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Title: Intraosseous Versus Intravenous Drug Administration in Out-of-Hospital Cardiac Arrest: A Systematic Review and Meta-Analysis of Randomized Controlled Studies

Running Title: Different Drug Routes in Out-of-Hospital Cardiac Arrest

Authors: Yang-Zi Zhao[1], Fei Teng[2], Ya Zhang[3], Ren-Qing Zeng[4]

[1]Department of Accident & Emergency, The University of Hong Kong-Shenzhen Hospital, Shenzhen, China

[2]Department of Radiology, Fuwai Shenzhen Hospital, Chinese Academy of Medical Sciences, Shenzhen, China

[3]Department of Radiology, Shenzhen Maternity and Child Healthcare Hospital, Shenzhen, China

[4] Department of Accident & Emergency, First Affiliated Hospital of Gannan Medical University, Jiangxi, China

Correspondence: Ren-Qing Zeng

Address: 23 Qingnian Rd, Zhanggong District, Ganzhou, Jiangxi, China, 341000

Department of Accident & Emergency, First Affiliated Hospital of Gannan Medical University

Tel: +86 797 826 6010

Fax: +86 797 826 6010

Email: renqingz20635@163.com

Clinical Question Box

Which vascular access route is recommended for drug administration in out-of-hospital cardiac arrest (OHCA)?

Moderate- to high-certainty evidence indicates no significant clinical difference between intravenous and intraosseous drug administration in improving survival or achieving favorable neurological outcomes in OHCA. However, intravenous access remains the preferred route due to its cost-effectiveness and ease of accessibility. When intravenous access is challenging or delayed, particularly in prehospital settings, intraosseous access serves as a crucial alternative to ensure timely medication administration.

Abstract

Introduction: Optimal vascular access during out-of-hospital cardiac arrest (OHCA) is a critical consideration in resuscitation. While intravenous (IV) access is traditionally preferred, intraosseous (IO) access provides a rapid alternative when IV placement is challenging. This systematic review and meta-analysis compared the effectiveness of IO versus IV drug administration in OHCA.

Methods: To identify randomized controlled trials (RCTs) comparing IO and IV drug administration in OHCA, a systematic search was conducted in PubMed, Embase, Cochrane Library, and Web of Science. The primary outcomes included survival to hospital discharge, favorable neurological outcomes, and return of spontaneous circulation (ROSC).

Results: This meta-analysis included six RCTs with a total of 20,002 patients. No significant differences were found between the IO and IV routes in terms of survival to hospital discharge (OR: 0.83, 95% CI: 0.58–1.19), favorable neurological outcomes (OR: 0.86, 95% CI: 0.59–1.30), 30-day survival (OR: 0.76, 95% CI: 0.43–1.33), ROSC (OR: 1.04, 95% CI: 0.64–1.70). Although there was high heterogeneity for ROSC, a sensitivity analysis suggested a greater likelihood of ROSC with IV access (OR: 0.91, 95% CI: 0.84–0.99).

Conclusion: Although IV access is often the preferred route because of its potential pharmacokinetic benefits, IO access is an essential alternative when IV placement is challenging or delayed. Considering the similar survival and neurological outcomes, IO access should be promptly employed in time-sensitive resuscitation situations.

Keywords: out-of-hospital cardiac arrest, intraosseous, intravenous, drug administration, survival, meta-analysis

Introduction

Out-of-hospital cardiac arrest (OHCA) is a significant global health concern, with an estimated annual incidence ranging from 55 to 82.1 cases per 100,000 people[1,2] As a critical public health challenge, OHCA accounts for approximately 10% of global mortality and nearly half of all cardiovascular-related deaths[3] In the United States alone, more than 356,000 OHCAs occur each year, with nearly 90% resulting in death[4] The financial burden is also substantial. Thanks to advancements in emergency medical services (EMS), the survival rate for hospital admission has improved to about 27.3%[5,6] However, among those who survive the initial event, healthcare costs vary based on prognosis. An analysis of the IBM MarketScan Commercial Claims and Encounters Database revealed that, in the year following discharge, average healthcare costs were $52,746 for patients under 65 who returned home, while those requiring rehabilitation or extended hospitalization faced costs of up to $130,530[7] These figures underline the significant healthcare demands and economic impact associated with OHCA.

The primary treatment approach for OHCA follows a structured chain of survival, which includes immediate high-quality cardiopulmonary resuscitation (CPR), early defibrillation, airway management, pharmacologic intervention, and post-resuscitation care.[8] High-quality CPR, characterized by an optimal compression rate and minimal interruptions, is crucial for maintaining coronary and cerebral perfusion.[9] Early defibrillation, particularly through automated external defibrillators (AEDs), significantly improves survival in patients with shockable rhythms.[10] Airway management strategies range from basic maneuvers to advanced interventions such as supraglottic airways and endotracheal intubation, with recent evidence supporting the efficacy of supraglottic devices.[11] Pharmacologic therapy, particularly epinephrine administration, remains a standard component of advanced life support, although its impact on long-term neurological

outcomes remains debated.[12] Antiarrhythmic medications such as amiodarone and lidocaine may be utilized in cases of refractory shockable rhythms[13] Post-resuscitation care, including targeted temperature management and hemodynamic stabilization, is vital for improving neurological outcomes and long-term survival[14]

A comprehensive approach to OHCA management—integrating early recognition, rapid intervention, and post-resuscitation strategies—is essential for improving patient outcomes. Intravenous (IV) access has traditionally been the standard route for drug administration during OHCA. However, establishing IV access can be challenging in critically ill patients due to peripheral vasoconstriction and circulatory collapse. Intraosseous (IO) access offers a rapid and reliable alternative, particularly when IV access is difficult or time-consuming. Recent studies have explored the efficacy of IO versus IV access in OHCA.[15,16] Conversely, a meta-analysis suggested that IV access might be superior to IO access in improving outcomes for OHCA patients, including favorable neurological outcomes, survival to hospital discharge, and ROSC.[17] However, significant heterogeneity across studies necessitates cautious interpretation of these findings. Another randomized trial reported that an IO-first vascular access strategy did not lead to higher 30-day survival compared to an IV-first strategy.[18]

These mixed results emphasize the necessity for additional research to identify the optimal vascular access route during OHCA resuscitation. This systematic review and meta-analysis aim to synthesize current evidence from randomized controlled trials (RCTs) that compare IO and IV drug administration in OHCA. Several meta-analyses have been conducted comparing IO and IV administration using direct study designs.[19,20] However, subgroup analyses from previous RCTs comparing IO and IV routes have also provided valuable insights into the differences in their effectiveness. By assessing critical clinical outcomes, such as ROSC, survival to hospital

admission, and survival to hospital discharge, this study seeks to provide evidence-based recommendations for the best route of drug administration in cardiac arrest. These findings may provide insights that could inform future considerations in developing or refining emergency medical services (EMS) protocols, pending further high-quality evidence.

Methods

Study Design and Registration

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[21] The study protocol was registered in the Open Science Framework.[22]

Eligibility Criteria

The inclusion criteria were as follows: 1) Adults aged 18 years or older with out-of-hospital cardiac arrest; 2) RCT design; 3) Reported clinical outcomes such as mortality, return of spontaneous circulation (ROSC), and other relevant measures. The exclusion criteria were: 1) Studies in which the drug administration route was not randomized to IO or IV; 2) Subgroup analyses of previously included studies; 3) Studies with non-extractable data. There were no restrictions on the language of publication.

Search Strategy

A comprehensive literature search was conducted across PubMed, Embase, the Cochrane Library, and Web of Science from their inception until February 10, 2025. The search strategy included the keyword "cardiac arrest" to identify the patient population ("Intraosseous" AND "Intravenous") OR "Drug Route" to capture the intervention, and "randomized" OR "controlled" to specify the study design. The detailed search formula in each database was shown in Table S1. Additionally, relevant systematic reviews and reference lists of selected studies were manually screened to enhance the completeness of the literature search.

Study Selection

All identified studies were imported into EndNote 20 (Clarivate Analytics) for reference management, and duplicate records were removed. Two independent reviewers (YZ.Z. and F.T.) screened the titles and abstracts based on predefined eligibility criteria. Full-text articles of potentially relevant studies were then assessed independently. Discrepancies were resolved through discussion, and if consensus could not be reached, a third reviewer (Y.Z.) was consulted for the final decision.

Data Extraction

A standardized data extraction form was used to collect relevant information from the included studies. Extracted data included study characteristics such as author, year of publication, country, study design, and sample size. Population details, including inclusion criteria and baseline characteristics, were also recorded. Information on interventions, specifically the route of drug administration (IO versus IV), was extracted. There were no restrictions regarding the anatomical site of IO or IV access. Outcomes of interest, including ROSC, survival to hospital admission, survival to hospital discharge, and neurological outcomes, were collected. Two reviewers independently extracted the data, and any discrepancies were resolved through discussion.

Data Synthesis and Statistical Analysis

Pooled estimates were calculated using random-effects models to account for expected heterogeneity among studies. Odds Ratios (ORs) with 95% confidence intervals (CIs) were used for dichotomous outcomes, including ROSC, survival to hospital admission, survival to hospital discharge, and neurological outcomes. Heterogeneity was assessed using Cochran's Q test and the I^2 statistic, with an I^2 value greater than 50% indicating substantial heterogeneity.[23] Publication bias was evaluated using Egger's test and visual inspection of funnel plots. All statistical analyses

were conducted using R (version 4.4.1), with a p-value of less than 0.05 considered statistically significant.

Sensitivity and Subgroup Analyses

Predefined subgroup analyses were performed to explore potential sources of heterogeneity. These analyses included stratification based on the timing of drug administration, distinguishing between early and late dosing. Patient characteristics, such as age and initial cardiac rhythm, were analyzed to determine their impact on outcomes. Additionally, sensitivity analyses were conducted by excluding studies with a high risk of bias to evaluate the robustness of the overall findings.

Risk of Bias and Quality Assessment

The risk of bias in individual studies was evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool, which assesses bias across five domains: 1) the randomization process; 2) deviations from intended interventions; 3) missing outcome data; 4) measurement of the outcome, and 5) selection of the reported result. Each study was categorized as having a low risk of bias, some concerns, or a high risk of bias.[23] Additionally, the certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework.[24]

Ethical Considerations

Since this study is a systematic review and meta-analysis of previously published randomized controlled trials, ethical approval and informed consent were not required. No patient-identifiable data were used, and all included studies had received prior ethical clearance from their respective institutions.

Results

Characteristics of Included Studies

A comprehensive database search identified 559 studies. After removing duplicates and conducting two rounds of screening, 87, 430, and 36 studies were excluded, respectively. Ultimately, five RCTs were included in the final meta-analysis (Figure S1). This analysis comprised 20,002 patients from the United Kingdom, North America, Taiwan, and Denmark (Table 1). [25-30] Among them, 7,557 received IO drug administration, while 12,445 received IV access. The mean age of participants ranged from 62.4 to 69.5 years, with a male predominance across all studies. The proportion of patients who underwent bystander cardiopulmonary resuscitation (CPR) before advanced life support interventions varied considerably, with the highest rate reported in Vallentin et al. 2021 (79.3%) and the lowest in Vallentin et al. 2025 (23.4%). Automated external defibrillator (AED) use was reported in 5.6% to 11.4% of cases across the included studies, while one study did not provide information on AED usage.

Survival to Hospital Discharge

Three RCTs directly compared the efficacy of IO versus IV administration. In contrast, the other three RCTs were primarily designed to compare different medications with a placebo in OHCA, and the differences between IO and IV routes were extracted through subgroup analyses, forming the indirect comparison group (Figure 1). The pooled odds ratio (OR) for the direct comparison studies was 1.03 (95% CI: 0.87–1.22; $I^2 = 0\%$), while the pooled OR for the indirect comparison group was 0.63 (95% CI: 0.32–1.23; $I^2 = 87\%$). The overall pooled analysis of all six RCTs yielded an OR of 0.83 (95% CI: 0.58–1.19; $I^2 = 80\%$). No statistically significant difference

was observed between the direct and indirect comparison groups (p = 0.17). A sensitivity analysis, shown in Figure S2, yielded an OR of 0.95 (95% CI: 0.84–1.09; I^2 = 0%).

Favorable Neurological Outcomes

Six RCTs identified the difference in favorable neurological outcomes at hospital discharge between IO and IV administration groups (Figure 2). The pooled odds ratio (OR) for the direct comparison studies was 1.07 (95% CI: 0.88–1.31; I^2 = 0%), while the pooled OR for the indirect comparison group was 0.65 (95% CI: 0.32–1.30; I^2 = 81%). The overall pooled analysis of all six RCTs yielded an OR of 0.86 (95% CI: 0.59–1.30; I^2 = 76%). No statistically significant difference was observed between the direct and indirect comparison groups (p = 0.17). A sensitivity analysis, shown in Figure S3, yielded an OR of 0.98 (95% CI: 0.80–1.20; I^2 = 33%).

Return of Spontaneous Circulation (ROSC)

Five RCTs evaluated the difference in ROSC between IO and IV administration groups (Figure 3). The pooled OR for the direct comparison studies was 0.91 (95% CI: 0.84–0.99; I^2 = 0%), while the pooled OR for the indirect comparison group was 1.26 (95% CI: 0.26–6.19; I^2 = 97%). The overall pooled analysis of all five RCTs yielded an OR of 1.04 (95% CI: 0.64–1.70; I^2 = 93%). No statistically significant difference was observed between the direct and indirect comparison groups (p = 0.71). Due to the high heterogeneity in the indirect studies, a sensitivity analysis was performed only on the direct comparison studies, yielding the same OR as the direct subgroup analysis.

30-Day Survival

Four RCTs identified 30-day survival between the IO and IV groups (Figure S4). The pooled OR for the direct comparison studies was 1.0 (95% CI: 0.75–1.32; I^2 = 51%), while the

pooled OR for the indirect comparison group was 0.54 (95% CI: 0.19–1.50; $I^2 = 81\%$). The overall pooled analysis of all five RCTs yielded an OR of 0.76 (95% CI: 0.43–1.33; $I^2 = 87\%$). No statistically significant difference was observed between the direct and indirect comparison groups ($p = 0.26$). A sensitivity analysis, shown in Figure S5, yielded an OR of 0.99 (95% CI: 0.78–1.25; $I^2 = 2\%$).

Publication Bias and Risk of Bias

Publication bias was assessed using funnel plots (Figures S6–S9) and further evaluated with Egger's test, yielding p-values of 0.89, 0.85, 0.21, and 0.93, respectively. These results indicate no significant evidence of publication bias. The risk of bias assessment is shown in Figure S10, where three studies demonstrated a high risk of bias related to random sequence generation and allocation concealment. The certainty of evidence is summarized in Table 2, with high confidence for outcomes such as survival to hospital discharge, favorable neurological outcome, and 30-day survival, whereas ROSC was rated as having moderate certainty.

Discussion

This systematic review and meta-analysis synthesized data from RCTs to compare IO and IV drug administration in out-of-hospital cardiac arrest (OHCA). The findings indicate that IV drug administration was associated with a greater likelihood of ROSC in sensitivity analysis. However, no statistically significant differences were observed between the two routes regarding survival to hospital discharge, 30-day survival, or favorable neurological outcomes. These results align with prior research, reinforcing IV access as the preferred route.[31] Nonetheless, IO access remains a critical alternative when IV access is challenging or delayed, ensuring timely medication administration in resuscitation efforts. The certainty of evidence was rated high for survival and favorable neurological outcomes and moderate for ROSC. The consistency of these findings with previous studies highlights the importance of selecting an optimal vascular access strategy in emergency settings and offers evidence-based insights to inform clinical decision-making.

From a clinical perspective, these results underscore the importance of selecting the most effective vascular access route based on the patient's condition and the capabilities of emergency medical services. Given its potential to improve ROSC rates, IV access should remain the first-line approach. However, due to the challenges of IV placement in critically ill patients, IO access serves as a vital alternative, particularly in prehospital environments where rapid drug administration is essential.[32] The comparable survival and neurological outcomes between IO and IV routes suggest that IO access should be used without delay if IV access cannot be established quickly. Cost considerations also influence decision-making. While IV access is typically more cost-effective in well-equipped hospital environments, IO access may offer greater economic advantages in prehospital or resource-limited settings due to its reduced reliance on highly trained

personnel.[33] These findings support emergency protocols that integrate both access routes to maximize the effectiveness of advanced life support interventions.

Variations in resuscitation protocols, timing of drug administration, and patient characteristics across the included studies may have contributed to the observed heterogeneity. In addition, the effects of different IO access techniques, catheter types, and the pharmacokinetics of drugs delivered via the IO route remain insufficiently explored. [34] Although IO access sites, such as humeral, tibial, and sternal, differ in flow capacity and drug delivery kinetics, the included studies offered limited or inconsistent data on site-specific outcomes. One study focused exclusively on humeral access,[27] while others combined multiple IO sites without stratified analysis. Due to this heterogeneity and lack of detailed reporting, subgroup analyses by IO location could not be conducted. Nevertheless, pooling the available data remains valuable for identifying general trends in efficacy between IO and IV access. Given the unique physiological characteristics of intraosseous circulation, future research should investigate whether modifications to IO drug delivery, such as optimized dosing strategies, alternative formulations, or adjusted infusion rates, could improve clinical effectiveness.

Furthermore, although drug classes commonly used during cardiopulmonary resuscitation, such as catecholamines and antiarrhythmic agents, have distinct pharmacokinetic and pharmacodynamic profiles, our analysis was constrained by the available evidence. Three RCTs directly comparing IV and IO administration did not specify the medications used, while the remaining studies either lacked consistent reporting or involved non-standard interventions. Consequently, subgroup analyses based on drug class were not feasible. Future large-scale, well-designed trials should aim to evaluate the comparative effectiveness of IO versus IV access within

specific drug categories and patient subgroups, particularly in scenarios involving difficult IV access or prolonged resuscitation, to help refine guidelines and optimize outcomes.

Despite the insights gained from this meta-analysis, several limitations must be considered. Although only RCTs were included, study heterogeneity remains a concern. Differences in emergency medical service protocols, provider training levels, and patient demographics may have contributed to outcome variations. Second, while the meta-analysis included six studies, all were conducted in developed countries, raising concerns about the generalizability of the findings to a global context. Thirdly, bystander CPR and AED may have influenced the results, whereas drug administration routes might not have been the predominant treatment factor in these cases. Fourth, Data on the timing of vascular access placement and its potential effects on delayed drug administration were lacking, limiting the applicability of these findings. While publication bias was not evident, it cannot be entirely ruled out, emphasizing the need for future high-quality, multicenter trials to validate these results.

Conclusion

This systematic review and meta-analysis compared IO and IV drug administration in out-of-hospital cardiac arrest (OHCA), revealing that while IV access may improve ROSC rates, overall survival and neurological outcomes do not significantly differ between the two routes. These findings reaffirm IV access as the preferred approach but also highlight the critical role of IO access when IV placement is difficult or delayed, particularly in prehospital settings.

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Data Availability: The corresponding author will provide datasets upon reasonable request.

Ethical Statement: Institutional Review Board approval was waived due to the nature of this meta-analysis.

Conflict of Interest: The authors declare no conflicts of interest.

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Table 1: Characteristics of Enrolled Studies

Study	Country	No. of Intraosseous	No. of Intravenous	Medicine administered	Age (years)	Male (%)	CPR (%)	AED (%)
Couper 2025	UK	3030	3034	Not specified	68.1 (16.1)	3892 (64.2%)	4234 (69.8%)	489 (8.1%)
Daya 2020	North America	661	2358	Amiodarone, Lidocaine, or Placebo	62.4 (14.7)	2416 (80.0%)	1697 (56.2%)	170 (5.6%)
Ko 2024	Taiwan	741	991	Not specified	64.7 (13.4)	1234 (71.2%)	762 (44.0%)	129 (7.4%)
Nolan 2020	UK	2237	5080	Adrenaline or Placebo	66.9 (16.5)	4179 (57.1%)	4326 (59.1)	NS
Vallentin 2025	Denmark	731	748	Not specified	69.5 (14.5)	1033 (69.8%)	346 (23.4%)	168 (11.4%)
Vallentin 2021	Denmark	157	234	Calcium or Saline	68.2 (14)	277 (70.8%)	310 (79.3%)	27 (6.9%)

CPR: cardiopulmonary resuscitation, AED: automated external defibrillator, NS: not specified

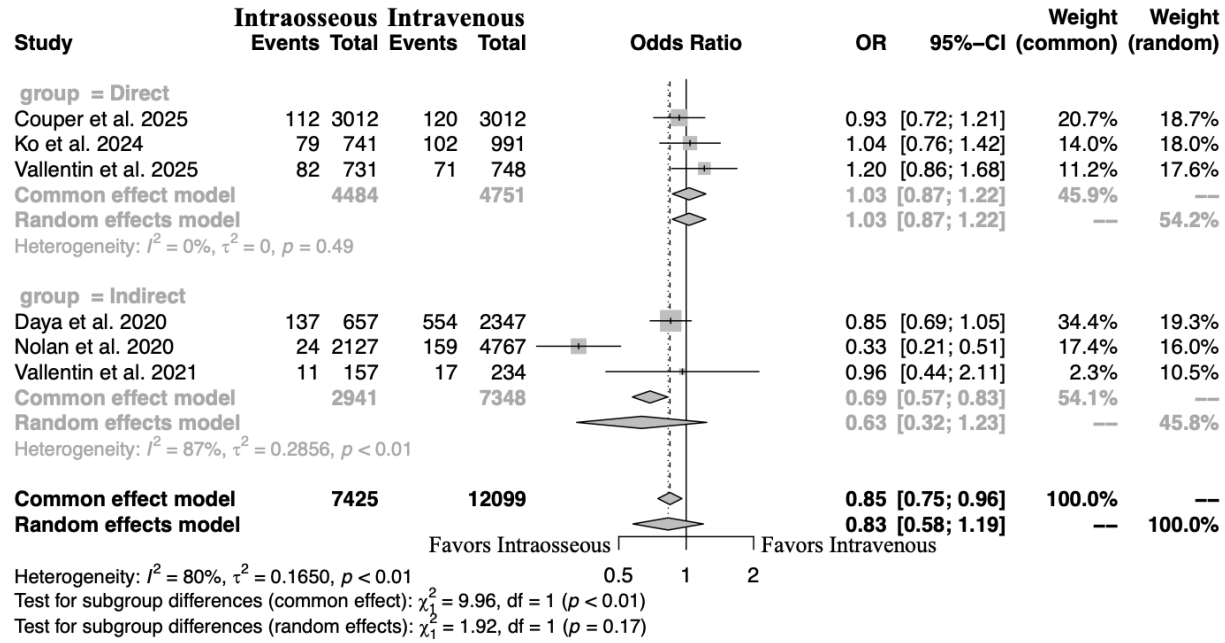
412 Table 2: Summary of Certainty of Evidence

Outcome	**Impact (Intraosseous vs Intravenous)[a]**	**No. of participants (Studies)**	**Certainty of the Evidence (GRADE)**
Survival to Discharge	OR: 0.83 (95% CI: 0.58–1.19)	19,524 (6 studies)	⊕⊕⊕⊕ High
Favorable Neurological Outcomes	OR: 0.86 (95% CI: 0.59–1.30)	19,557 (6 studies)	⊕⊕⊕⊕ High
Return of Spontaneous Circulation	OR: 1.04 (95% CI: 0.64–1.70)	16,522 (5 studies)	⊕⊕⊕⊖ Moderate
30-day survival	OR: 0.76 (95% CI: 0.43–1.33)	14,823 (4 studies)	⊕⊕⊕⊕ High

413 a: a value less than 1 favors intraosseous access; GRADE: the Grading of Recommendations,
414 Assessment, Development, and Evaluation; OR: odds ratio

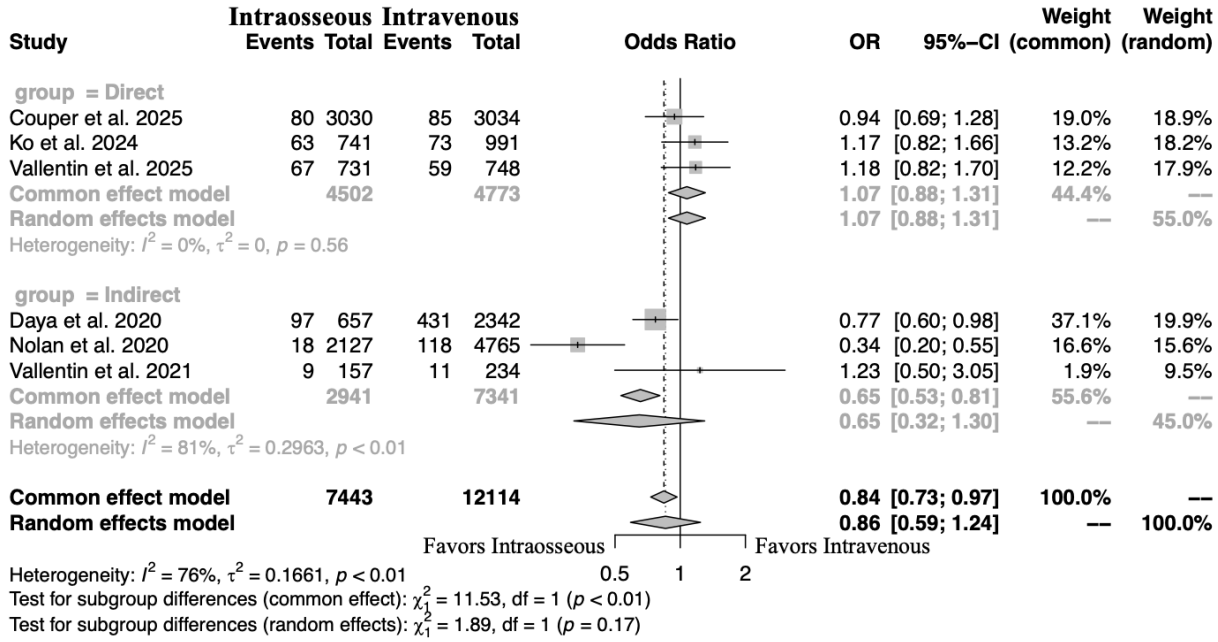
415

Figure 1. Meta-analysis of the Odds Ratio for Survival to Discharge



OR: odds ratio, CI: confidence interval

421 Figure 2. Meta-analysis of the Odds Ratio for Favorable Neurological Outcomes

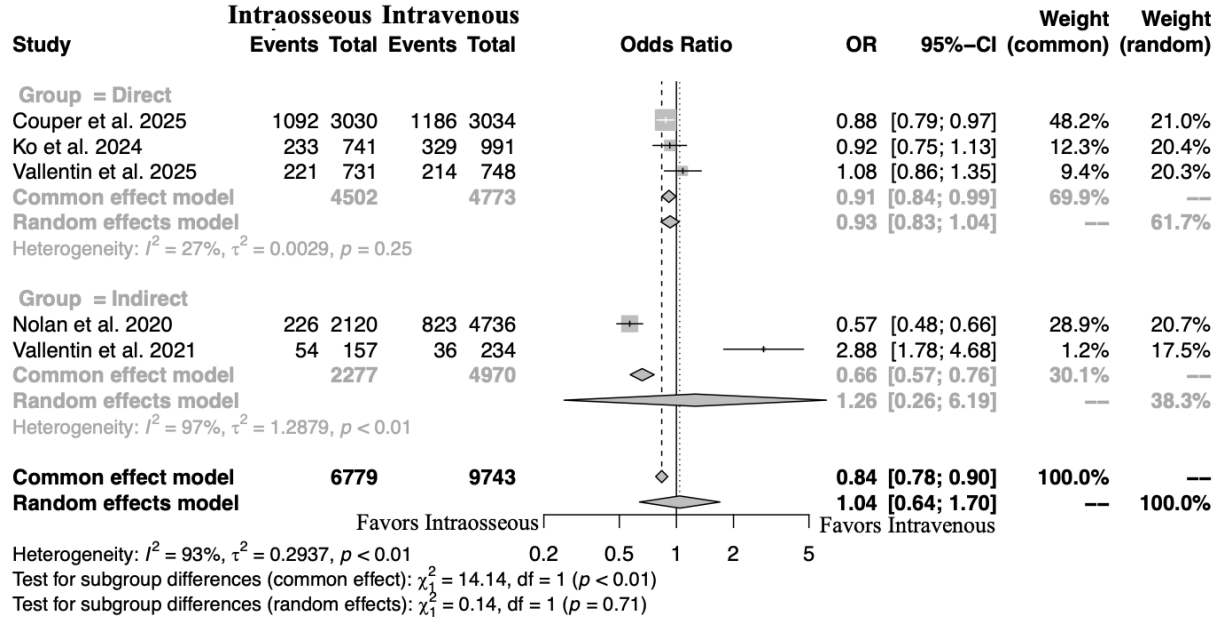


422

423 OR: odds ratio, CI: confidence interval

424

425 Figure 3. Meta-analysis of the Odds Ratio for Return of Spontaneous Circulation



426

427 OR: odds ratio, CI: confidence interval

428