to INR correction (MD = − 1.30; 95% CI − 2.08 to − 0.53) and reduction of hematoma expansion (HE) rate (OR = 0.37; 95% CI 0.23–0.60). Although PCC use revealed a statistical reduction at 30-day mortality (OR = 0.62; 95% CI 0.50–0.78), the result was inconsistent with mortality at discharge (OR = 1.03; 95% CI 0.68–1.57) and 90-day follow-up (OR = 0.50; 95% CI 0.24–1.07), both of which yielded no significant difference. When subgroup analyses were performed focus on PCC only treatment with FFP, no statistically significant difference was observed in 30-day mortality (OR = 0.43; 95% CI 0.11–1.71) as well. Besides, significant difference was not found in neurologic improvement at discharge (OR = 1.85; 95% CI 0.32–10.75), 30-day follow-up (OR = 3.00; 95% CI 0.93–9.70), or 90-day follow-up (OR = 1.55; 95% CI 0.84–2.86). No statistically significant difference was noted in the risk of thromboembolism following PCC administration (OR = 0.61; 95% CI 0.23–1.63).

Conclusions PCC use for VKA-ICH reversal was associated with a significant reduction in INR and HE rate, without an increased risk of thromboembolic events. However, this reduction was not associated with improvement in neurologic deficits or overall survival. Well-designed randomized trials with special considerations to the aspect are necessary.

Keywords Intracranial hemorrhage · Vitamin K antagonists · Prothrombin complex concentrate · Meta-analysis

Introduction

Vitamin K antagonists (VKAs) are widely used for preventing venous thrombosis, pulmonary embolism, stroke, and other systemic embolism in patients with atrial fibrillation or prosthetic heart valves. However, long-term anticoagulation therapy carries a significant risk of bleeding complications. A systematic review [1] of global studies in VKA-treated patients reported the annual rates of major hemorrhage, especially intracranial hemorrhage (ICH) as 1.3–7.2% and 0.1–2.5% respectively. ICH is a major cause of morbidity and mortality in these patients [2]. The poor outcome after VKA-associated intracranial hemorrhage (VKA-ICH) is related to large baseline volume of hemorrhage and continued hematoma

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expansion (HE) after admission [3], which is primarily relative to VKA-induced hemostatic defects. Therefore, urgent correction of coagulopathy is necessary to prevent HE and tissue damage.

The traditional therapies to reverse anticoagulation include intravenous vitamin K and fresh frozen plasma (FFP). However, the full effect of vitamin K may take up 24 h to develop [4]; thus, it is usually not recommended as a monotherapy for acute major bleeding [5]. Although more rapid restoration of coagulation factors can be achieved by infusion of FFP [6], its use is limited by potentially life-threatening adverse effects, including transmission of infectious agents, allergic reactions, and volume overload. Prothrombin complex concentrates (PCCs) are plasma-derived factor concentrates originally developed to treat hemophilia, containing variable amounts of factors II, VII, IX, and X. In contrast to FFP, PCC can be reconstituted and administered rapidly in a small volume without cross-matching and has been processed to inactivate infectious agents.

Although two systemic reviews [7, 8] have been published before comparing PCC and traditional therapy in cases of major bleeding, none of them focused on patients with VKA-ICH, who had worse outcomes. Whether use of PCC for rapid INR reversal directly correlates with clinical hemostasis or whether doing so can actually modify the course of VKA-ICH is unclear. European treatment guidelines for VKA-associated ICH had no specific recommendation for the lack of evidence from randomized controlled trials (RCTs) [9]. US guidelines propose PCC may be considered over plasma, mainly because of more rapid INR reduction time [10], but the relationship between INR reversal and clinical outcome of ICH is uncertain. Recently, more RCTs, as well as prospective and retrospective studies, have been published about this relationship. Therefore, a systematic review and meta-analysis of clinical studies is conducted to investigate the efficacy and safety of PCC for VKAs reversal in patients with VKA-ICH.

Methods

A detailed protocol including literature-search strategies, inclusion and exclusion criteria, outcome measurements, and methods of statistical analysis was designed before conducting the systematic review. The protocol was based on the Meta-Analysis of Observational Studies in Epidemiology [11] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Search strategy

Literature was searched among articles published from January 1999 to December 2018. A computerized search of the MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Chinese databases including China National Knowledge Infrastructure, China Science Periodical Database, and China Science and Technology Journal Database was performed without restriction on the language of publication. Three concepts were searched. The first search exploded the MeSH headings "Intracranial Hemorrhages," "Cerebral Hemorrhage," "Subarachnoid Hemorrhage," "Hematoma, Subdural," and "Cerebral Intraventricular Hemorrhage" and used the text words "Brain Hemorrhage," "Cerebrum Hemorrhage," "Intracerebral Hemorrhage," "SAH," "Subdural Hematoma," "Subdural Hemorrhage," and "Cerebral Intraventricular Haemorrhage" to map the search. The second search exploded the MeSH heading "Anticoagulants," "Warfarin," "Phenprocoumon," and "Acenocoumarol" and used the text words "Anticoagulation Agents," "Coumadin," "Marcumar," "Liquamar," "Acenocoumarin," "Sinthrome," and "Syncumar, Sintrom" to map the search. The third search exploded the MeSH headings "Hemostasis," "Prothrombin," "Plasma," "Vitamin K," and "Hemostatic Therapy," "Prothrombin Complex Concentrate," "PCC," "Fresh Frozen Plasma," and "FFP" to map the search. All terms for the three searches were connected through the Boolean operator "OR". The concepts were combined using the Boolean operator "AND." A manual review of reference lists was also conducted. Potential sources of unpublished data were searched through www.clinicaltrials.gov up to January 2018. The most current report was selected when a study generated multiple publications.

Study selection

Two reviewers (R.P. and J.P.C.) performed study selection independently using pre-specified inclusion and exclusion criteria. RCTs and observational studies (prospective or retrospective) were eligible. Studies on patients with VKA-ICH that required urgent VKAs reversal and comparing PCC with traditional reversal therapy (FFP and/or vitamin K) were selected. Those studies that evaluated a combination of PCC, FFP, and/or vitamin K as a co-intervention were classified as the PCC group. If same patients were included in multiple studies, the study with the largest sample size or most complete outcome report was chosen. Studies that evaluated spontaneous ICH or traumatic ICH were excluded from selection. Discrepancies between reviewers were resolved by consensus or the senior author (Y.M.T.).

Data extraction

Data were extracted independently by two reviewers (R.P. and J.P.C.) using a standardized data record form, with disagreements settled by the senior author (Y.M.T.). The primary

outcomes were efficacy of INR reversal and HE rate. Efficacy of INR reversal was evaluated by two measures. One was "rapid INR reduction," defined as the proportion of patients who had a rapid INR reduction (as defined in individual studies). The other was "time to INR correction," defined as the treatment time needed to correct the INR. HE rate was defined as relative parenchymal volume (as defined in individual studies) increase on follow-up CT scan. The secondary outcomes were all-cause mortality, favorable outcome rate, and thromboembolic events. Favorable outcome was defined as independence in daily activities (modified Rankin scale of 0–2 or 0–3). Thromboembolic events were defined as outcome composite of venous thromboembolism, coronary artery disease, pulmonary embolism, stroke or transient ischemic attack, and peripheral arterial disease.

Quality assessment

Studies were rated for the level of evidence provided according to the criteria by the Centre for Evidence-Based Medicine in Oxford. The Cochrane Risk of Bias Tool was used to assess the quality of the RCTs. Criteria proposed by the Newcastle-Ottawa scale were used to assess the quality of the observational studies.

Statistical analysis

Meta-analysis was performed on studies with data on outcomes of patients who received PCC or traditional reversal therapy by the Stata 12.0 software. Dichotomous variables were presented as odds ratios (OR; PCC versus non-PCC) with a 95% confidence interval (CI). Pooled results of continuous outcomes were summarized with mean difference (MD) and corresponding 95% CI. Fixed- and random-effects models were used, with significance set at $P = 0.05$. Statistical heterogeneity was assessed using the I^2 statistic. An I^2 value of < 25% indicated low heterogeneity; a value between 25 and 50%, moderate heterogeneity; and > 50%, high heterogeneity. The random-effects model was used if high heterogeneity was observed between studies; otherwise, the fixed-effects model was used. Subgroup analysis was carried out to evaluate the impact of different definitions of HE on the results. Furthermore, RCTs were analyzed separately from prospective and retrospective studies if possible, for the clinical or methodological heterogeneity. Subgroup analysis was performed according to the different treatments. Interaction tests were applied to assess for differential effects across subgroups. Influence analysis (sensitivity analysis) was performed to explore the robustness of positive results. Studies were deleted one at a time to identify any study that may have exerted a disproportionate influence on the summary treatment effect. Funnel plots were used to screen for potential publication bias.

Results

Flow of included studies

As shown in Fig. 1, a total of 4578 citations were identified from MEDLINE, EMBASE, CENTRAL, and WANFANG. One study was also identified from clinicaltrials.gov. After screening of the title and abstract using the predefined inclusion and exclusion criteria, 34 studies were retrieved for full-text review. Four reviews and two letters were excluded. Three articles were also excluded for not containing original data, as well as four papers in which part of patients presented with ICH secondary to the non-vitamin K antagonist oral anticoagulant. Finally, 21 studies [12–32] met all inclusion criteria and were included in the analysis. Agreement between the two reviewers was 96% for study selection and 94% for quality assessment of trials.

Study characteristics

Baseline characteristics of the included studies are summarized in Table 1. A total of 3536 participants were included, with sample size ranging from 13 to 1547. Among the included participants, 1994 received PCC therapy while 1542 received traditional therapy including FFP, vitamin K, or no reversal agent. The percentage of included male patients ranged from 12.5 to 90%, and the mean age of study patients ranged from 33.6 to 83.56 years. The types of PCCs evaluated included 4-factor PCC (4F-PCC) and 3-factor PCC (3F-PCC). All PCCs contained coagulation factors II, IX, and X at high concentration, whereas factor VII was present at high concentration only in 4F-PCC. Nine studies [15, 17, 19, 21, 22, 24, 25, 28, 30] used 3F-PCC, eight studies [12, 13, 18, 20, 26, 27, 29, 31] used 4F-PCC, and one study [16] used 3F-PCC together with 4F-PCC. Three studies [14, 30, 32] did not report the type of PCC used. The dose calculation of PCC treatment is also described in Table 1. PCC were administered at a weight-adjusted dose in 10 studies [12, 13, 15, 18–20, 24, 25, 27, 29] and at a fixed dose in only one study [32]. Baseline or target INR was considered to select the dose of PCC in four studies [17, 24, 30, 31]. Seven studies [14, 16, 21, 22, 26, 28, 30] did not report the regimen for dose calculation.

Quality of included studies

Two studies [12, 13] were RCTs, two [14, 15] were prospective, and 16 [16–32] were retrospective. The risk of bias in the two published RCTs using the Cochrane Risk of Bias Tool (Supplemental Table 1) was evaluated. Allocation sequence generation and allocation concealment were clearly described by one RCT [12]. Although treatment masking was not possible because of the different appearance of the reversal products, the INR normalization in coumadin-associated

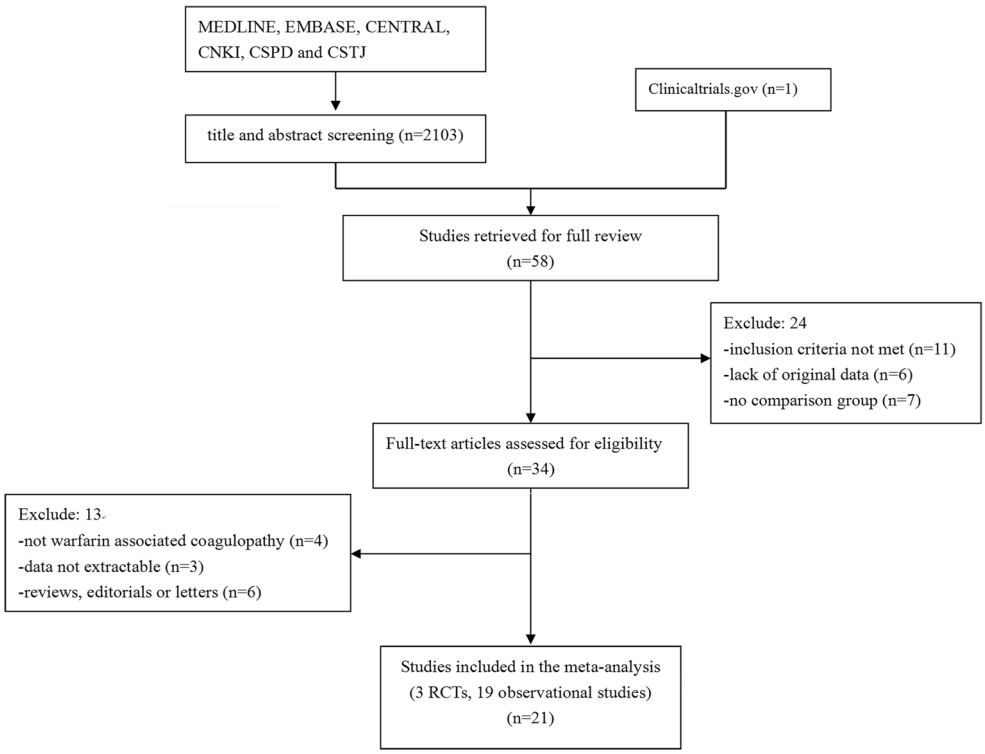

Fig. 1 Study flow diagram according to the Quality of Reporting of Meta-analyses (QUOROM) statement

intracerebral hemorrhage (INCH) trial [12] recently published was observer masked for all laboratory data, including the primary endpoint, and for neuroradiological and clinical outcome assessments. For the 19 observational studies [14–32], the risk of bias was evaluated with a modification of the Newcastle-Ottawa scale (Supplemental Table 2). Most of the cohort studies were at risk of bias for confounding and selection of the participants and the substantial differences on baseline clinical characteristics of the patients in the PCC and control groups. Moreover, methods for handling missing data were not adequately described in most studies.

Synthesis of results

Primary outcome

Five studies [12, 15, 24, 27, 31] reported the proportion of patients who had a rapid INR reduction. Figure 2a demonstrates the use of PCC was associated with increased likelihood of INR normalization as compared with non-PCC therapy (PCC versus non-PCC, 56.7% versus 29.3%; OR = 3.76; 95% CI 1.74–8.12; $P = 0.001$). Subgroup analysis was performed according to the study design (Supplemental Figure 1A). Result of RCT (PCC versus non-PCC, 66.7% versus 8.7%; OR = 21; 95% CI 4.01–110.06; $P < 0.001$) was highly consistent with cohort studies (PCC versus non-PCC, 55.4% versus 31.5%; OR = 3.10; 95% CI 2.02–4.77; $P < 0.001$). Five other studies [13, 19, 22, 24, 32] reported time to INR correction in VKA-ICH. More rapid INR reduction was also observed in patients who received PCC. The MD of INR correction in favor of PCC was − 1.30 h (95% CI − 2.08 to − 0.53; $P = 0.001$). Subgroup analysis showed similar results between RCT subgroup (MD = − 4.81 h; 95% CI − 7.11 to − 2.51; $P < 0.001$) and cohort subgroup (MD = − 0.85 h; 95% CI − 1.21 to − 0.50; $P < 0.001$) (Supplemental Figure 1B).

Ten studies [12, 14, 15, 17, 19–21, 23, 26, 30] reported HE rate after VKA-ICH. HE occurred in 282 of 849 (33.2%) patients who received PCC and 73 of 196 (37.2%) patients treated without PCC (Fig. 3). PCC use was associated with a significant reduction in HE (OR = 0.37; 95% CI 0.23–0.60; $P < 0.001$). Subgroup analysis was carried out according to different definitions of HE (a relative parenchymal volume increase of more than 33%, 40%, 5 ml, or subjective judgment on follow-up CT scan). The point estimates of effect size was almost identical for 33%, subgroup (OR = 0.39; 95% CI 0.19–0.82); 40%, subgroup (OR = 0.35; 95% CI 0.12–1.00); 5 ml, subgroup (OR = 0.29; 95% CI 0.08–1.14); and subjective, subgroup (OR = 0.39; 95% CI 0.15–1.02), with largely overlapping Cis and nil heterogeneity ($I^2 = 0\%$; $P = 0.937$) (Supplemental Figure 2). Sensitivity analysis was performed by removing studies one at a time. The result did not change from the primary analysis (Supplemental Figure 3).

Secondary outcomes

Ten studies [13, 19, 21–25, 27, 31, 32] including 621 patients reported in-hospital mortality (Fig. 4a). Death occurred in 59

Table 1 Design and baseline characteristics of included studies

Author	Study design	Level of evidence	Indication for VKA	Patient number, *n*		Age, years		Male, %		PCC protocol	Non-PCC protocol	Follow-up, days
				PCC	Non-PCC	PCC	Non-PCC	PCC	Non-PCC			
Steiner [12] 2016	RCT	II	AF	27	23 (FFP)	74.7	76.6	59	65	4F-PCC (Octaplex) 30 IU/kg + vitamin K, 10 mg	FFP, 20 ml/kg + vitamin K, 10 mg	90
Boulis [13] 1999	RCT	II	NA	5	8 (FFP)	NA		NA		4F-PCC (Konyne) IU request = kilograms of weight × *x*, where *x* = 40 to 50	FFP ± vitamin K	At discharge
Alonso [14] 2013	P	III	AF, MI, VT, PE	50	6 (FFP) 3 (vitamin K) 12 (no reversal)	78		52.1		PCC+ vitamin K	FFP ± vitamin K or vitamin K alone	90
Frontera [15] 2014	P	III	NA	16 (PCC alone) 23 (PCC + FFP)	25 (FFP)	73.5 (PCC) 75 (PCC + FFP)	74.5	37.5 (PCC) 47.8 (PCC + FFP)	56	3F-PCC (Bebulin VH) PCC alone, 47.9 IU/kg (mean dose) or PCC 47.4 IU/kg + FFP 11.4 ml/kg	FFP 12.5 ml/kg (mean dose)	90
Parry-Jones [16] 2015	R	III	NA	585 (PCC alone) 131 (PCC + FFP)	377 (FFP) 454 (no reversal)	77 (PCC) 76 (PCC + FFP)	78 (FFP) 78 (no reversal)	58 (PCC) 66 (PCC + FFP)	58 (FFP) 53 (no reversal)	3F-PCC or 4F-PCC ± FFP	FFP or no reversal	30
Fong [17] 2014	R	III	NA	41	44 (FFP)	74	70	56.1	43.2	3F-PCC (Prothrombinex-HT) 500 IU (INR 1.3–1.5), 1500 IU (INR 1.5–3), 2000 IU (INR 3–4), 3000 IU (INR ≥ 4)	FFP	30, 90
Majeed [18] 2014	R	III	AF, VP, VT,	100	35 (FFP)	73.4	72.8	54	66	4F-PCC (The Netherlands and Sweden) median 23 IU/kg	FFP median 4 units	30
Edavettal [19] 2014	R	III	NA	28 (PCC + FFP)	34 (FFP)	83.6	77.2	57.1	52.9	3F-PCC (Profilnine SD) 25 IU/kg + vitamin K, 10 mg	FFP 4 units or 15 ml/kg	At discharge
Wong [20] 2016	R	III	LVAD implantation	10	10 (FFP) 11 (no reversal)	46.6	50.1 (FFP) 59 (no reversal)	50	50 (FFP) 73 (no reversal)	4F-PCC (Kcentra) 25 IU/kg	FFP or no reversal	30
Kuwashiro [21] 2011	R	IV	NVAF, VP, VT, DC, MI, CABG, complicated atheromatous lesions in the aortic arch, peripheral arterial disease	22	28 (FFP or vitamin K)	69.7	68.7	68	71	3F-PCC (PPSB-HT Nichiyaku) 500–1500 units were administered	FFP or vitamin K	At discharge, 30
Woo [22] 2012	R	IV	AF, VP, VT, PE,	8	46 (FFP)	79	76	NA		3F-PCC (Bebulin VH) average dose 2866 IU	FFP > 4 units in the first 24 h	At discharge
Yasaka [23] 2002	R	IV	NVAF, VP, VT, DC, MI	12	4 (Vitamin K)	64	69.5	66.7	75	3F-PCC (PPSB-HT Nichiyaku) 500 or 1000 IU administered	Vitamin K 10 or 20 mg	At discharge

Table 1 (continued)

Author	Study design	Level of evidence	Indication for VKA	Patient number, *n*		Age, years		Male, %		PCC protocol	Non-PCC protocol	Follow-up, days
				PCC	Non-PCC	PCC	Non-PCC	PCC	Non-PCC			
										first, additional administration was considered according to the INR value		
Siddiq [24] 2008	R	IV	NA	10	9 (FFP)	67.2	76.9	50	55.6	3F-PCC (Profilnine SD) 25 units/kg (INR ≤ 4), 50 units/kg (INR > 4) + vitamin K 10 mg	FFP 10–15 ml/kg + vitamin K 10 mg	At discharge
Fredriksson [25] 1992	R	III	VT, PE, AF, VP, mitral valve prolapse, severe carotid artery stenosis, brain infarct or TIA	10	7 (FFP)	71.9	70	90	85.7	3F-PCC (Preconativ) Average dose, 25.8 IU, 0.43 ml/kg + vitamin K 10 mg	FFP 8.0 ml/kg + vitamin K 10 mg	At discharge
Kuramatsu [26] 2015	R	III	AF, VP, PE, VT	650	11 (FFP)	74.1		58.7		4F-PCC median 2000 IU	FFP ± vitamin K	1 year
Rowe [27] 2016	R	III	NA	128	148 (FFP)	56.1	69	60.2	54	4F-PCC median 6.9 UI/kg	FFP median 10 ml/kg	at discharge
Takahashi [28] 2010	R	IV	LVAD implantation	24	14 (FFP)	39.9	33.6	12.5	78.6	3F-PCC (PPSB-HT) 500–1000 IU	FFP ml request = body weight (kg) × 0.08 × (100-hematocrit/100) × 0.3 × 0.2 × 1000	30
Huhtakangas [29] 2015	R	III	NA	41	38 (FFP ± vitamin K) 96 (no reversal)	68	69	56	56	4F-PCC (Co-fact) 12.5–30 IU/kg + vitamin K 10 mg	FFP ± vitamin K or no reversal	90
Yasaka [30] 2003	R	III	NVAF, VP, VT, DC, CABG, complicated atheromatous lesions at the aortic arch, atherosclerotic obliterans and homograft-shunt operation for hemodialysis	11	2 (FFP) 10 (vitamin K) 13 (no reversal)	69		74.5		PCC 500–1500 IU ± vitamin K	FFP or vitamin K	At discharge
DeLoughery [31] 2017	R	IV	AF, VP, APLA, clot, intracranial hemorrhage	50	37 (no reversal)	70.9	73.1	64	70.3	4F-PCC (Kcentra) INR-dependent dose	No reversal	At discharge
Lihai [32] 2010	R	IV	VP, CABG	10	17 (vitamin K)	48	52	40	47.1	PCC 300 IU + vitamin K 20 mg	Vitamin K 10–20 mg	At discharge

NA not available, *P* prospective cohort study, *R* retrospective cohort study, *RCT* randomized controlled trial, *AF* atrial fibrillation, *VT* venous thrombosis, *PE* pulmonary embolus, *DC* dilated cardiomyopathy, *MI* myocardial infarction, *VP* valve prosthesis, *CABG* coronary artery bypass graft, *LVAD* left ventricular assist devices, *NVAF* non-valvular atrial fibrillation, *TIA* transient ischemic attack, *APLA* antiphospholipid antibodies

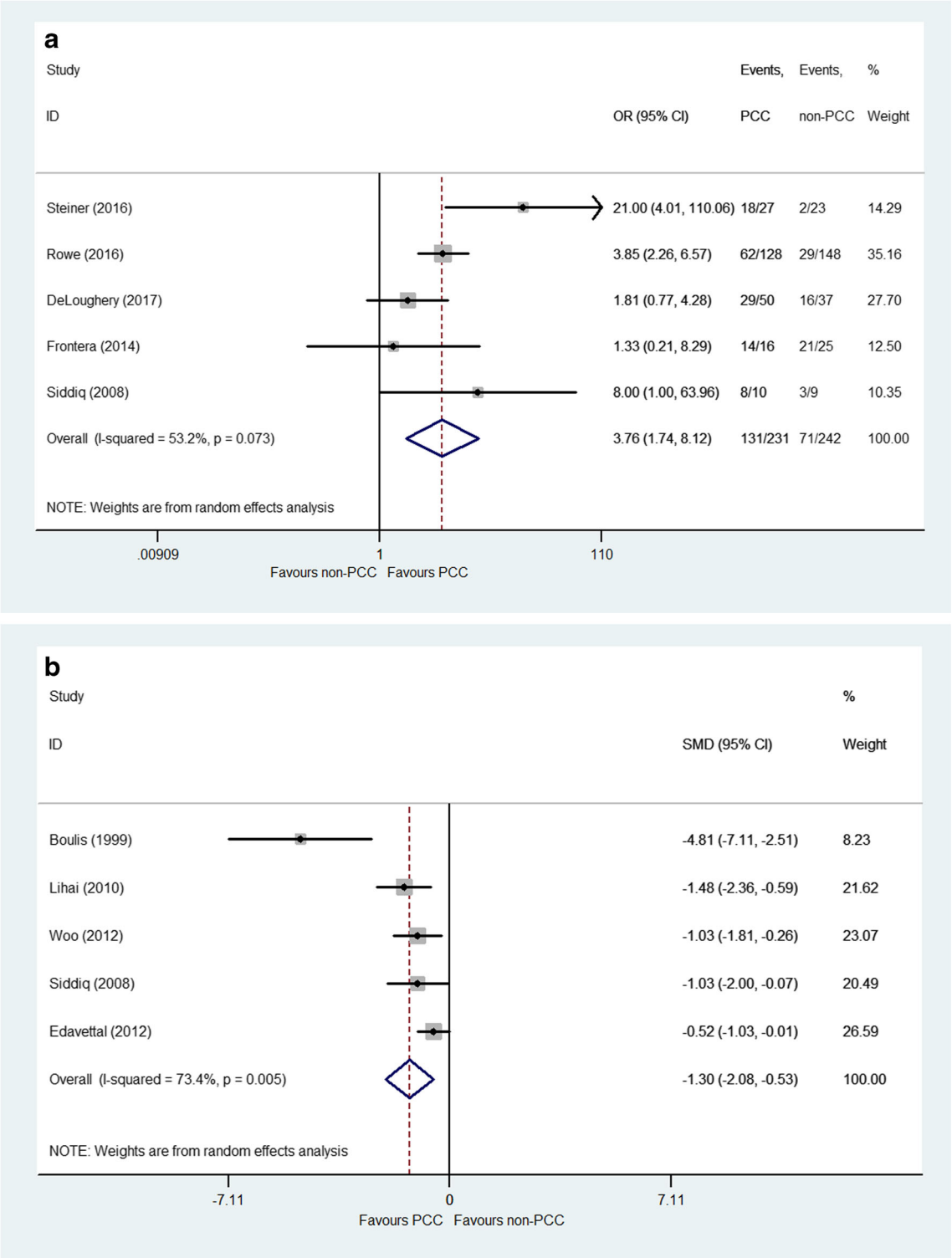

Fig. 2 Forest plot of the efficacy outcomes in patients receiving PCC comparing with non-PCC reversal therapy. **a**) Rapid INR reduction. **b**) Time to INR correction

of 283 (20.8%) patients treated with PCC and 75 of 338 (22.2%) patients who received non-PCC reversal therapy. Use of PCC showed no statistical reduction in in-hospital mortality (OR = 1.03; 95% CI 0.68–1.57; $P = 0.879$). The result is consistent with mortality for long-term follow-up (90 days) including 343 patients (Fig. 4c). PCC use showed a non-significant reduction in the risk of 90-day mortality (PCC versus non-PCC, 35.1% versus 60.3%; OR = 0.50; 95% CI 0.24–1.07; $P = 0.073$). The only statistically significant result was 30-day mortality including 1382 patients. Use

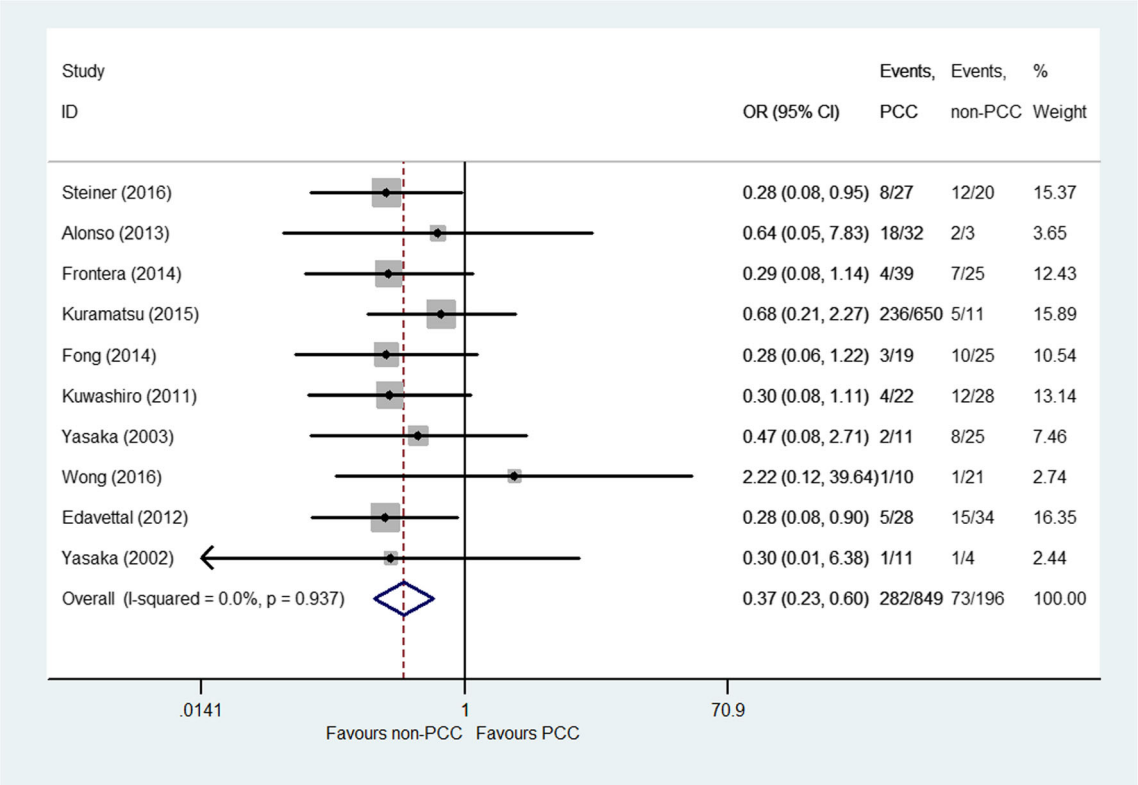

Fig. 3 Forest plot of hematoma expansion rate in patients receiving PCC comparing with non-PCC reversal therapy

of PCC yielded a lower death rate (34.9% versus 45.6%; OR = 0.62; 95% CI 0.50–0.78; $P < 0.001$) as compared with non-PCC therapy (Fig. 4b). Sensitivity analysis showed the result was highly influenced by the study reported by Parry-Jones [16] (Supplemental Figure 4).

Two studies [25, 30] including 34 patients reported in-hospital favorable outcome (Fig. 5a). Pooling the data according to the ranking of mRS, no significant difference in neurologic improvement was observed at discharge, no matter in the mRS 0–3 subgroup (PCC versus non-PCC, 56.5% versus 36.4%; OR = 1.85; 95% CI 0.32–10.75; $P = 0.493$) or the mRS 0–2 subgroup (PCC versus non-PCC, 38.5% versus 75.0%; OR = 0.21; 95% CI 0.02–2.60; $P = 0.223$). Only one study [21] reported evaluated patients' neurologic deficits at 30-day follow-up (Fig. 5b) with a non-significant improvement in neurological function in patients who received PCC (PCC versus non-PCC, 54.5% versus 28.6%; OR = 3.00; 95% CI 0.93–9.70; $P = 0.066$). Four trials [12, 14, 15, 17] mentioned 90 days follow-up in 282 patients (Fig. 5c). Similar results were identical between mRS 0–3 subgroup (PCC versus non-PCC, 39.3% versus 29.3%; OR = 1.55; 95% CI 0.84–2.86; $P = 0.162$) and mRS 0–2 subgroup (PCC versus non-PCC, 78.0% versus 69.7%; OR = 1.54; 95% CI 0.57–4.19; $P = 0.396$), none of which showed statistical improvement of neurologic deficits.

Four studies [13, 15, 22, 31] assessed thromboembolic events. Thromboembolic complications occurred in 7 of 102 (6.9%) patients treated with PCC and 10 of 116 (8.6%) patients without PCC treatment (Fig. 6). Statistically significant difference was not found in the risk of thromboembolism between treatments (OR = 0.61; 95% CI 0.23–1.63; $P = 0.329$).

Subgroup analysis

Subgroup analysis was performed according to each treatment first. For most of the studies enrolled, vitamin K was recommended as a co-intervention both in the PCC and control group. Therefore, subgroup analysis mainly focus on PCC as compared with FFP. In order to reduce clinical heterogeneity, two studies [15, 16] that simultaneously enrolled patients who received PCC in combination with FFP or PCC alone in the treatment group were excluded from subgroup analysis. Studies [14, 16, 18, 20, 21] that simultaneously enrolled patients who received FFP, vitamin K, or even no reversal therapy in the control group were also excluded. Assessment of ten studies [12, 13, 17, 19, 22, 24–28] compared PCC only treatment with FFP was summarized in Table 2. Although significant improvement to reverse INR (OR = 4.67; 95% CI 2.85–7.65; $P = 0.000$) and prevent HE (OR = 0.36; 95% CI 0.19–0.67; $P = 0.001$) were still observed, no significant reduction in overall mortality at discharge (OR = 1.09; 95% CI 0.67–1.76; $P = 0.729$), 30-day follow-up (OR = 0.43; 95% CI 0.11–1.71; $P = 0.228$), or 90-day follow-up (OR = 0.43; 95% CI 0.12–1.56; $P = 0.197$) were demonstrated. In addition, use

of PCC was not associated with any improvement in neurologic deficits at discharge (OR = 6.00; 95% CI 0.52–69.75; $P = 0.152$) or 90-day follow-up (OR = 1.18; 95% CI 0.58–2.38; $P = 0.650$) as compared with FFP. Statistically significant difference was not found in the risk of thromboembolism between treatments (OR = 0.92; 95% CI 0.09–9.71; $P = 0.994$). Two studies [23, 32] compared PCC only treatment with vitamin K monotherapy (Supplemental Table 3).

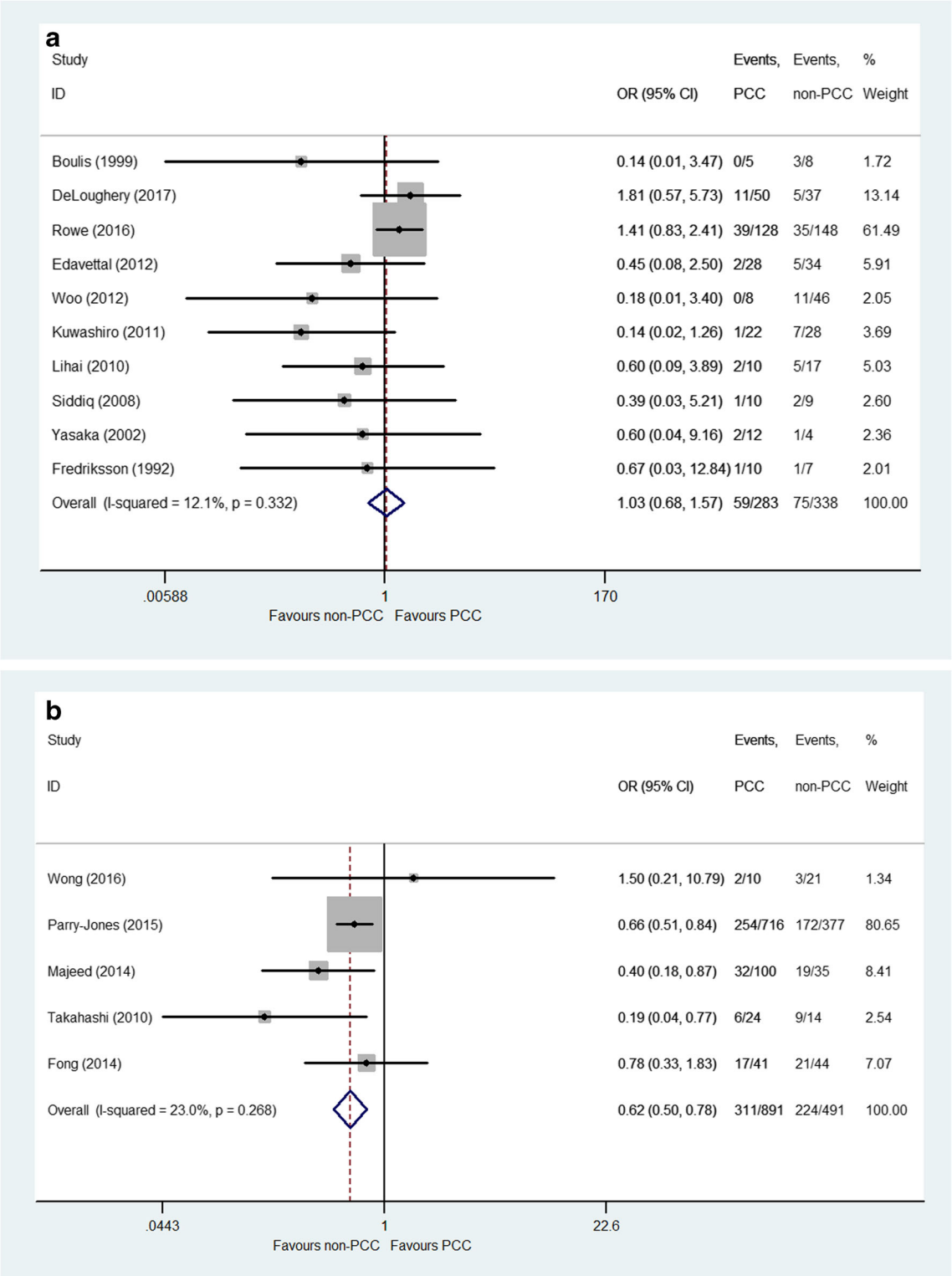

Fig. 4 Forest plot of the all-cause mortality in patients receiving PCC comparing with non-PCC reversal therapy. **a**) In-hospital mortality. **b**) 30-day mortality. **c**) 90-day mortality

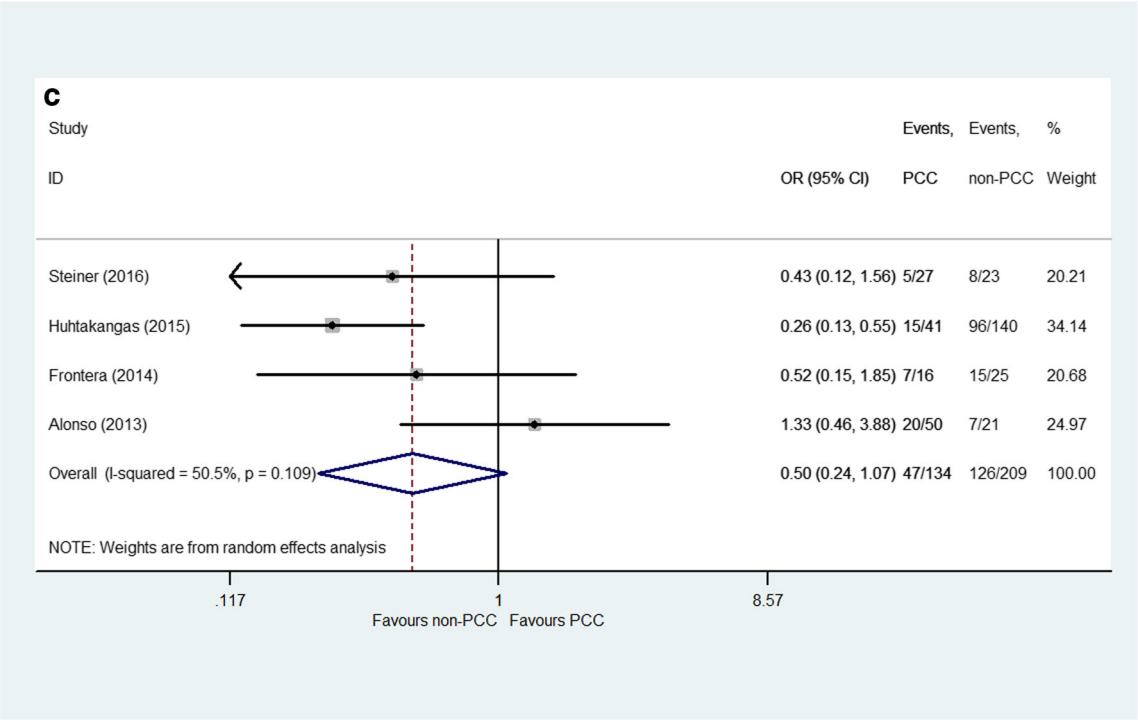

Fig. 4 (continued)

No statistically significant difference was observed in overall mortality (OR = 0.60; 95% CI 0.13–2.80; $P = 0.516$) or favorable outcome (OR = 0.53; 95% CI 0.04–6.66; $P = 0.625$) at discharge.

Secondly, subgroup analysis according to the types of PCCs was performed. Use of 3F-PCC (Supplemental Table 4) demonstrated no significant reduction in overall mortality at discharge (OR = 0.40; 95% CI 0.12–1.30; $P = 0.128$), 30-day follow-up (OR = 0.43; 95% CI 0.11–1.71; $P = 0.228$), or 90-day follow-up (OR = 0.52; 95% CI 0.15–1.85; $P = 0.311$). Besides, 3F-PCC treatment was not associated with any improvement in neurologic deficits at discharge (OR = 6.00; 95% CI 0.52–69.75; $P = 0.152$) or 90-day follow-up (OR = 1.91; 95% CI 0.93–3.95; $P = 0.08$). Similar results was identical for 4F-PCC (Supplemental Table 5). No significant reduction in overall mortality at discharge (OR = 1.33; 95% CI 0.79–2.25; $P = 0.290$) or 90-day follow-up (OR = 0.43; 95% CI 0.12–1.56; $P = 0.197$) were demonstrated. Favorable outcome at 90-day also yielded no significant difference (OR = 0.92; 95% CI 0.29–2.88; $P = 0.879$). Statistically significant difference of thromboembolic events was not observed in neither 3F-PCC subgroup (OR = 1.78; 95% CI 0.07–47.58; $P = 0.730$) or 4F-PCC subgroup (OR = 0.46; 95% CI 0.02–13.41; $P = 0.648$).

Sensitivity analysis and publication bias

The findings were similar regardless whether fixed- or random-effects models were used. Begg's funnel plots analysis on the efficacy of INR reversal, HE rate, favorable outcome, and mortality did not indicate significant publication bias, and the P values of Egger's test were 0.721, 0.189, 0.782, and 0.328, respectively (Supplemental Figures 5–8).

Discussion

Our findings favor PCC over traditional therapy on efficacy and speed of INR normalization, which is the main reason for PCC preference in clinic. In the absence of heterogeneity for the overall pooled analysis, a HE benefit of PCC over traditional therapy was demonstrated in patients with VKA-ICH. Although results of subgroup analysis according to definition of HE were inconsistent, the point estimates of effect size was almost identical with largely overlapping CIs. In support of this, the influence analysis conducted in our study based on overall pooled result confirmed the robustness of our findings.

Despite the significant improvement to reverse the INR and prevent HE effectively, whether the use of PCC would change the clinical outcomes is uncertain. In this study, PCC use showed a significant reduction of 30-day mortality for VKA-ICH. The most recent meta-analysis [7] also demonstrated a 30-day survival benefit of PCC. However, among 13 studies in that meta-analysis, only 5 were conducted exclusively in patients with ICH, 2 of which were unproperly included (one [13] collected data of in-hospital rather than 30-day mortality; the other [33] did not clearly mention the follow-up time). In our meta-analysis, two more studies [17,

20] were identified and added to the analysis. Although the updated result revealed a survival benefit of PCC with 30-day follow-up, it was highly influenced by Parry-Jones' study [16], which exerted a disproportionate influence on the summary treatment effect. However, clinical heterogeneity existed in the study, for they simultaneously enrolled patients who received PCC + FFP or PCC alone in the treatment group and patients who received FFP, vitamin K, or even no reversal therapy in the control group. When subgroup analyses were performed focusing on PCC only treatment with FFP, significant improvement to reverse the INR and prevent HE still remained. However, none of the secondary outcomes showed significant difference, including 30-day mortality. Besides, most of the other available evidences point to the contrary.

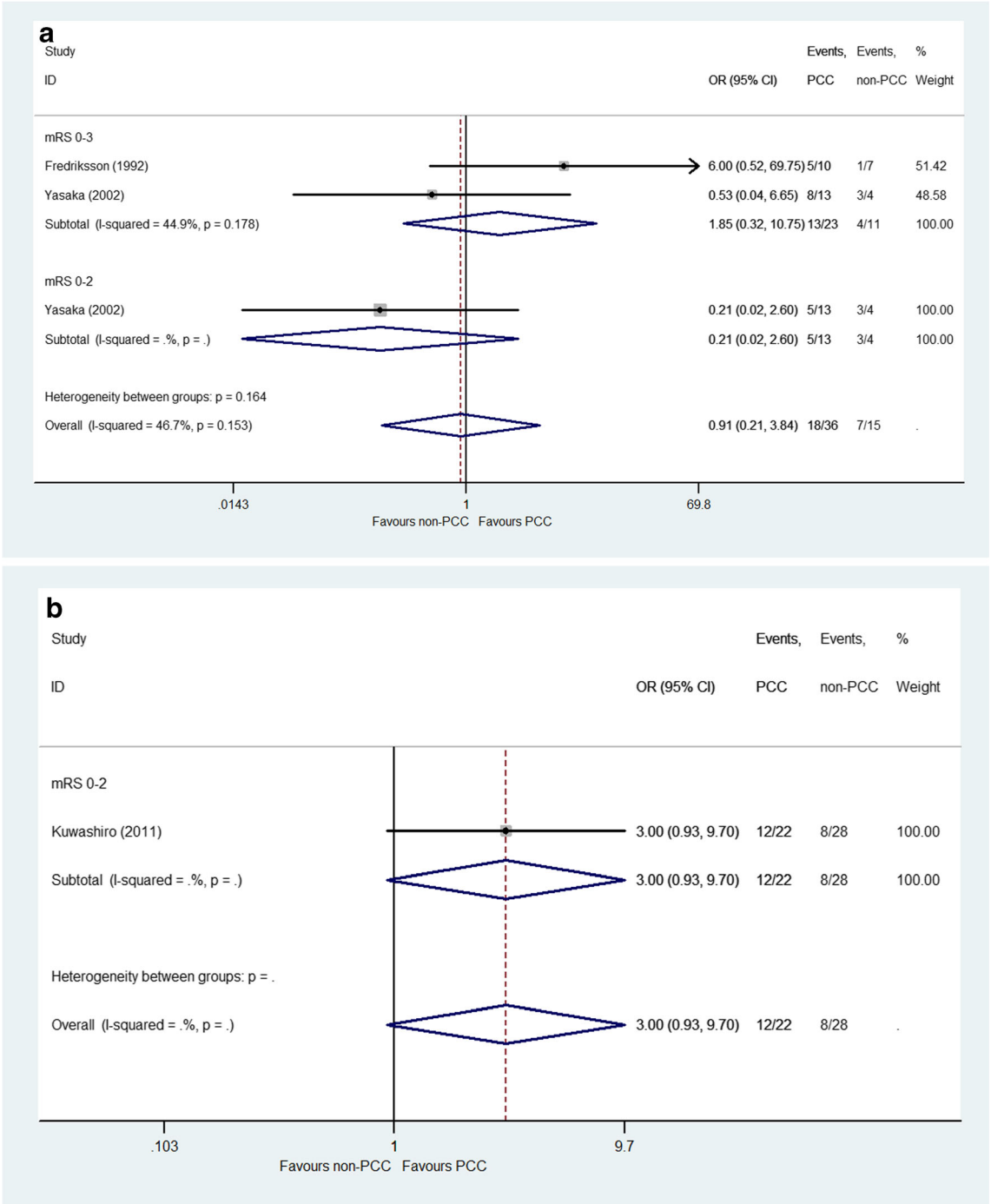

Fig. 5 Forest plot of favorable outcome in patients receiving PCC comparing with non-PCC reversal therapy. **a**) In-hospital favorable outcome. **b**) 30-day favorable outcome. **c**) 90-day favorable outcome

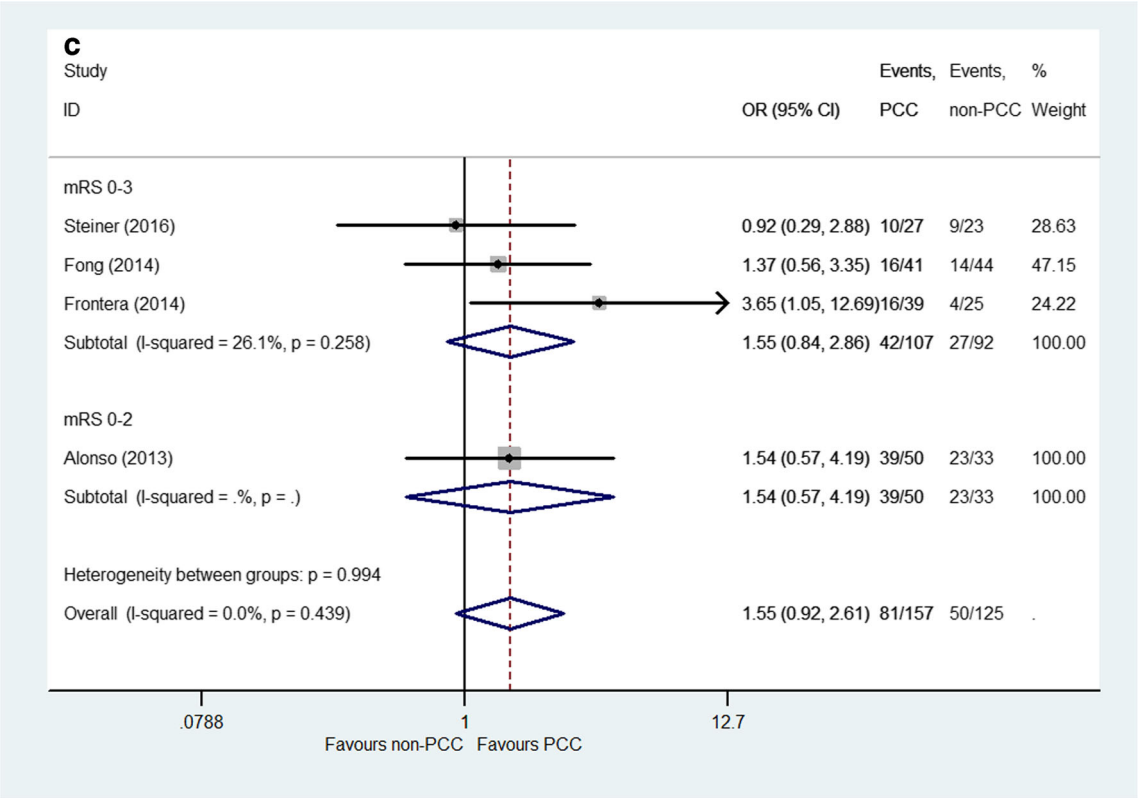

Fig. 5 (continued)

No significant improvement in overall survival at discharge or 90-day follow-up were demonstrated in patients treated with PCC. PCC use was not associated with any improvement in neurologic deficits at discharge or long-term follow-up. Subgroup analyses were performed considering the differences in effectiveness and safety of each treatment or types

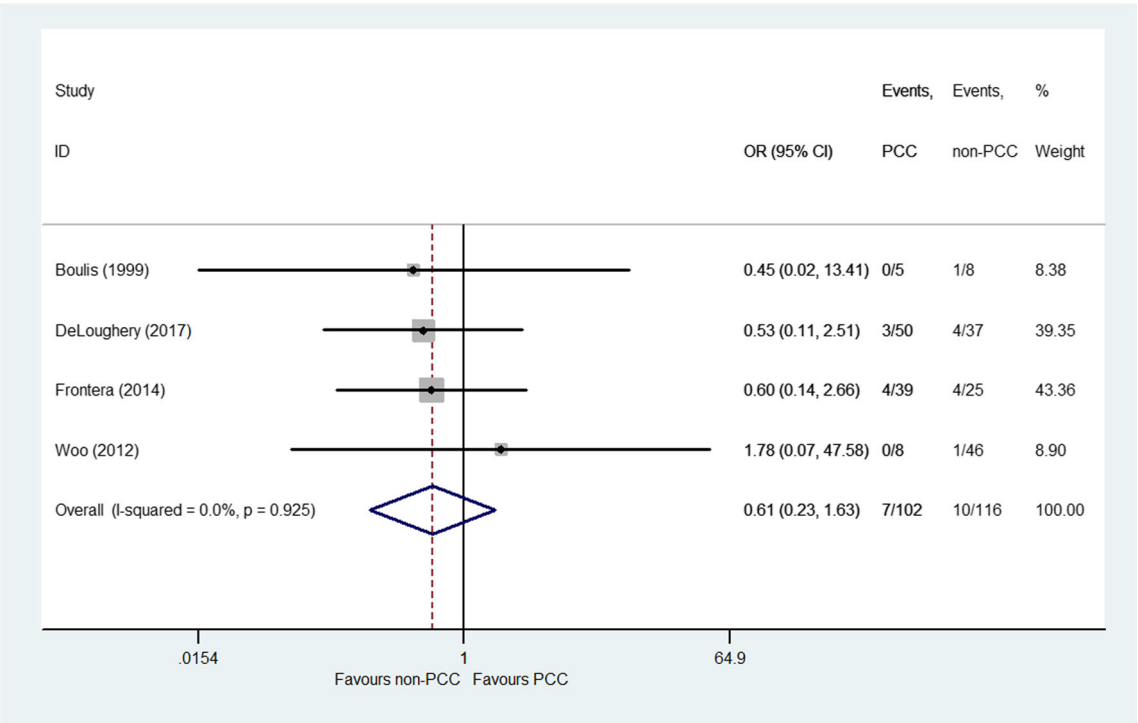

Fig. 6 Forest plot of thromboembolic complications in patients receiving PCC comparing with non-PCC reversal therapy

Table 2 Results of meta-analysis comparing PCC only treatment with FFP

Outcomes of interest	Studies, no.	PCC only patients no.	FFP patients no.	OR (95%CI)	*P* value	Study heterogeneity			
						X^2	*df*	I^2, %	*P* value
Efficacy of INR reversal	3	165	180	4.669 (2.850–7.648)	0.000	3.92	2	49.0%	0.141
Hematoma expansion	4	724	90	0.356 (0.191–0.666)	0.001	1.57	3	0.0%	0.666
Mortality									
In-hospital	6	189	252	1.089 (0.673–1.762)	0.729	5.66	5	11.6%	0.341
30-day	2	65	58	0.427 (0.107–1.705)	0.228	2.83	1	64.7%	0.092
90-day	1	27	23	0.426 (0.117–1.557)	0.197	0.00	0	–	–
Favorable outcome									
In-hospital	1	10	7	6.000 (0.516–69.754)	0.152	0.00	0	–	–
90-day	2	68	67	1.177 (0.582–2.379)	0.650	0.30	1	0.0%	0.585
Thromboembolic events	2	13	54	0.919 (0.087–9705)	0.994	0.32	1	0.0%	0.570

OR odds ratio, *df* degree of freedom, *CI* confidence interval;

of PCCs. None of the subgroups showed significant difference in mortality, favorable outcome, or thromboembolic events.

It is surprising that consistently demonstrating any effect of PCC use for rapid INR reversal on clinical outcomes in VKA-ICH remains so difficult, while significant benefit has been found in other types of bleeding [7]. There are multiple possibilities for the results. First, there may be a therapeutic time window for INR reversal [34]. HE is the most rapid in the first few hours after the bleeding. However, administration of reversal agent occurs in most studies after this initial period, due to delays caused by time from onset of symptoms to presentation to the emergency department and diagnostic imaging. Critical brain damage may thus have occurred prior to reversal, and the reversal strategies will then have a limited effect on prevention from HE. The study by Kuramatsu et al. [26] dose suggested that the use of PCC is best within 4 h.

Second, the inconsistency may partially result from the insufficient power of coagulation normalization to alter poor prognosis in the acute phase of ICH. The best medical management plan should include normalization of vital parameters besides INR value, including blood glucose, blood pressure, body temperature, and prevention and appropriate treatment of secondary complications, such as infection, seizures, and deep vein thrombosis [35, 36]. Kuramatsu et al. [26] found that only when rapid reversal is combined with blood pressure reduction, an association with improved outcomes is observed.

Third, mortality for long-term follow-up are more likely to be associated with underlying medical condition and potential delay in reinitiating VKA therapy, independently of the reversal strategy used. ESC/EACTS guidelines [37] recommend reinitiating VKA therapy within 4 to 8 weeks after ICH. Thus, delayed deaths beyond this point may not be directly attributable to the effectiveness or safety of reversal agents.

Fourth, INR may be an inadequate marker of clinical hemostasis. Even when the INR is normalized, effective hemostasis may not be achieved yet. Evidence come from the fact that recombinant factor VIIa, which only replaces one of the vitamin K-dependent factors, can always normalize the INR immediately, regardless of the levels of other coagulation factors or bleeding status [38], but did not improve outcome of intracerebral hemorrhage as well [39]. For the studies included in our meta-analysis, PCCs come from different countries, containing different products, some of which only have minimal factor VII [40]. As a result, PCC use for rapid INR reversal may be limited to accurately capture true clinical hemostasis.

The main concern in using PCC is the potential risk of thrombosis observed in patients with hemophilia treated with large, repeated doses of PCC [41]. Notably, the risk of thromboembolic events (TEEs) was similar between PCC and non-PCC groups in our meta-analysis. The result corresponds with a systematic review [8] of 27 studies in patients treated with PCC for VKA reversal in various settings (including ICH), which found PCC therapy to be associated with a low but quantifiable risk of thromboembolic complications (1.4%). However, conclusions on the relative safety of PCC should be made cautiously. The underlying risk of TEEs in populations receiving VKAs is critical. Once the VKA has been reversed, the potential risk of TEEs in these patients is restored. Therefore, TEEs may occur for the underlying medical condition and potential delay in reinitiating VKA therapy [42], independently of the reversal strategy used.

Limitations

This study has potential limitations. First, of the 21 studies included, there are only 2 RCTs, with a relatively small sample

size, probably resulting in insufficient power to prove the efficacy of PCC as compared with traditional hemostatic therapy. Second, the analysis of the non-randomized studies was not adjusted for some confounding variables. In most observational controlled trials, allocation to PCC was based on clinician preference according to patients' past medical history, clinical status, and the experience of the clinician. PCC may have been preferred in patients with higher INR value or more severe hemorrhage in admission, causing selection bias. Third, INR may be an inadequate marker of effective hemostasis. A standardized definition of hemostasis, a subjective outcome at high risk of bias and likely contributed to variability between studies, has not been established.

Conclusion

Results suggest that in patients with VKA-ICH, administration of PCC is associated with increased likelihood of INR normalization, shortened time to INR correction, and effective reduction of HE, without an increased risk of thromboembolic complications. Although PCC use revealed a statistical reduction at 30-day mortality, no significant improvement of clinical outcome or long-term survival was observed. Further studies focusing on the possibility of therapeutic time window for reversal are needed. Multiple processes of care and faster INR reversal should also be evaluated.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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