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REVIEW

# Regional Citrate Anticoagulation Versus Systemic Heparin in Continuous Kidney Replacement Therapy: Examining the Role of Evidence in Health Technology Assessment

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## ABSTRACT

***Introduction***: Continuous kidney replacement therapy (CKRT) is an established treatment supporting kidney function in patients with severe acute kidney disease. Systemic heparin and regional citrate anticoagulation (RCA) are the main anticoagulation strategies to prevent dialysis filter loss due to clotting, a complication of all KRT, including CKRT. The present study aims to comprehensively compare two anticoagulation strategies by collecting available clinical and economic evidence for an adult population under CKRT through a systematic literature review and meta-analysis.

***Methods***: Randomized controlled trials, prospective/retrospective observational studies and economic analyses, involving systemic heparin or RCA, were searched through PubMed and Web of Science databases. Extracted data focused on clinical parameters, adverse events and cost items. Meta-analyses were conducted on data points with numeric outcomes to compare the two anticoagulation techniques. An evaluation of the quality of the evidence was also conducted using the GRADE system.

***Results***: Seventy-two studies were eligible for this meta-analysis. Statistically significant differences between heparin and RCA were observed in ionized calcium levels (mmol/l; heparin 1.19, RCA 1.13), bleeding events (heparin 12.6%, RCA 2.4%), filter lifespan (hours; heparin 16.43, RCA 36.69), clotting issues (heparin 50.7%, RCA 21.3%), filter failure rate (heparin 67.7%, RCA 13.5%), hypocalcemia (heparin 0.1%, RCA 4.4%) and alkalosis (heparin 0.4%, RCA 6.6%) rates. Limitations include heterogeneity across studies, particularly for RCA, and potential biases, although the overall methodological quality ranged from moderate to low.

***Conclusions***: Based on the evidence presented, despite higher rates of hypocalcemia and alkalosis, RCA demonstrates advantages over heparin, including a reduction in bleeding events, prevention of filter clotting and improvement in filter lifespan. Additionally, the cost outcome demonstrated comparable statistics depending

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on the RCA protocol considered, which supports the potential cost-effectiveness of RCA. RCA provides clear clinical and potential organizational benefits and comparable cost statistics with a reasonable level of confidence in the evidence for the economic data.

**Keywords:** Systemic heparin; Regional citrate; Anticoagulation; Systematic literature review; Meta-analyses; Clinical parameters; Costs; Economic evaluation

| Key Summary Points |
| --- |
| Kidney replacement therapy is essential for critically ill patients with severe acute kidney injury, but clotting-related filter loss can hinder treatment effectiveness and lead to complications like blood loss and transfusions |
| Systemic heparin and regional citrate anticoagulation (RCA) are standard strategies, with KDIGO AKI guidelines favoring RCA despite low evidence levels |
| A comprehensive review of clinical and economic data found RCA superior to heparin in reducing bleeding, clotting and filter failure while extending filter lifespan, though it had higher hypocalcemia and alkalosis rates that require closer clinical monitoring during treatment |
| RCA provides clear clinical benefits, but study heterogeneity limits conclusions on budget impact |

## INTRODUCTION

Acute kidney injury (AKI) is a sudden loss of kidney function, typically assessed by urine output and serum creatinine levels. It falls within the spectrum of acute kidney diseases, where prolonged dysfunction can cause irreversible kidney damage, potentially leading to chronic kidney disease (CKD) [1].

Continuous kidney replacement therapy (CKRT) is essential for supporting kidney function in critically ill patients with severe acute kidney injury. However, a major complication is the premature clotting of dialysis filters, which disrupts blood flow and filtration, reducing KRT effectiveness. This requires replacing the entire circuit, leading to lost treatment time, increased healthcare workload [2], potential blood loss and a higher risk of transfusion [3].

Historically, systemic heparin has been the preferred anticoagulant. However, its use is associated with an elevated risk of bleeding [4]. Many studies propose that regional citrate anticoagulation (RCA), an alternative to heparin, may offer a longer filter lifespan [3]. The Kidney Disease: Improving Global Outcomes (KDIGO AKI) guidelines in 2012 suggested using RCA for continuous kidney replacement therapy, but the evidence level was considered low [5]. The evidence was reinforced by subsequent publications that showed the efficacy and safety of RCA [3, 6, 7].

The effectiveness of RCA apparently stems from its ability to achieve anticoagulation within the extracorporeal circuit by chelating ionized calcium, which is needed at several crucial steps in the clotting cascade [8, 9]. Furthermore, due to its interaction with white blood cells and platelets, it might also behave as an anti-inflammatory agent [10]. Of note, calcium and calcium-citrate complexes are often lost in the effluent fluid and calcium replacement is needed [11], a process requiring close monitoring by a medical professional. The use of RCA remains limited compared to heparin [12] because of concerns about the risk of metabolic complications, the complexity of proposed protocols and the need for customized solutions. Based on these limitations, a health technology assessment (HTA) was funded by the National Institute for Health Research (NIHR) in the UK based on the setting of NHS (National Health Service) adult general intensive care units in England and Wales. The authors of the report stated that the introduction of RCA does not improve patients' outcomes and is likely linked to a substantial increase in costs [13]. However, the conclusions of the NIHR report combine data elements of several partly small observational studies, limiting the breadth of its foundation and the strength of its conclusions [14].

The study aimed to compare systemic heparin and RCA anticoagulation strategies by reviewing all available clinical and economic evidence. It focused on the challenges and solutions in evidence collection, highlighting the importance of incorporating both experimental and real-world data. The goal was to emphasize the need for a comprehensive understanding of the type, quantity and quality of evidence necessary to support healthcare decision-making. This discussion is particularly relevant to the effectiveness of experimental data in conjunction with real-world data, especially when experimental data face challenges such as learning curve issues, influential hospital processes and incremental innovation [15].

# METHODS

All available data on the two anticoagulation methods were systematically collected through a literature review within the study's scope. Following data collection, parameters with sufficient quantitative data for an accurate comparison underwent investigation through meta-analyses. Economic data were subsequently collected and analyzed in a separate step.

## Systematic Literature Review

A systematic literature review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria [16]. This study was designed using the PICO (Population, Intervention, Comparator and Outcomes) framework to ensure a structured and comprehensive comparison of anticoagulation strategies. The *Population* consisted of adult patients with acute kidney failure undergoing CKRT. The *Intervention* was RCA, while the *Comparator* was systemic heparin anticoagulation. Selected study *Outcomes*, chosen in consultation with a clinician for their relevance in comparing the two anticoagulation methods, were: bicarbonate levels, magnesium levels, systemic ionized calcium levels, citrate accumulation episodes, hypocalcemia rate, hypercalcemia rate, alkalosis rate, acidosis rate, bleeding episodes, filter clotting events, filter failure, filter lifespan, transfusion volume, % of patients transfused, length of stay in ICU, length of stay in hospital, hospital mortality, ICU mortality, 28-day mortality, 30-day mortality, 90-day mortality and cost data. The study aimed to synthesize both clinical and economic evidence to support informed decision-making in CKRT anticoagulation strategies.

Studies from the year 2000 onward were considered to exclude older techniques and procedures. The review included randomized controlled trials, prospective or retrospective observational studies, and economic analyses. Exclusions comprised studies with fewer than five participants, articles in languages other than English and those related to specific populations outside the scope of this research. Notably, pediatric studies were removed. COVID population studies, prevalent in recent publications, were excluded to mitigate potential biases towards unfavorable outcomes in KRT [17, 18]. Studies comparing dosages of anticoagulants or attempting to combine both into the same protocol were excluded from the review as a direct and accurate comparison was essential. A detailed research protocol was formulated for the study and registered in PROSPERO, the international prospective register of systematic reviews (ID CRD42023396091).

Studies were selected from two databases, PubMed and Web of Science, using the same query initiated on January 19, 2023:

> ("renal replacement therapy" OR "rrt" OR "crrt" OR "kidney replacement therapy" OR "krt" OR "ckrt" OR dialysis OR hemodialysis OR haemodialysis OR "vvhd" OR "cvvhd" OR hemofiltration OR haemofiltration OR hemodiafiltration OR haemodiafiltration OR "vvhdf" OR "cvvhdf") AND "anticoagulation" AND (Citrate OR "systemic heparin").

Duplications across the two databases were eliminated using RefWorks, followed by a manual double-check to ensure accuracy, as minor format variations can sometimes result in undetected duplicates.

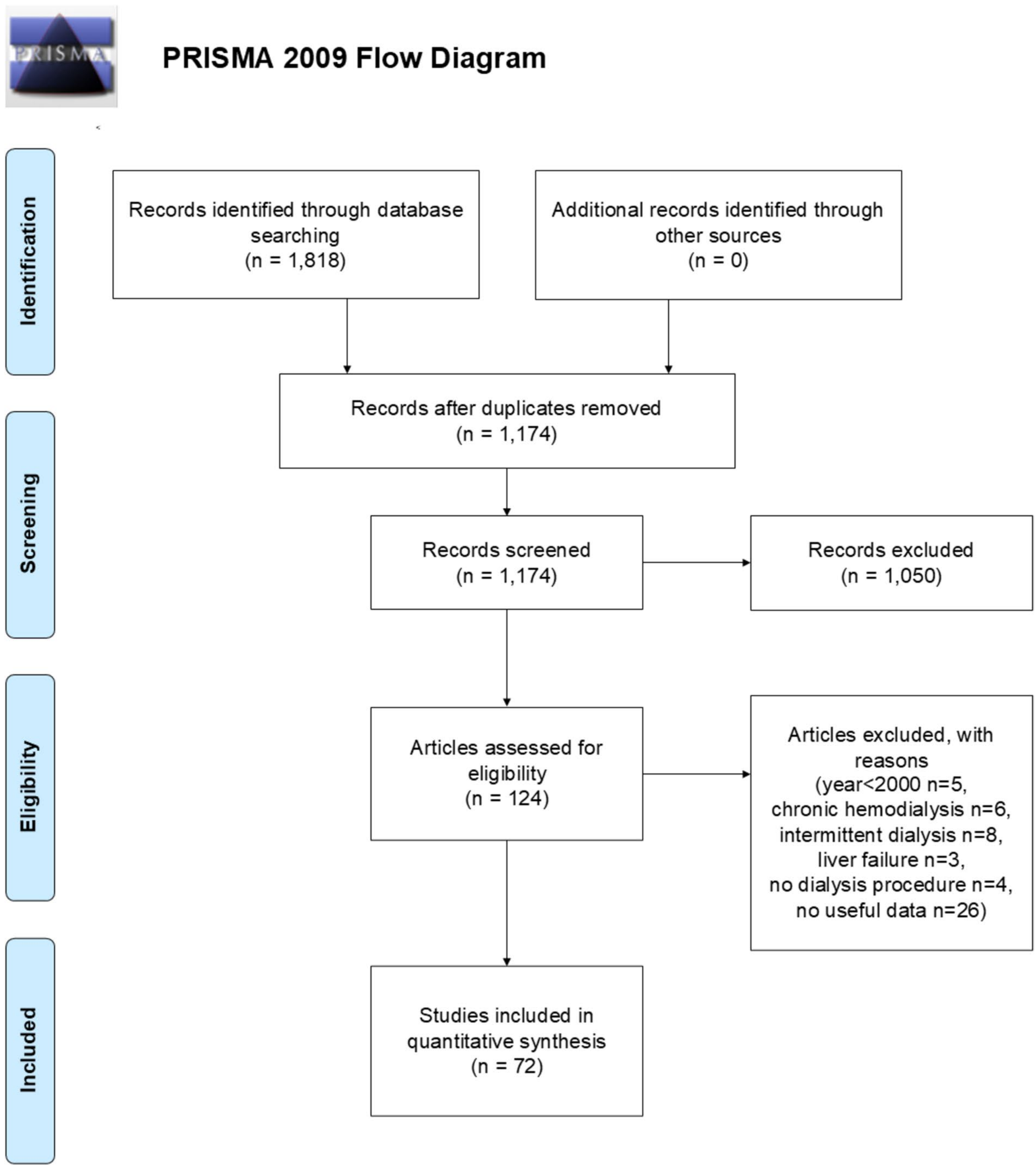



**Fig. 1** PRISMA diagram

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## Data Extraction

The data were extracted into an Excel file, including the country/countries, study type

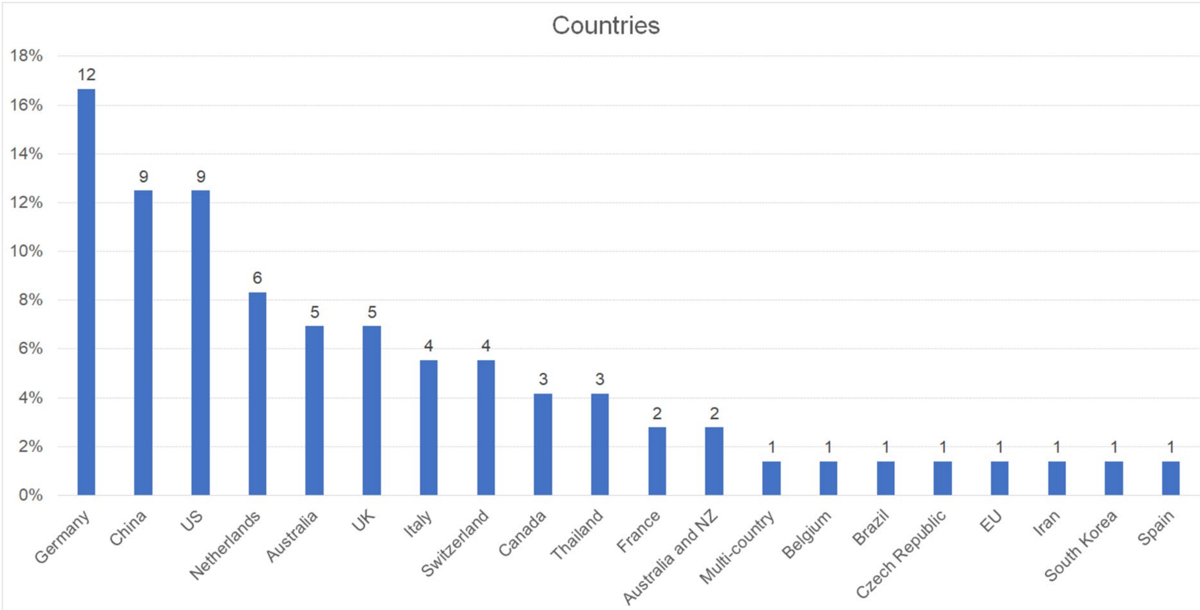



**Fig. 2** Distribution of studies by country

(RCT, observational, or other), number of patients, hospital department (e.g., Intensive Care Unit—ICU) and assessed risk of bleeding. Additionally, the type of heparin used in the study was recorded when available, enabling a more nuanced comparison. Given the lack of significant differences in anticoagulation results among different types of heparin [19, 20], they have been collectively grouped under the term "heparin anticoagulation."

For continuous variables, the standard deviation (SD) was needed to conduct a meta-analysis. While some studies reported this value directly, others provided only the

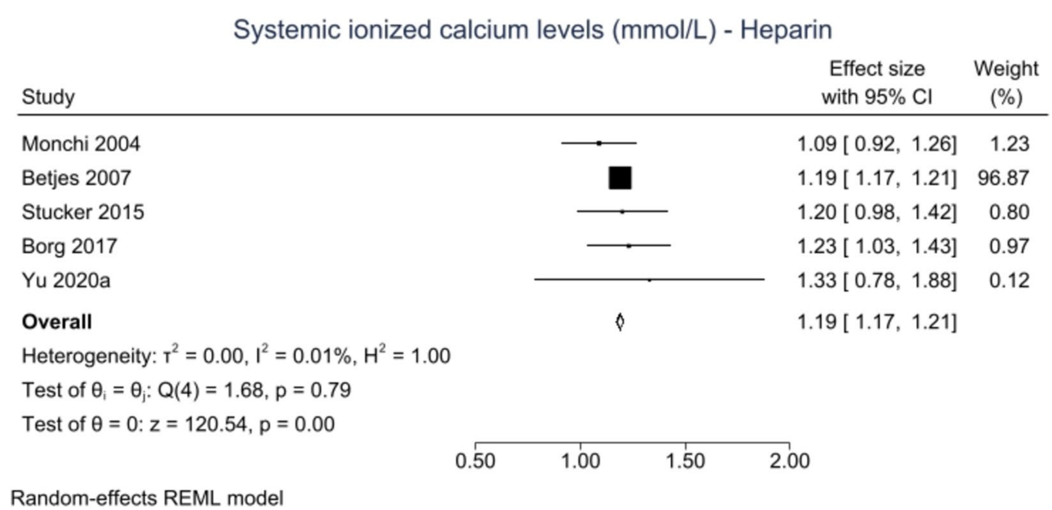



**Fig. 3** Forest plots for heparin and regional citrate anticoagulation (RCA) ionized calcium levels (*95% CI* 95% confidence interval)

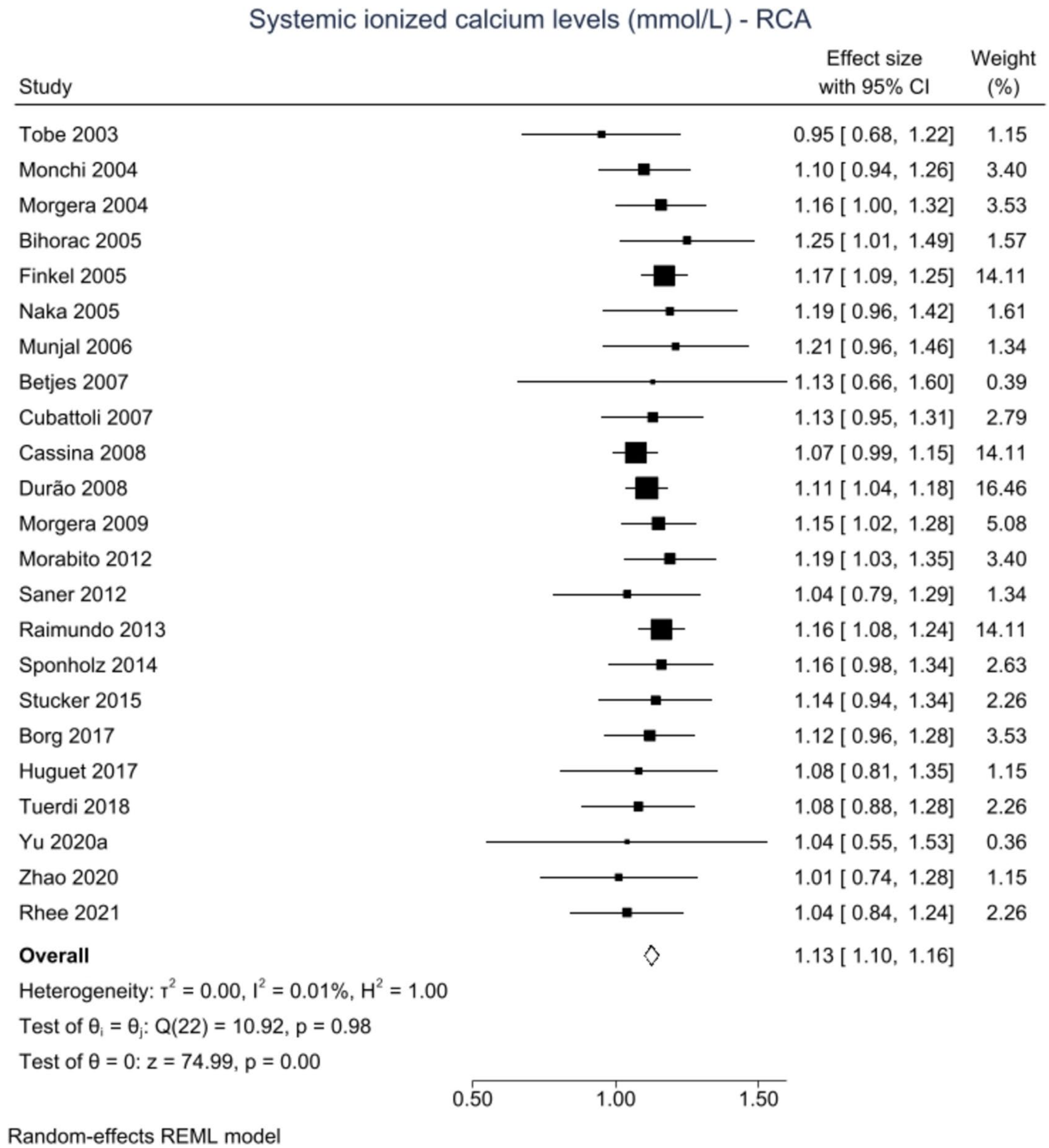



**Fig. 3** continued

interquartile range, 95% confidence interval or range (minimum-maximum). Therefore, conversion was necessary to estimate the SD [21]. For a 95% confidence interval, the formula $SD = \sqrt{N} \times \frac{Upper\ limit - Lower\ limit}{3.92}$ was applied where $N$ is the number of patients in the study, while for the IQR, the formula was: $SD = \frac{IQR}{1.35}$, and for the range, the formula was: $SD = \frac{Range}{4}$.

For the economic analysis, cost and economic impact data were collected from the retrieved papers to analyze the costs of different anticoagulation methods across various settings. To ensure comparative consistency, monetary amounts were converted to euros using the exchange rate on January 1 of the publication year [22] and adjusted for inflation as of January 1, 2023 [23]. Common metrics, such as cost per day, were used, given that costs per hour or per day were the most frequently reported outcomes. Non-monetary outcomes, such as quality-adjusted life years (QALYs), were also considered for comparison.

### Statistical Analyses

Meta-analyses were conducted on data points with numeric outcomes to compare the two anticoagulation techniques. Studies involving systemic heparin and RCA were analyzed separately to consider all available evidence, including both comparative and single-arm studies. The analysis followed the Cochrane Guidelines for Systematic Reviews [24]. STATA statistical software was used to conduct the meta-analyses using the standard package "meta." Throughout the study, the analysis was conducted using a random effects maximum likelihood model for all parameters. The results are shown graphically using a forest plot, which shows the effect size (ES) of each study with the corresponding 95% confidence interval (95% CI), the overall ES of all selected studies and the degree of heterogeneity across them (quantified using the $I^2$ metric: the higher the value, from 0 to 100%, the larger the heterogeneity). To compare outcome values between anticoagulation groups and assess statistical significance, the confidence intervals for each group were compared. If the intervals

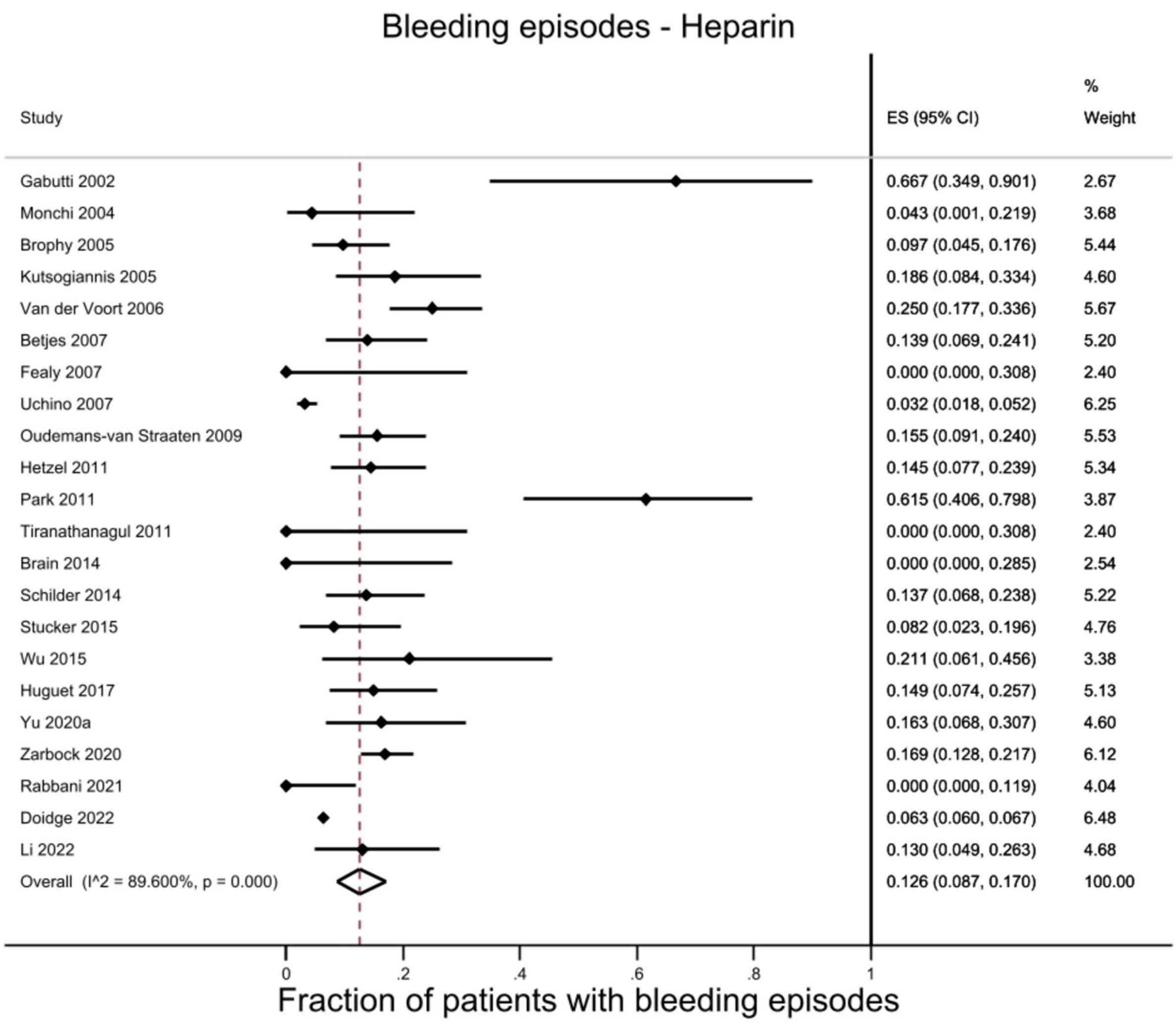



**Fig. 4** Forest plots for heparin and regional citrate anticoagulation (RCA) bleeding episodes (*ES* effect size, *95% CI* 95% confidence interval)

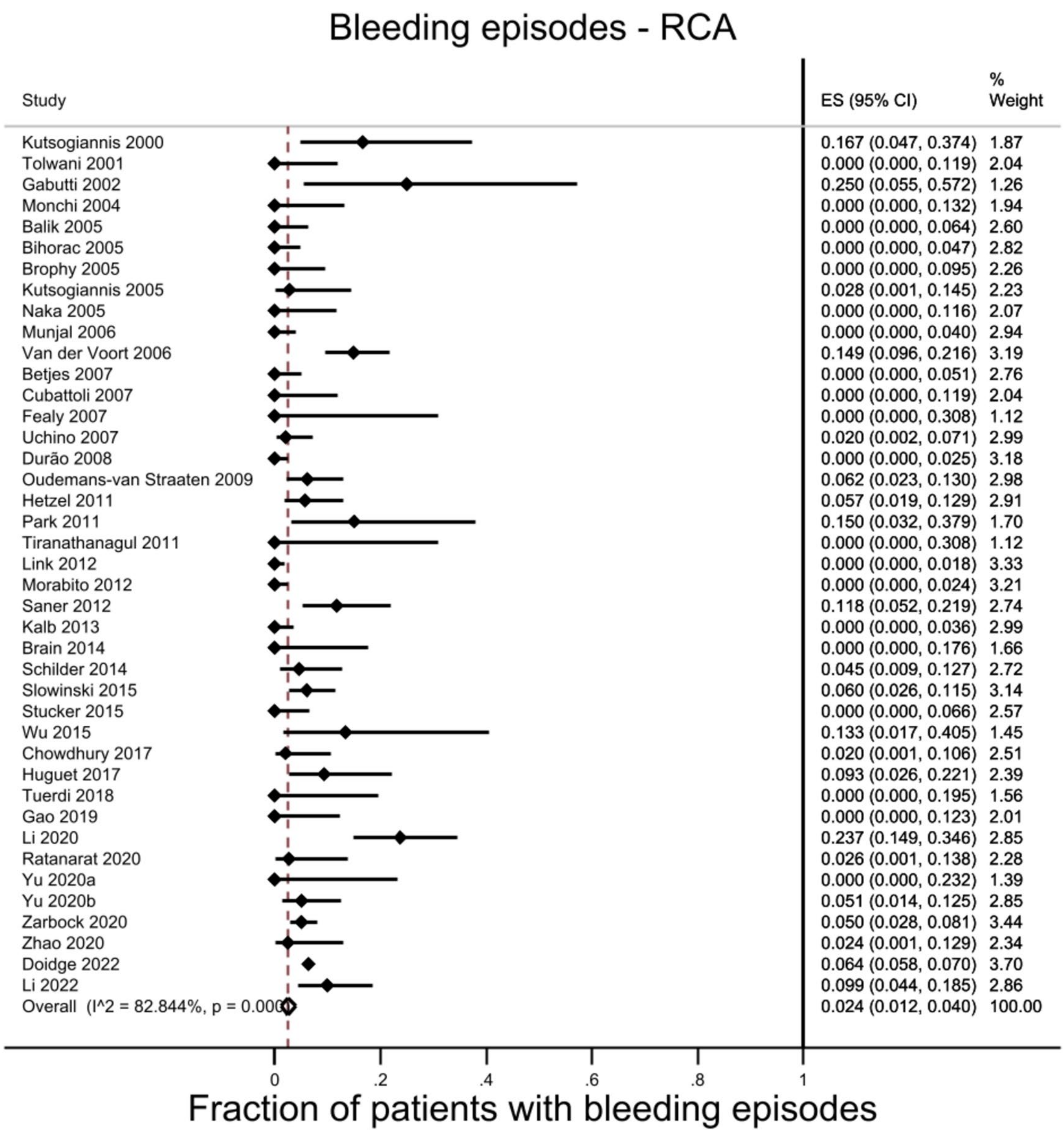



**Fig. 4** continued

overlapped, no statistically significant difference was conservatively assumed; however, if they did not overlap, a statistically significant difference between population means was considered [25].

Subgroup analyses were conducted on studies involving patients at high risk of bleeding. This assessment aimed to evaluate the performance of different populations concerning the two anticoagulation methods, providing insights for future decision-making.

## Quality of Evidence Assessment

The studies included in the meta-analyses underwent an appraisal to assess methodological quality and potential biases in their design, conduct and analysis. All papers chosen for the systematic review were evaluated using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) system [26, 27]. It is widely adopted by organizations such as WHO, Cochrane and NICE to ensure transparency and consistency in evidence-based decision-making. GRADE categorizes evidence into four levels—high, moderate, low and very low—based on study design and methodological rigor. While randomized controlled trials (RCTs)

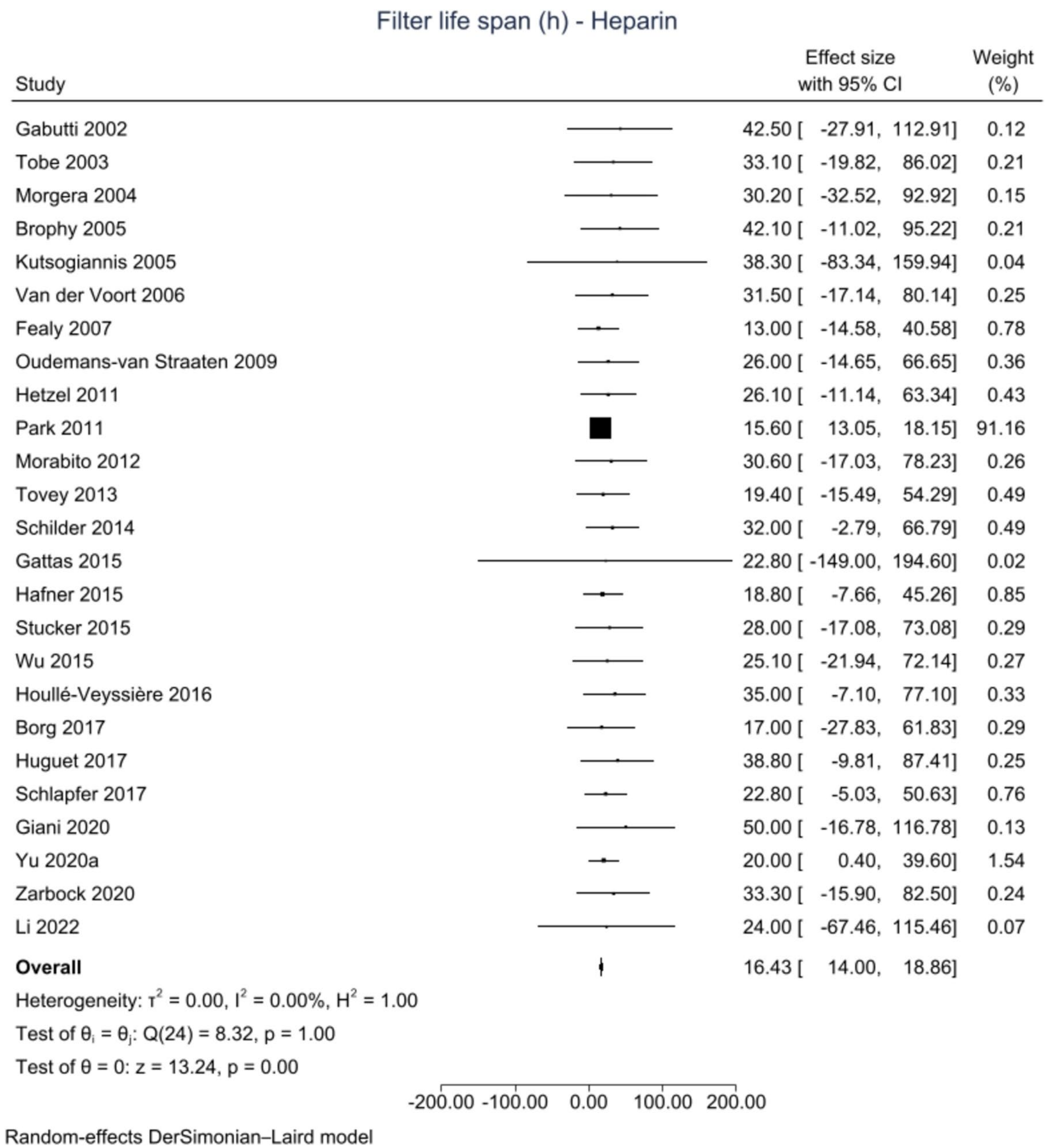



**Fig. 5** Forest plots for heparin and regional citrate anticoagulation (RCA) filter lifespan (*h* hours) (*95% CI* 95% confidence interval)

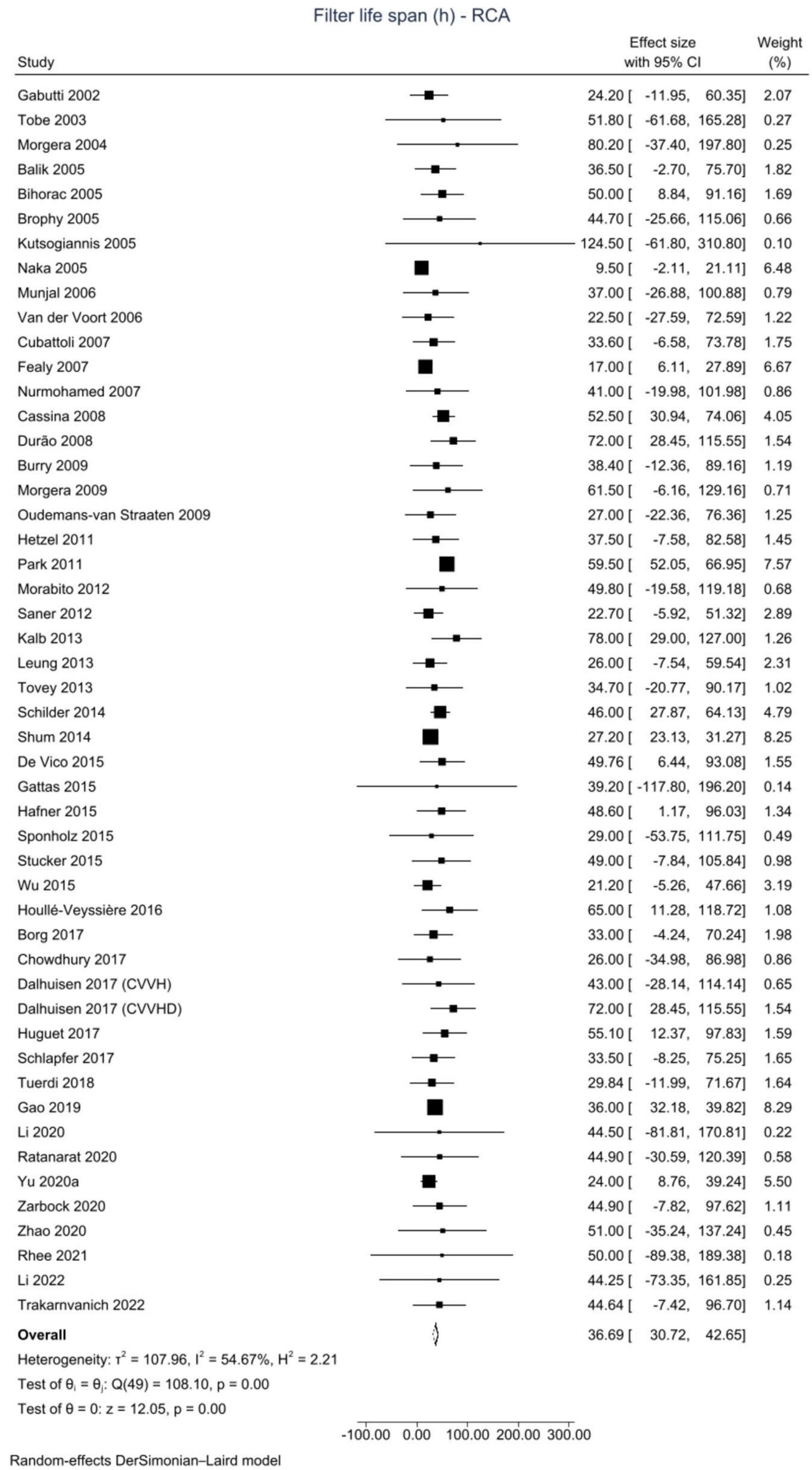



**Fig. 5** continued

typically start as high-quality evidence, observational studies begin as low quality but can be upgraded if they demonstrate a large effect size, a dose-response relationship or minimal bias. Conversely, evidence may be downgraded because of risk of bias, inconsistency, indirectness, imprecision or publication bias. Publication bias can be assessed through a funnel plot, which is a graphical meta-analysis tool used to assess by plotting study effect sizes against their precision. Symmetry in the funnel plot suggests an absence of publication bias, while asymmetry may indicate selective reporting or other reporting biases. While visually informative, funnel plots require complementary statistical analysis to draw definitive conclusions about potential systematic biases in research evidence. A formal statistical test (Egger's test) was perfomed to quantify the degree of asymmetry. A $p$-value < 0.05 suggests significant funnel plot asymmetry and potential publication bias.

GRADE also differentiates between strong recommendations, which indicate clear benefits outweighing risks, and conditional recommendations, where uncertainty exists or decisions should be individualized. By systematically evaluating evidence, GRADE provides a reliable framework for developing clinical guidelines, systematic reviews and healthcare policies.

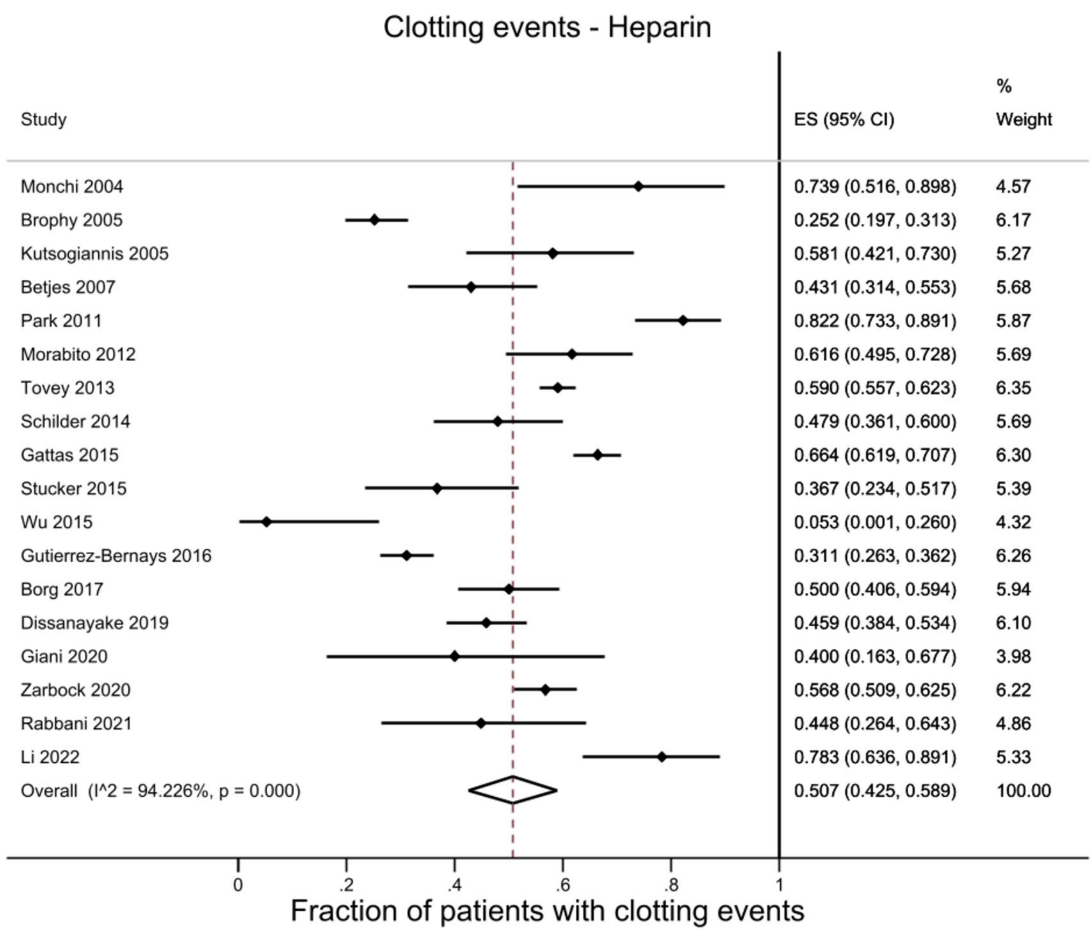



**Fig. 6** Forest plots for heparin and regional citrate anticoagulation (RCA) clotting issues (*ES* effect size, *95% CI* 95% confidence interval)

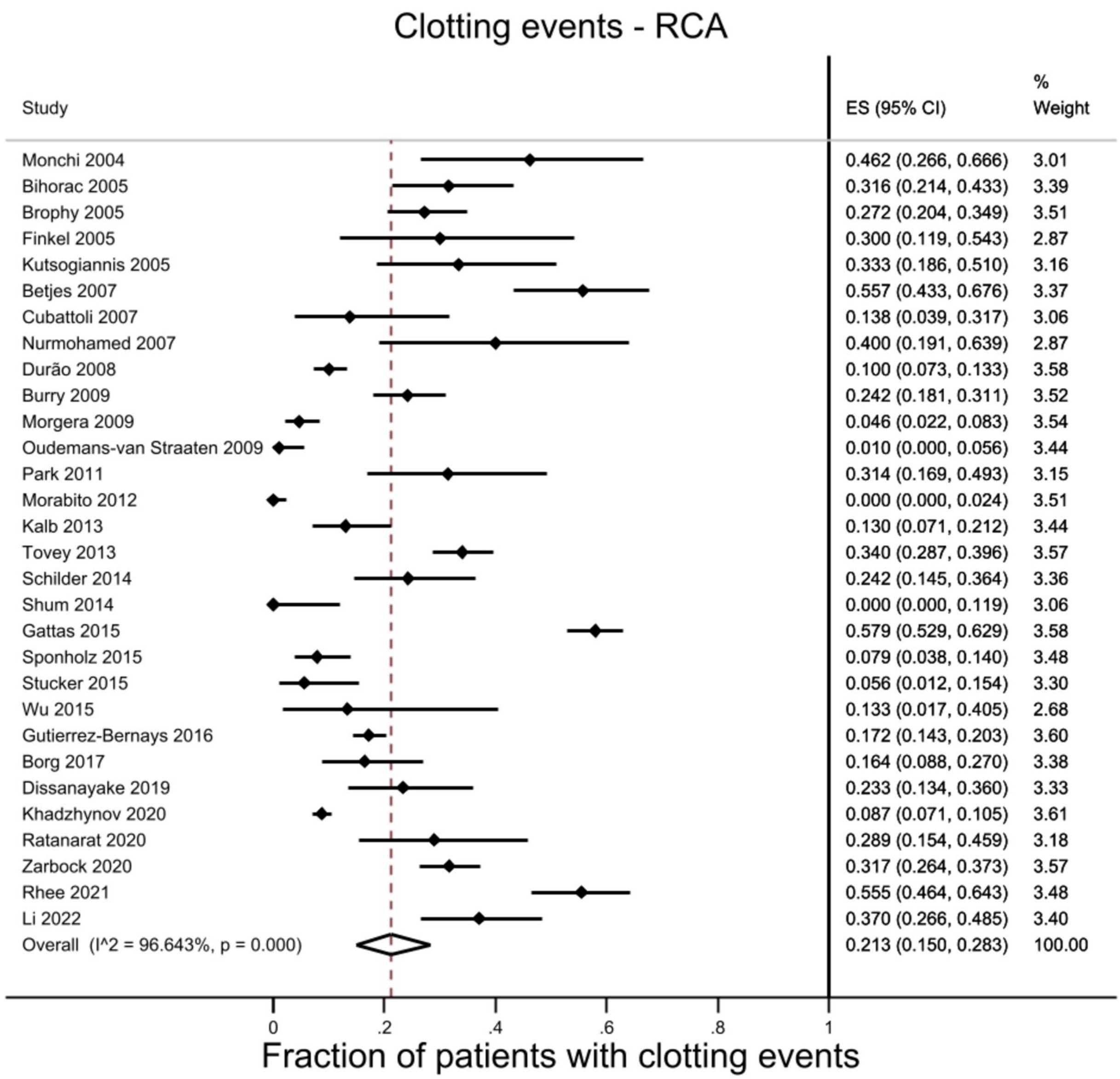



**Fig. 6** continued

# RESULTS

The screening process is outlined in Fig. 1. A total of 1818 studies were retrieved from PubMed and Web of Science databases. After removing 644 duplicates, the remaining 1174 articles were screened by title and abstract to determine their relevance to the study's scope. Of these, 124 papers were deemed relevant and subjected to a full read. Ultimately, 72 papers [3, 14, 28–97] were included in the final analysis.

Looking at the breakdown of the origin of the papers in this study, a pattern starts to emerge. Authors from Germany, China and the US have published the most studies on this subject. Furthermore, Fig. 2 highlights a notable absence of contributions from developing countries among the selected papers.

Examining the distribution of studies on different anticoagulation strategies, a significant majority involve RCA alone ($N=35$, 48.7%) or compared heparin ($N=35$, 48.7%). Only a minimal proportion ($N=2$, 2.6%) focus solely on heparin. An analysis of study types reveals a predominant number of prospective studies ($N=55$, 76%) compared to a smaller proportion of RCTs ($N=17$, 24%). The limited number of RCTs can be attributed to challenges in executing and obtaining permissions for such trials, particularly in the context of studies conducted in ICUs. The following section reports the results of the meta-analyses for clinical parameters that exhibit statistically significant differences between heparin and regional citrate anticoagulation.

### Ionized Calcium Levels

This parameter refers to prefilter $iCa^{2+}$ (mmol/l) ionized calcium levels (mean) when available or (mean) systemic ionized calcium (mmol/l) during citrate anticoagulation.

The ionized calcium levels (Fig. 3) show statistically significant differences, with mean values of 1.19 and 1.13 mmol/l for heparin and RCA, respectively. However, this difference does not suggest a clinically relevant difference regarding the patient's condition as the recommended range for ionized calcium in patients is 1.10–1.30 mmol/l [98]. Heterogeneity across studies was higher for RCA compared to heparin, partly attributable to differences in the RCA protocol design, e.g., the respective guidance for adjusting calcium substitution.

### Bleeding Episodes

Heparin exhibits a significantly higher incidence of bleeding (12.6%) compared to its RCA counterparts (2.4%) (Fig. 4). This not only raises costs associated with bleeding for the management of the patients and for the healthcare personnel but also amplifies treatment complexity, potentially leading to anemia or other complications from the bleeding event. Heterogeneity across studies was high for both anticoagulation strategies, likely because of using different definitions and varying levels of attention in documenting each bleeding episode.

### Filter Lifespan

The filter lifespan comparison between heparin and RCA is statistically significant, with the heparin upper bound for the confidence interval being 18.86 h, while the lower bound for the confidence interval of RCA filter life is 30.72 h (Fig. 5). This significant difference is underscored by an average filter lifespan approximately 2.2 times longer for RCA (36.69 vs. 16.43 h). These results indicate the significantly better performance of RCA, ensuring prolonged functionality of dialysis filters, thereby reducing downtime and potentially lowering the overall cost of treatment. Heterogeneity across studies was higher for RCA compared to heparin, probably because of the differences in protocols used.

### Clotting Issues

The comparison of filter/circuit clotting issues reveals a significant increase in clotting problems with the heparin anticoagulation method; heparin's lower bound is 0.425, while the upper bound of RCA is 0.283 (Fig. 6). The difference between the averages of the two methods is about 30%, indicating that patients receiving heparin are more likely to experience clotting issues during CKRT. This apparently is a contributing factor to the significantly lower dialysis filter lifespan of heparin, as clotting is often a leading cause of filter failure or change. Heterogeneity across studies was high for both RCA and heparin.

### Filter Failure

The graphs in Fig. 7 suggest that heparin anticoagulation experiences significantly higher

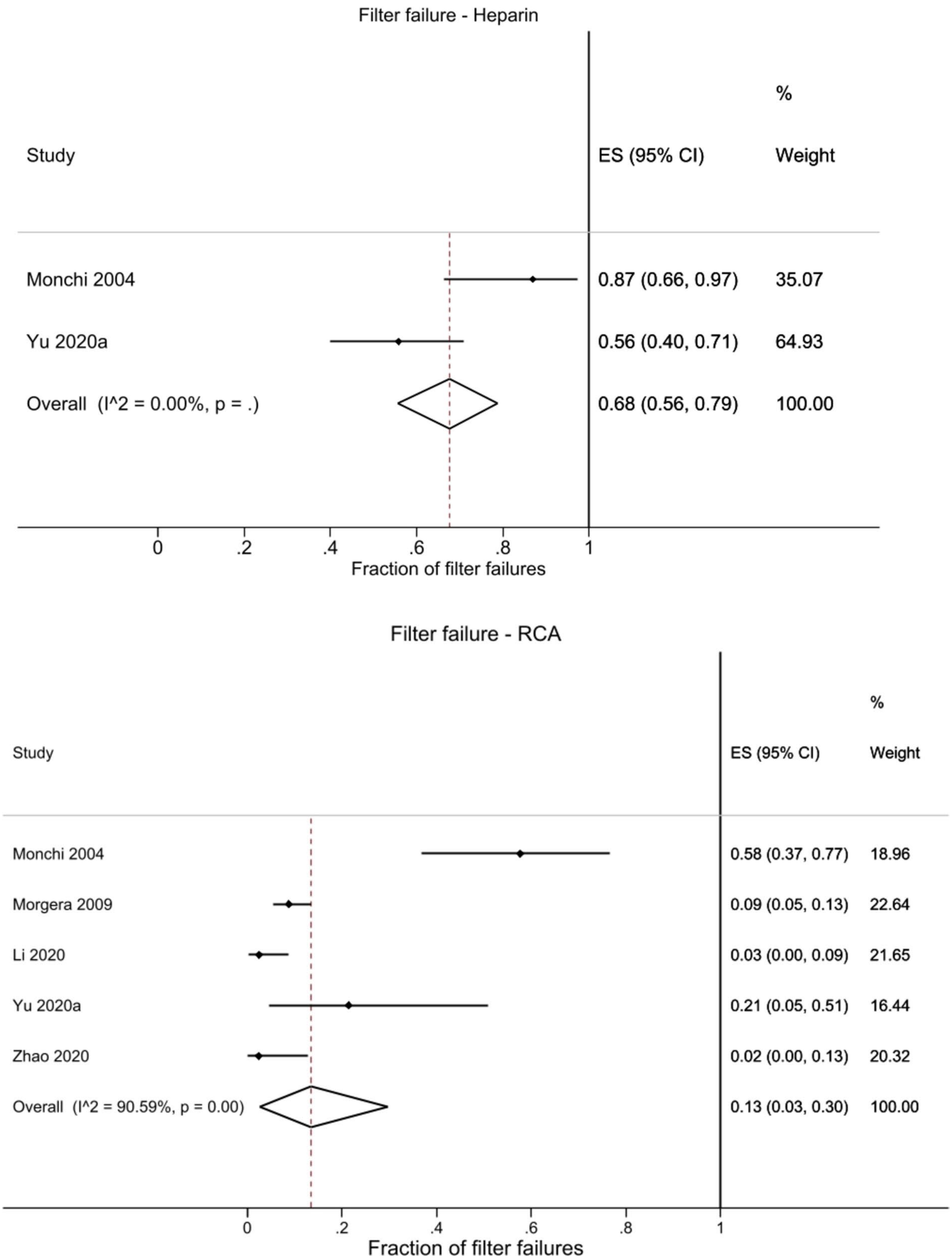



**Fig. 7** Forest plots for heparin and regional citrate anticoagulation (RCA) filter failures (*ES* effect size, *95% CI* 95% confidence interval)

levels of filter failure compared to RCA (67.7% versus 13.5%). Although there is a reported 55% difference, notably, only two studies contribute to heparin results, potentially introducing bias. However, both studies, while presenting both anticoagulation methods, consistently report a higher incidence of filter failure for heparin. While the definition of failure is broad and overlaps with filter/circuit clotting, these findings contribute to the understanding of the challenges associated with implementing heparin procedures, including increased downtime and filter replacement costs. Heterogeneity across studies was higher for RCA compared to heparin.

## Hypocalcemia Rate

Hypocalcemia is reported to be significantly more common in patients receiving RCA for their treatment (4.4% vs. 0.1%) (Fig. 8). This calcium deficiency aligns with the above results on ionized calcium levels, indicating significantly lower levels for patients receiving RCA. These results indicate that calcium levels may pose a complication for RCA in CKRT, possibly necessitating more frequent monitoring and increasing treatment costs. Heterogeneity across studies was higher for RCA compared to heparin, likely because of differences in the protocols applied.

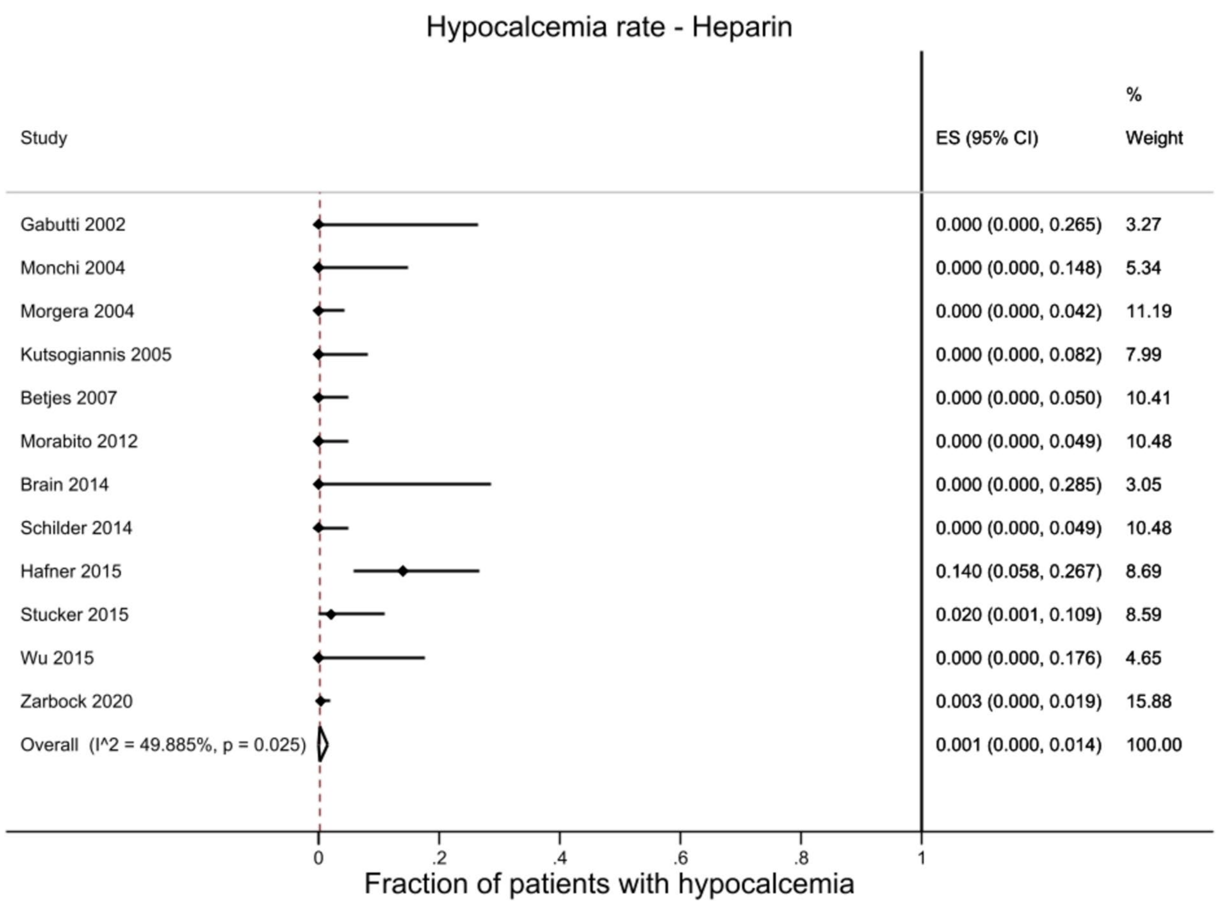



**Fig. 8** Forest plots for heparin and regional citrate anticoagulation (RCA) hypocalcemia rates (*ES* effect size, *95% CI* 95% confidence interval)

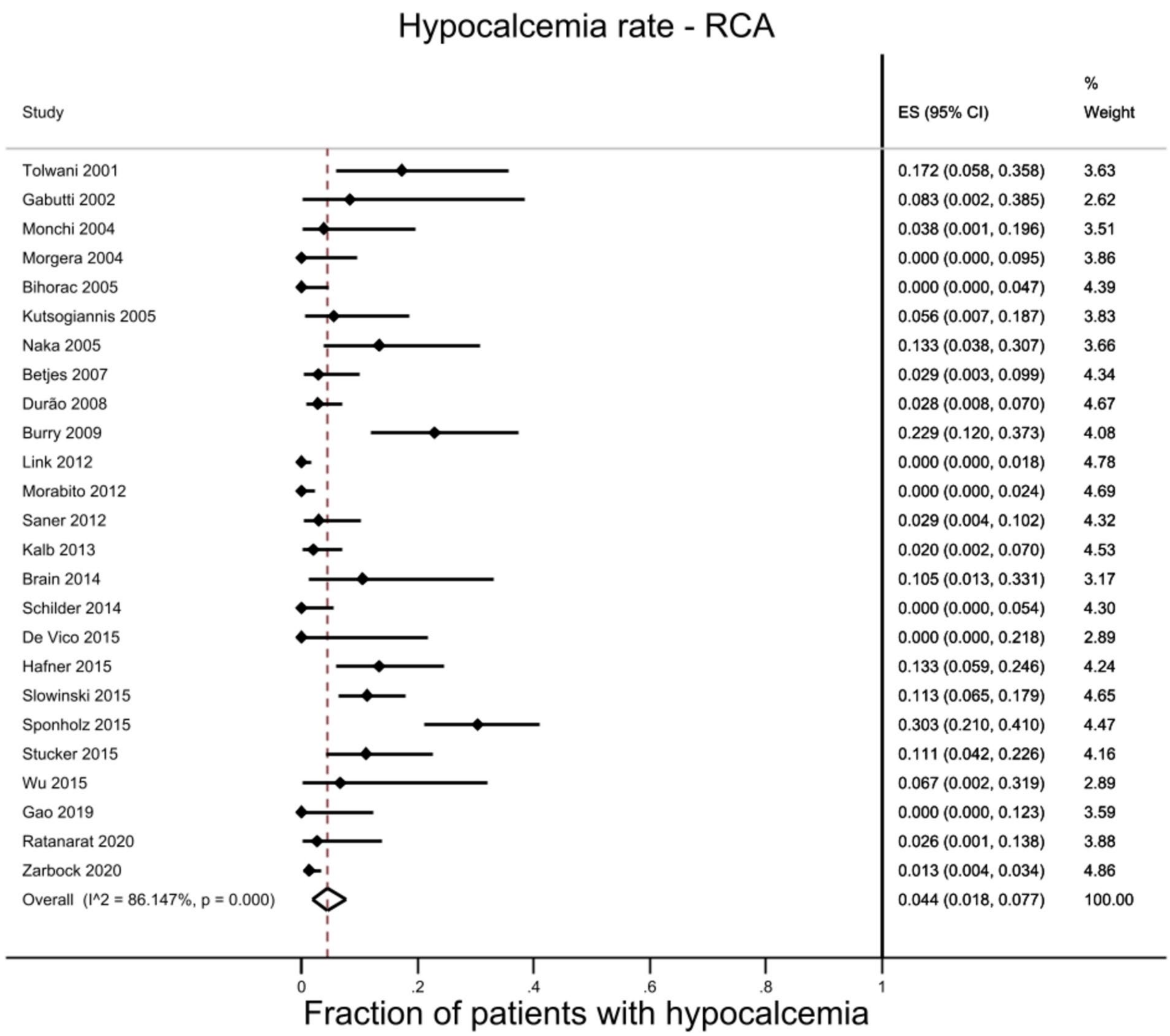



**Fig. 8** continued

## Alkalosis Rate

Alkalosis showed significantly higher rates for RCA compared to heparin (6.6% vs. 0.4%) (Fig. 9). This suggests a notable difference in the metabolic impact of the two anticoagulation methods. Additionally, heterogeneity among the studies was particularly high for RCA, likely because of variations in RCA protocols, including differences in citrate dosing, calcium supplementation and patient management strategies. These discrepancies may have contributed to the inconsistent findings across studies, highlighting the need for standardized RCA protocols to improve comparability and reduce variability in outcomes.

## Citrate Accumulation

Citrate accumulation occurs when the body is unable to effectively metabolize the citrate used in RCA, typically during CKRT. Under normal conditions, citrate is metabolized in tissues rich in mitochondria, such as liver, skeletal muscles and kidney, whereby it is converted into bicarbonate [56]. However, in patients with impaired liver function or severe illness, citrate metabolism may be reduced, leading to its accumulation. Monitoring ionized calcium levels and adjusting citrate infusion accordingly is essential to prevent toxicity and maintain metabolic balance. For the selection of patients with citrate accumulation, we referred to the following criterion: total Ca/iCa$^{2+}$ (ion) > 2.5. Overall, citrate accumulation involved a low percentage of patients (1.6%) (Fig. 10). The high heterogeneity across studies might reflect selection bias, e.g., most severely ill patients are in general excluded from RCTs [3], or the broad definitions used in reporting this issues [34].

## Other Parameters

Some variables showed a small difference that did not reach statistical significance. However, for completeness, they are presented in Table 1 to provide a full picture of our results.

While these results did not reach statistical significance, some interesting patterns emerged. Heparin seems associated with worse outcomes in terms of hospital length of stay and percent of transfused patients, while complications like acidosis appear to be more prevalent with RCA. Mortality shows overlapping outcomes, confirming that a reduction in mortality does not seem a realistic target of the anticoagulation strategies. Of note, only a few of studies were RCTs, while the rest were prospective studies, and possible

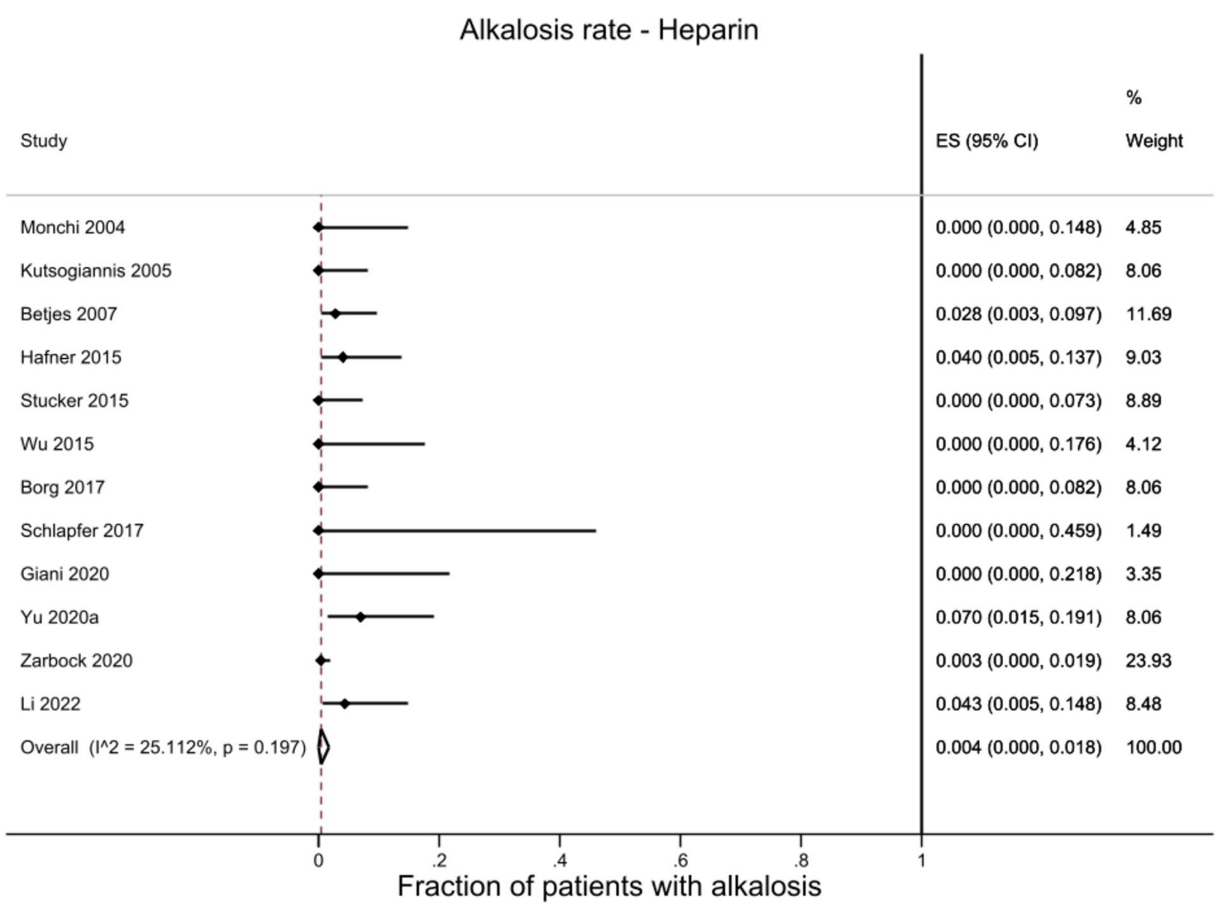



**Fig. 9** Forest plots for heparin and regional citrate anticoagulation (RCA) alkalosis rates (*ES* effect size, *95% CI* 95% confidence interval)

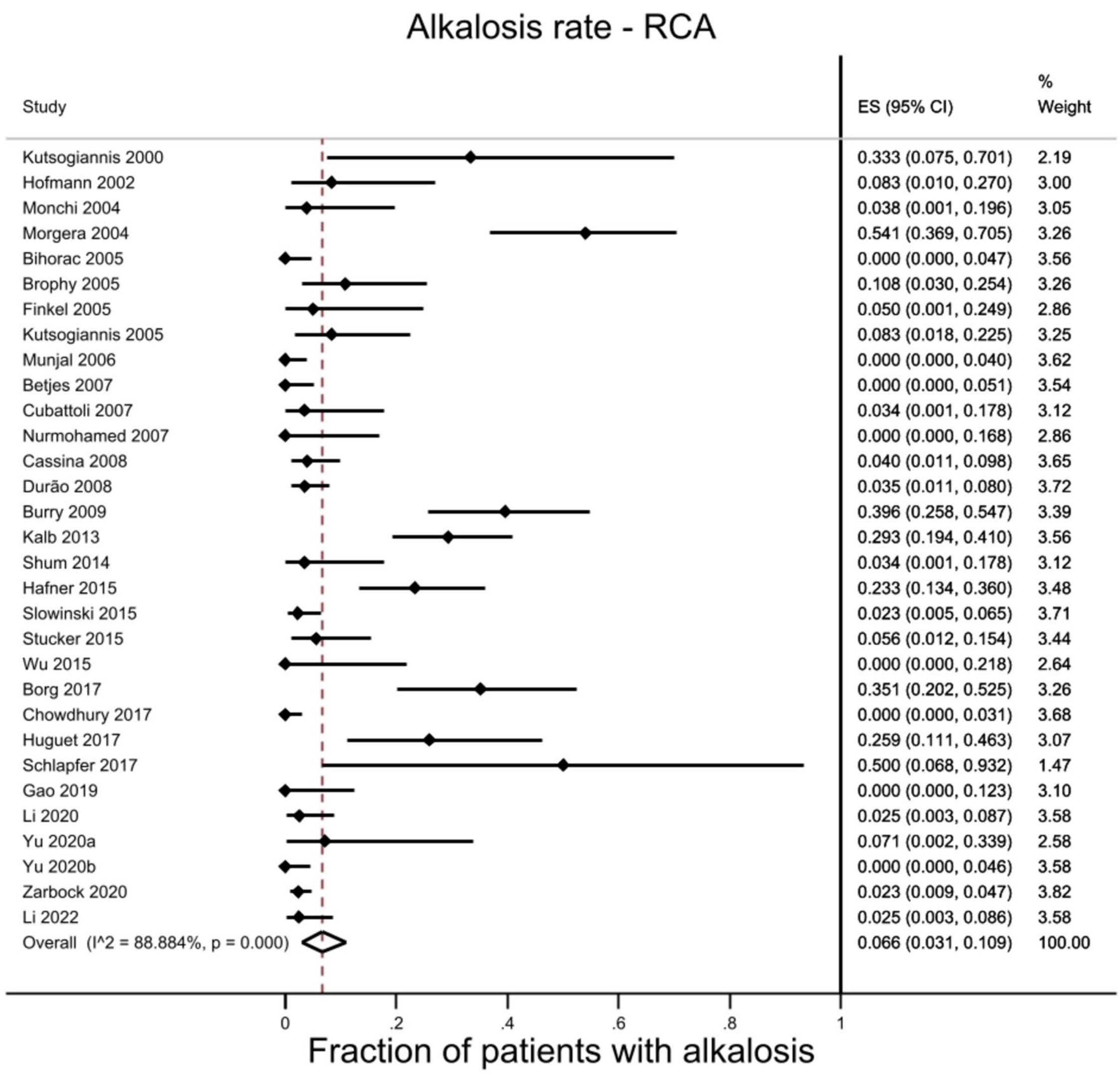



**Fig. 9** continued

allocation biases might have occurred, like the management of more severely ill patients (e.g., with multiorgan failure) with this anticoagulation option.

### Subgroup Analysis: Patients at High Risk of Bleeding

Of the 72 retrieved papers, 15 (21%) were focused on patients at high risk of bleeding. The definition varied across studies, considering patients with a definite site of gross bleeding and a drop in mean arterial pressure of at least 10 mmHg, need for transfusion within 24 h, decrease in hemoglobin of ≧ 20 g/l or failure of hemoglobin increase after RBC transfusion [89], or patients with coagulation abnormalities, thrombocytopenia, portal hypertension, or esophageal and gastric fundus venous hemorrhage [91]. Hence, there is a slight imbalance in the numbers, but this still gives high-level oversight of the potential differences between this subgroup compared to the overall population. For brevity, only statistically significant results are shown here.

Heparin shows a significantly higher incidence of bleeding (25%) than RCA (2%) in the

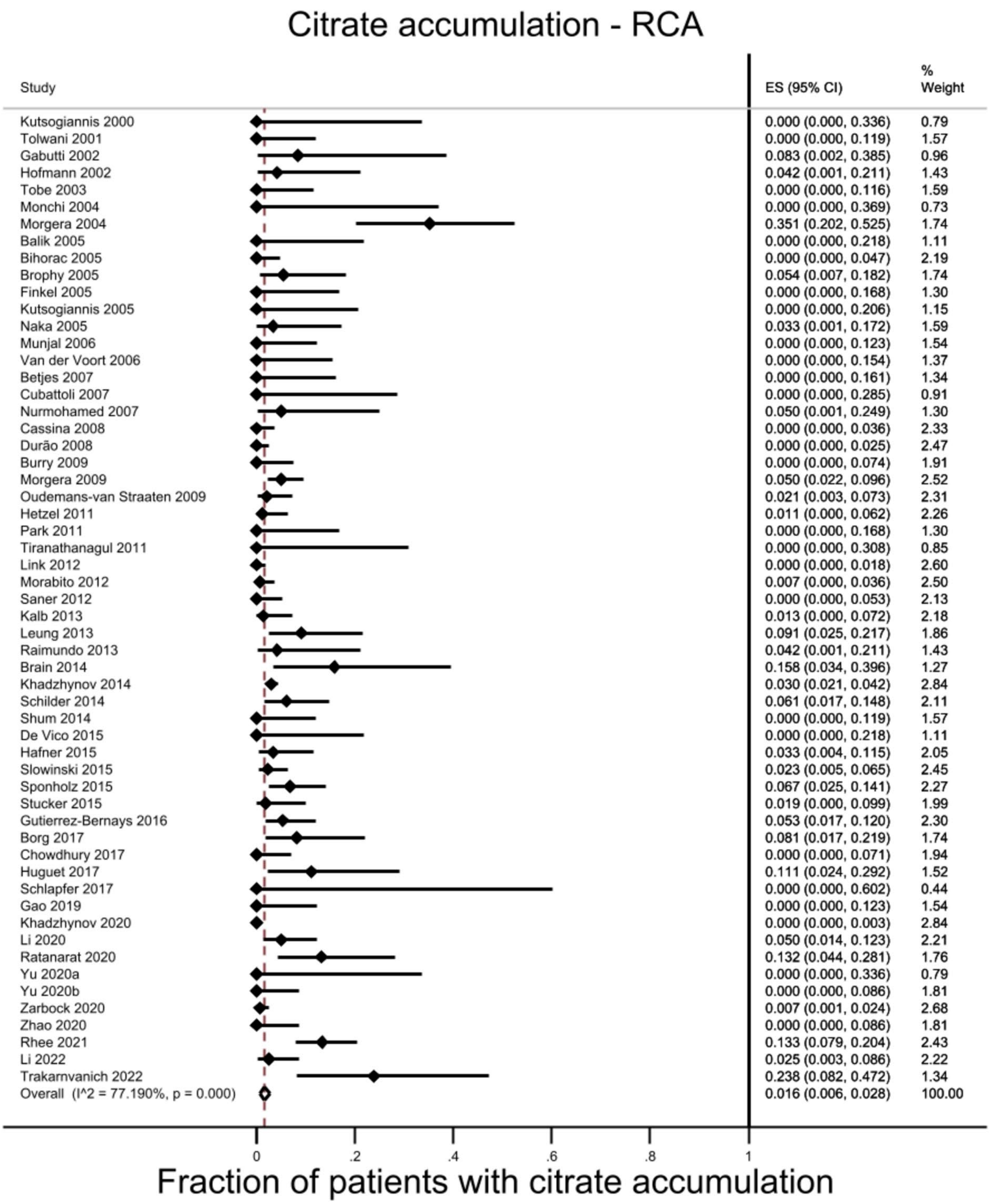



**Fig. 10** Forest plot for regional citrate anticoagulation (RCA) citrate accumulation rates (*ES* effect size, *95% CI* 95% confidence interval)

**Table 1** Results for comparisons that did not reach statistical significance

| Variable | Result | Heparin average (95% confidence interval) | RCA average (95% confidence interval) |
|---|---|---|---|
| Bicarbonate levels | RCA higher | 22.55 (21.06, 24.03) | 24.54 (23.40, 25.68) |
| Transfusion volume (units/day) | Heparin higher | 0.42 (– 0.30, 1.15) | 0.09 (– 0.07, 0.25) |
| Transfused patients (%) | Heparin higher | 44.7% (27.7%, 62.3%) | 27.3% (14.4%, 42.5%) |
| Length of ICU stay (days) | Heparin higher | 8.54 (4.06, 13.03) | 8.18 (6.74, 9.61) |
| Length of hospital stay (days) | Heparin higher | 20.67 (– 2.10, 45.43) | 15.22 (12.33, 18.12) |
| Hospital mortality | RCA higher | 43.4% (34.4%, 52.7%) | 49.2% (43.4%, 54.9%) |
| 28-Day mortality | RCA higher | 35.4% (26.7%, 44.5%) | 38.8% (28.3%, 49.9%) |
| 30-Day mortality | RCA higher | 44.0% (36.7%, 51.4%) | 44.4% (34.4%, 54.7%) |
| 90-Day mortality | Heparin higher | 49.2% (42.5%, 56.0%) | 41.8% (32.4%, 51.6%) |
| Hypercalcemia rate | RCA higher | 0.0% (0.0%, 1.0%) | 0.8% (0.0%, 2.8%) |
| Acidosis rate | RCA higher | 2.6% (0.0%, 9.2%) | 9.5% (3.6%, 17.4%) |

*RCA* regional citrate anticoagulation, *ICU* intensive care unit

subgroup population (Fig. 11). While the event rate is similar for RCA in both populations, with high risk of bleeding and total population (see Fig. 4), the subgroup population at high risk of bleeding shows worse performance with heparin, with an additional 12% bleeding events, suggesting preferential use of RCA in this subgroup population. Heterogeneity across studies was high for RCA, apparently because of the targeted inclusion of patients with high bleeding risk in one of the studies [89].

Concerning the clotting issues, the data suggest that, in patients receiving RCA, patients at high risk of bleeding are less likely to experience events (11.6%) than the total population (21.3%) (Fig. 12). This suggests that RCA may be a better option for minimizing clotting issues, particularly in patients at high risk of bleeding. Combined with the fact that patients receiving RCA experienced fewer bleeding episodes, there appears to be significant evidence pointing to better performance of RCA, specifically surrounding complications involving bleeding issues. RCA showed heterogeneity across studies.

Results on citrate accumulation for the subgroup of patients at high risk of bleeding (1.3%) (Fig. 13) are in line with those for the overall group of patients (1.6% of patients experiencing the event).

## Economic Data

Economic studies with varied costs were normalized to hourly rates for a comparative analysis of different anticoagulation methods. The initial economic comparison does not reveal a significant difference between heparin and RCA, with hourly costs of 20.94€ and 18.28€, respectively (Fig. 14). Heterogeneity across studies was higher for RCA compared to heparin, likely because of the different protocols applied.

### Cost-Consequence Data

Economic evaluations have become increasingly important in healthcare in recent years, aiming to assess the health gains compared to the costs of different health interventions [99]. Few studies reported conclusions about the possible economic profile of RCA compared to heparin, and methodologies applied generally consisted of simple comparisons of clinical outcomes to costs, mainly referred to anticoagulation agents or filter kits [34, 71, 100]. The narrow view of the comparisons was likely due to the lack of differentiation in mortality and quality of life between the two anticoagulation treatments. Therefore, most studies, although referring to cost-effectiveness, have rather applied a cost comparison/cost-consequence methodology in their assessment. Another study concluded that for patients likely to require only a short duration of CKRT, heparin is the most cost-efficient option, whereas for patients needing increased clearance and prolonged filter life, citrate may be the better choice [84]. Finally, a recently published NIHR HTA report [13] assessed ICU outcomes before and after switching from heparin to RCA, using electronic health records, and integrated them with an ICU practice survey and quality of life data from the ICON study [101]. The report stated that RCA anticoagulation was more expensive than systemic heparin and was associated with an incremental net monetary loss of 2376£ (95% CI 911–3841£), considering a willingness-to-pay threshold of 20,000£.

### Quality of Evidence Assessment

The assessment of studies using the GRADE system is detailed in the Supplementary Material. Given that the meta-analyses were conducted separately for RCA and heparin groups and included both randomized RCTs and observational studies, the highest achievable quality rating was moderate. A few assessed outcomes, including ionized calcium levels, bleeding

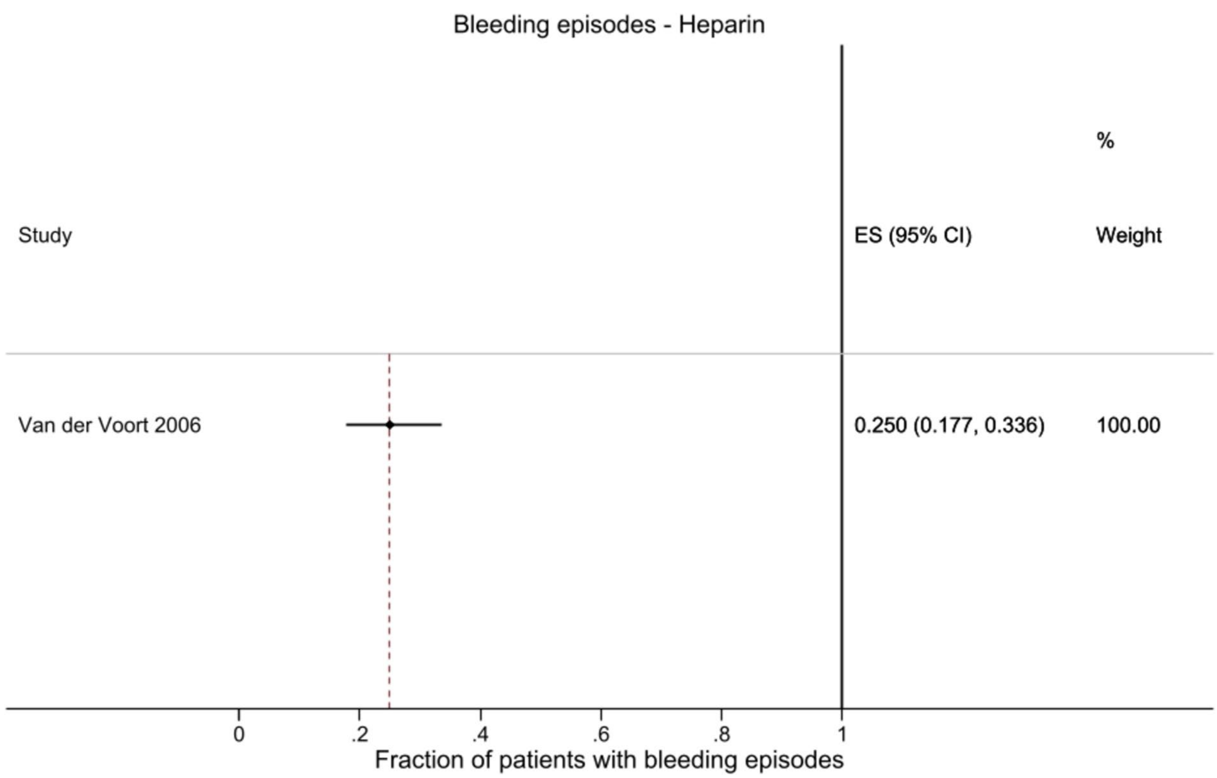



**Fig. 11** Forest plots for heparin and regional citrate anticoagulation (RCA) bleeding episodes (patients at high risk of bleeding) (*ES* effect size, *95% CI* 95% confidence interval)

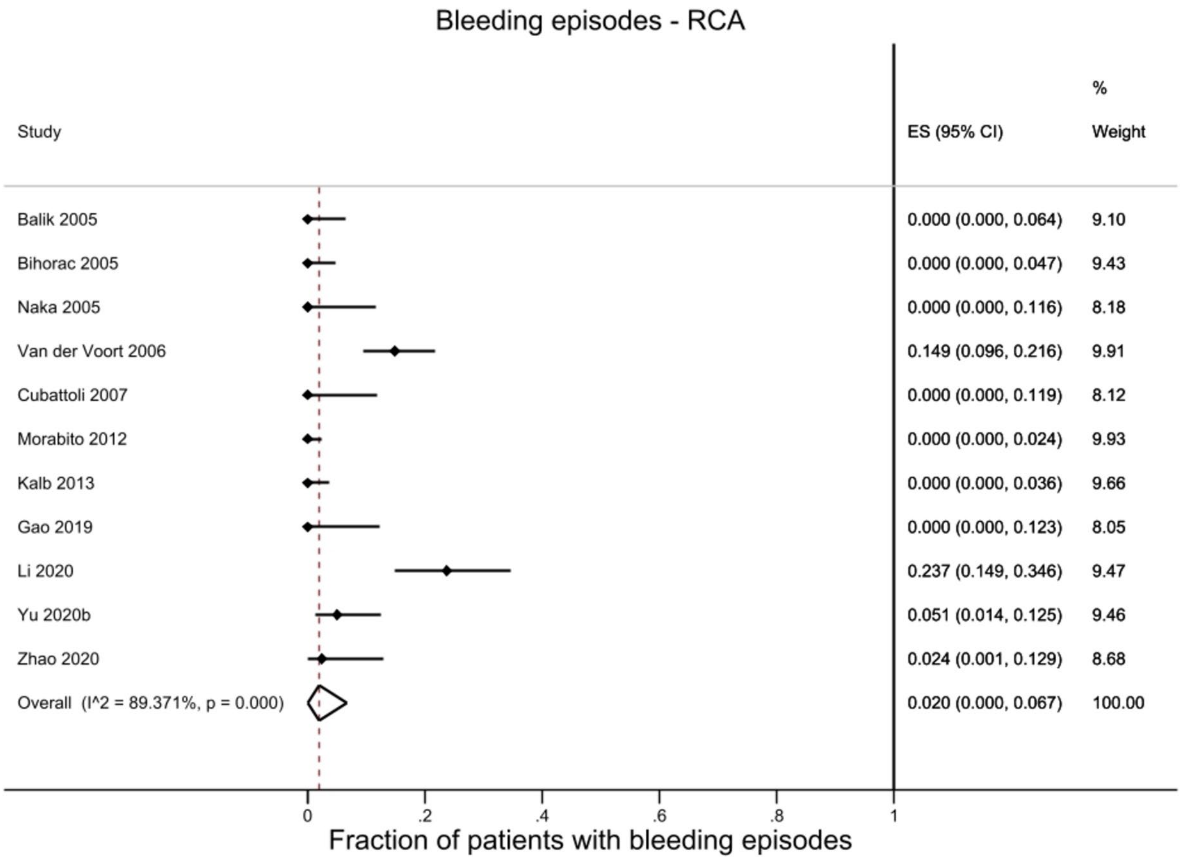



**Fig. 11** continued

episodes, filter lifespan and hourly cost, were rated as moderate quality. However, clotting issues, filter failure, alkalosis and hypocalcemia rates were classified as low quality. In the subgroup of patients at high risk of bleeding, both bleeding episodes and clotting events were also rated as low quality.

## DISCUSSION

Our study started with an extensive literature search to gather available evidence on using RCA and heparin to manage adult patients undergoing CKRT. Randomized settings through RCTs and real-world results from observational studies were considered to provide a balanced comparison, ensuring coverage and applicability of results to both situations. Also, various country settings were considered; however, a concentration on Europe and other more developed nations became apparent, underscoring the necessity to broaden the research scope to encompass diverse regions and contexts for more robust results from an economic perspective.

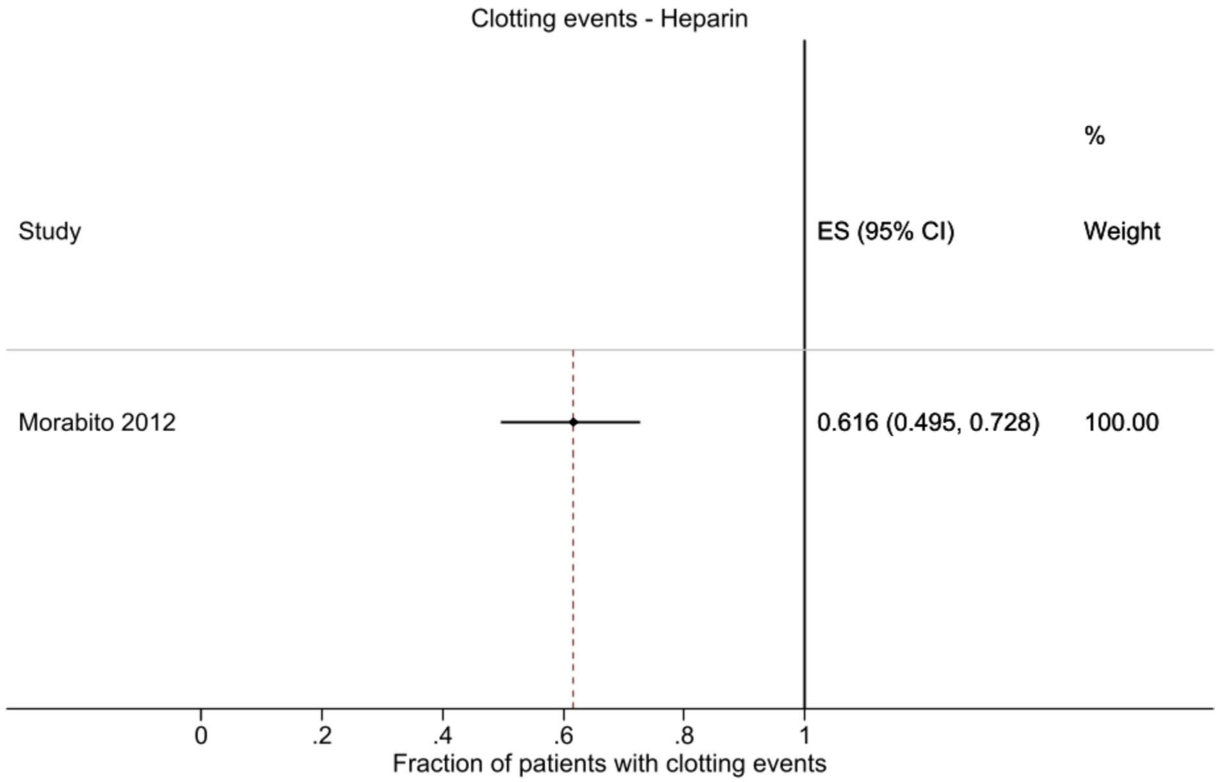
Based on the provided evidence, RCA demonstrates better effectiveness compared to heparin, as evidenced by a reduction in bleeding events, prevention of filter clotting, enhanced filter lifespan and decreased filter failure. Especially patients at high risk of bleeding benefit from lower rates of bleeding and clotting. Optimized management of the anticoagulation procedure of RCA may lower costs for consumables and healthcare personnel and reduce the burden of potential complications management. On the other hand, the increased performance of RCA entails a more complex treatment plan. It requires more monitoring from the medical staff and increases the likelihood of complications seen with CKRT, including the specific risk of citrate accumulation and an elevated risk of hypocalcemia. Depending on the specific technology used, the additional complexity increases the required attention and new training and skills from the professionals carrying out the procedure; however, extended filter duration and improved circuit predictability resulting from RCA could offer potential advantages in managing nursing and physician workload [59, 77].

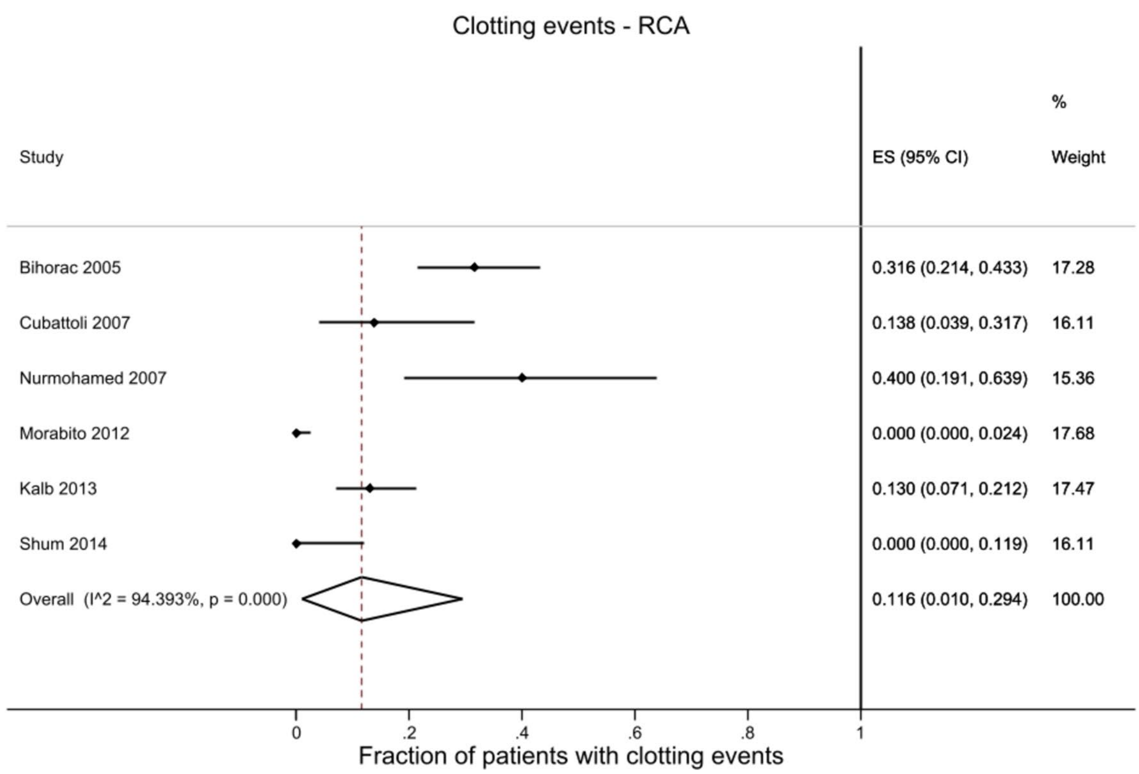
Regarding costs, from our analysis, RCA and heparin showed comparable figures, although costs may vary depending on the specific technology used. Published studies on cost data in general highlighted a beneficial economic profile of RCA compared to heparin, except for the NIHR HTA report [13]. According to the authors, the main study limitations include the lack of patient-level treatment data and variations in administrative data quality, which may have introduced potential biases. Furthermore, the NIHR HTA report focused on parameters such as mortality and hospital stay duration, which, in our extensive analysis, showed no significant differences across most studies. Moreover, the report combined different data sources leading to possible biases in the results. These aspects highlight that a more nuanced understanding is required when performing such health technology assessments. We further observed that most economic studies performed a cost comparison study because of key clinical outcome parameters with no significant difference between the two anticoagulation strategies such as mortality or quality of life. Therefore, using the term "cost-effectiveness" may not fully align with standard health economic principles.

A significant heterogeneity was observed across studies, particularly in the case of RCA, for which it affected both clinical outcomes and costs. Therefore, the generalizability of the study results should be interpreted with caution. This aspect appears to be linked to the varying protocols employed in the studies, thereby likely influencing the economic profile of RCA. Further analyses, potentially stratified by different protocols, are suggested to provide a more comprehensive perspective on the outcomes. Another important aspect to discuss is the overall quality of the studies included in the analysis, as the estimated outcomes demonstrated moderate to low methodological rigor. The quality assessment was primarily influenced by risk of bias, leading to downgrades and upgrades based on study design. RCTs were downgraded from high to moderate quality because of the lack of investigator blinding in most studies, whereas observational studies were upgraded from low to moderate quality because of strong study designs or consistent effect estimates. It is important to acknowledge that blinding investigators in ICU-based CKRT clinical studies is often impractical. While blinding outcome assessors or statisticians to treatment allocation might have been feasible, these studies likely represent the best possible design within the constraints of this complex clinical setting. In this context, the cost outcome, which demonstrated comparable statistics depending on the RCA protocol considered, was rated as moderate quality, reflecting a reasonable level of confidence in the economic data. This rating supports the potential cost-effectiveness of RCA while also identifying opportunities for further refinement and optimization in economic evaluations.

Another limitation concerns the data search, which was conducted using only two scientific databases. However, these databases are among the largest and most widely recognized sources, making this approach highly effective in minimizing the risk of missing relevant articles.

Additional evidence is essential to assess healthcare resource usage for both RCA and heparin. An extended collection of cost data, including materials, laboratory, healthcare personnel and possibly costs borne by the patients, may provide a broader view of the economic impact of the anticoagulation procedures considered. The RCA and heparin comparison underscores the need to include a real-world perspective in the analysis, since RCTs are often confined to limited patient populations and artificial settings and may not accurately reflect real-world


Clotting events - Heparin
Study
ES (95% CI)
%
Weight
Morabito 2012
0.616 (0.495, 0.728)
100.00
0
.2
.4
.6
.8
1
Fraction of patients with clotting events


Clotting events - RCA
Study
ES (95% CI)
%
Weight
Bihorac 2005
0.316 (0.214, 0.433)
17.28
Cubattoli 2007
0.138 (0.039, 0.317)
16.11
Nurmohamed 2007
0.400 (0.191, 0.639)
15.36
Morabito 2012
0.000 (0.000, 0.024)
17.68
Kalb 2013
0.130 (0.071, 0.212)
17.47
Shum 2014
0.000 (0.000, 0.119)
16.11
Overall (I^2 = 94.393%, p = 0.000)
0.116 (0.010, 0.294)
100.00
0
.2
.4
.6
.8
1
Fraction of patients with clotting events

◂**Fig. 12** Forest plots for heparin and regional citrate anticoagulation (RCA) clotting episodes (patients at high risk of bleeding) (*ES* effect size, *95% CI* 95% confidence interval)

conditions. Limited demographic distributions in these trials may exclude certain population segments from safety assurances [102]. Recognizing this limitation, real-world evidence has gained prominence, supported by initiatives like the 21st Century Cures Act, which emphasizes the acceleration of innovation adoption through real-world evidence generation [103]. While real-world evidence offers valuable insights, caution is needed in data collection and legitimacy considerations [104]. The NIHR HTA report serves as a notable example in this context. Its use should complement other forms of evidence, ensuring cost-effective and efficient technologies for the general population [15, 105, 106]. The integration of different sources like RCTs and real-world data [107], together with a continuous assessment, could give a clearer picture of the sustainability of the discussed anticoagulation strategies.

Pending the publication of new evidence, decision-making on the choice of anticoagulation in CKRT should consider the patient's specific context, CKRT modality and individual factors influencing the risk of bleeding and potential benefits of anticoagulation in maintaining circuit patency. However, according to the evidence provided, RCA offers medical

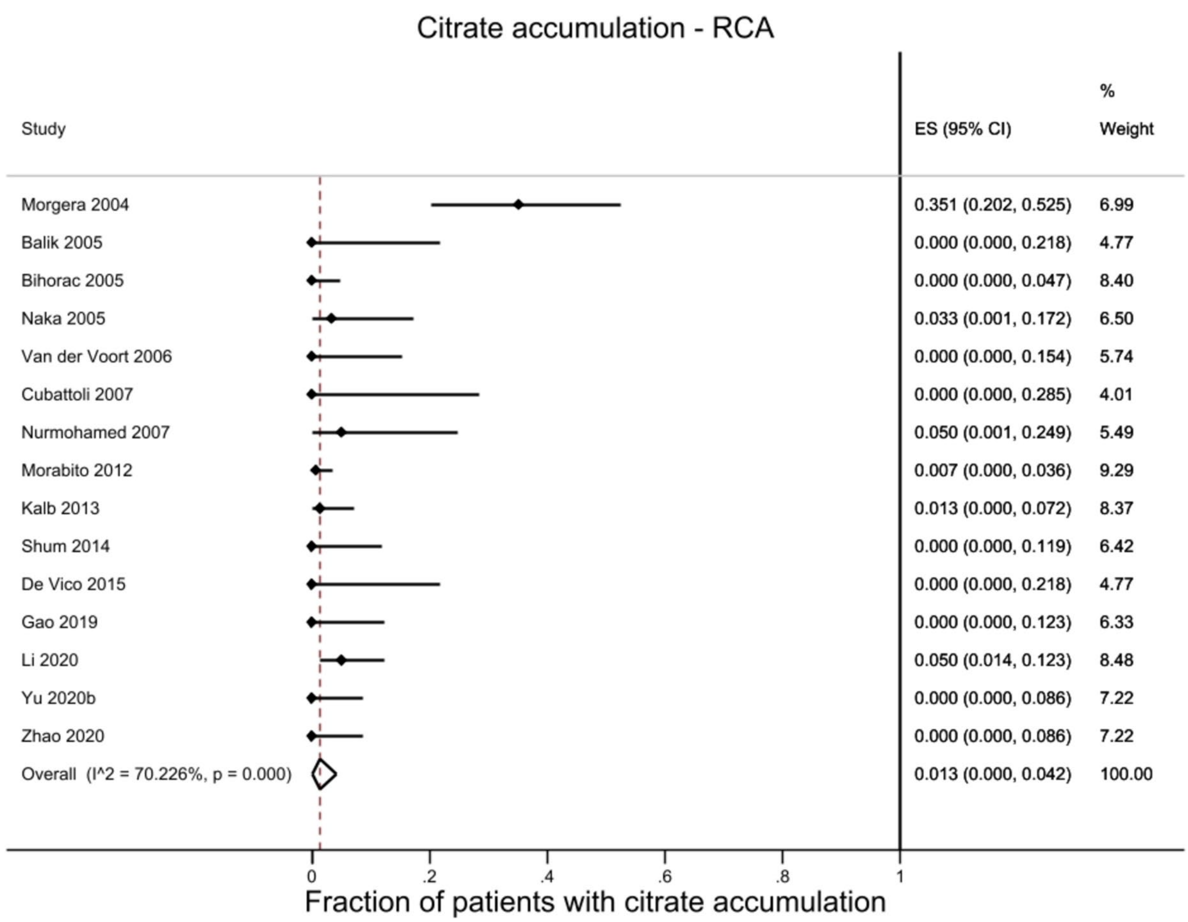



**Fig. 13** Forest plot for regional citrate anticoagulation (RCA) citrate accumulation episodes (patients at high risk of bleeding) (*ES* effect size, *95% CI* 95% confidence interval)

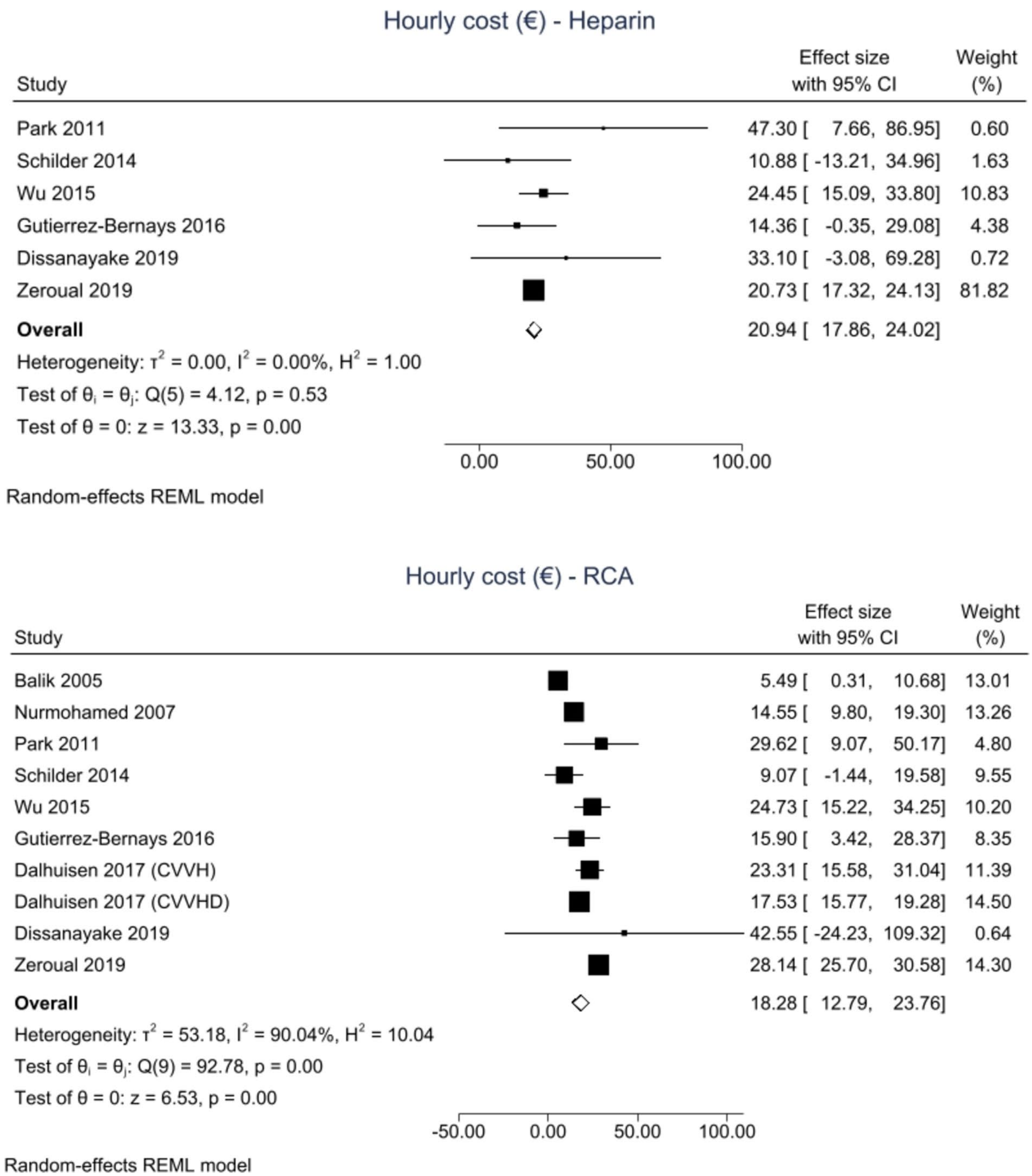



**Fig. 14** Forest plots for heparin and regional citrate anticoagulation (RCA) hourly costs (€) (*95% CI* 95% confidence interval)

advantages over heparin, keeping cost statistics comparable on average (depending on the RCA protocol used, this can be lower or higher).

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***Author Contributions.*** Carla Rognoni and Rosanna Tarricone contributed to the study concept and design. Material preparation, data collection and analysis were performed by Carla Rognoni. Robert Pohlmeier provided clinical advice and contributed to data collection. Rosanna Tarricone supervised the study. The first draft of the manuscript was written by Carla Rognoni, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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***Data Availability.*** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

***Declarations***

***Conflict of Interest.*** Carla Rognoni and Rosanna Tarricone (CERGAS, SDA Bocconi School of Management) have nothing to disclose. Robert Pohlmeier is an employee of Fresenius Medical Care Deutschland GmbH.

***Ethical Approval.*** This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.



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