Supplementary material: Meta-analysis of randomized controlled trials using tool-assisted target weight adjustments in chronic dialysis patients.

Contents

Appendix 1: Search strategy

Table S1: Search strategy across included databases

Database	Study design: randomized trial	Population: chronic dialysis	Intervention					
			Bioimpedance	Blood volume monitoring	Lung ultrasound	Inferior vena cava ultrasound	Natriuretic peptides	Chest X-ray
MEDLINE (Pubmed)	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] NOT (animals [mh] NOT humans [mh])) Validated filter from Lefebvre et al.[1]	(dialysis[tiab] OR peritoneal dialysis[tiab] OR hemodialysis[tiab] OR hemodiafiltration[tiab] OR haemodiafiltration[tiab] OR hemofiltration[tiab] OR haemofiltration OR extracorporeal blood cleansing[tiab] OR haemodialysis[tiab] OR Renal Dialysis[mh] OR Renal replacement[tiab] OR end stage kidney[tiab] OR end stage renal[tiab] OR stage 5 kidney[tiab] OR stage 5 renal[tiab])	(bioimpedance[tiab] OR body composition monitor*[tiab]OR electrical impedance[tiab] OR impedance cardiography[tiab] OR impedance spectroscopy[tiab] OR bioelectrical impedance[tiab] OR dielectric spectroscopy[tiab] OR impedance plethysmography[tiab])	(blood volume monitor*[tiab] OR plasma volume monitor*[tiab] OR BVM[tiab] OR continuous volume monitor*[tiab] OR biofeedback[tiab] OR blood volume[tiab] OR plasma volume[tiab] OR crit line[tiab] OR hematocrit[tiab])	(lung ultraso*[tiab] OR pleural ultraso*[tiab] OR comet tail[tiab] OR B line[tiab] OR extravascular lung water[tiab] OR LUS[tiab] OR B-line[tiab] OR B-lines[tiab] OR B lines[tiab] OR pulmonary echo*[tiab] OR lung echo*[tiab])	(vena cava ultraso*[tiab] OR IVC ultraso*[tiab] OR vena cava diameter[tiab] OR IVC diameter[tiab] OR vena cava measurement*[tiab] OR IVC measurement*[tiab])	(B-type[tiab] OR Atrial Natriuretic[tiab] OR ANP[tiab] OR BNP[tiab] OR NT-pro-BNP[tiab] OR pro-BNP[tiab] OR brain natriuretic[tiab] OR natriuretic peptide[tiab] OR N-terminal pro-B-type[tiab] OR proBNP[tiab] OR cyclic GMP[tiab] OR GMP[tiab] or Brain Natriuretic Peptide[mh] OR Atrial Natriuretic Factor[mh])	Chest X-ray[tiab] OR pulmonary X-ray[tiab] OR lung radiography [tiab] OR lung X-ray[tiab] OR chest radiography[tiab] OR lung radiography[tiab] OR chest roentgenogram[tiab] OR lung roentgenogram[tiab] OR pulmonary roentgenogram[tiab]
EMBASE (Ovid)	crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/ or (random* or factorial* or crossover* or cross over* or placebo* or (doubl* adj blind*) or (singl* adj blind*) or assign* or allocat* or volunteer*).tw. Validated filter from Lefebvre et al.[1]	#1 (dialysis or peritoneal dialysis or hemodialysis or hemodiafiltration or haemodiafiltration or extracorporeal blood cleansing or haemodialysis or Renal replacement or end stage kidney or end stage renal or stage 5 kidney or stage 5 renal).ab. #2(end stage renal disease or dialysis).sh. #1 OR #2	(bioimpedance or body composition monitor$ or electrical impedance or impedance cardiography or impedance spectroscopy or dielectric spectroscopy or impedance plethysmography).ab.	(blood volume monitor$ or plasma volume monitor$ or BVM or continuous volume monitor$ or biofeedback or blood volume or plasma volume or crit line).ab.	(lung ultraso$ or pleural effusion or comet tail or B line or extravascular lung water or LUS or B-line or B-lines or B lines or pulmonary echo$ or lung echo$).ab.	(vena cava ultraso$ or IVC ultraso$ or vena cava diameter or IVC diameter or vena cava measurement$ or IVC measurement$).ab.	(B-type or Atrial Natriuretic or ANP or BNP or brain natriuretic or natriuretic peptide or N-terminal pro-B-type or proBNP or cyclic GMP or GMP).ab.	(Chest X-ray OR pulmonary X-ray OR lung radiography OR lung X-ray OR chest radiography OR lung radiography OR chest roentgenogram OR lung roentgenogram OR pulmonary roentgenogram).ab.
CENTRAL	Not needed	(dialysis OR peritoneal dialysis OR hemodialysis OR hemodiafiltration OR haemodiafiltration or extracorporeal blood cleansing OR haemodialysis OR Renal Dialysis[mh] OR Renal replacement OR end stage kidney OR end stage renal OR stage 5 kidney OR stage 5 renal)	(bioimpedance OR body composition monitor$OR electrical impedance OR impedance cardiography OR impedance spectroscopy OR bioelectrical impedance OR dielectric spectroscopy OR impedance plethysmography)	(blood volume monitor$ OR plasma volume monitor$ OR BVM OR continuous volume monitor$ OR biofeedback crit line)	(lung ultrasound OR pleural ultrasound OR comet tail OR B line OR extravascular lung water OR LUS OR B-line OR B-lines OR B lines OR pulmonary echography OR lung echography)	(vena cava ultrasound OR IVC ultrasound OR vena cava diameter OR IVC diameter OR vena cava measurement$ OR IVC measurement$)	(B-type OR Atrial Natriuretic OR ANP OR BNP OR NT-pro-BNP OR pro-BNP OR brain natriuretic OR natriuretic peptide OR N-terminal pro-B-type OR proBNP OR cyclic GMP OR GMP or Brain Natriuretic Peptide[mh] OR Atrial Natriuretic Factor[mh])	(Chest X-ray OR pulmonary X-ray OR lung radiography OR lung X-ray OR chest radiography OR lung radiography OR chest roentgenogram OR lung roentgenogram OR pulmonary roentgenogram)

Appendix 2: Details on data extraction

Table S2: Summary of items included in data extraction

Identification and eligibility	
Study ID and Report ID	Citation and contact details
Review author ID	Eligibility or primary reason for exclusion
Methods	
Study design	Blinding of participants, personnel and blinding of outcome assessment
Study duration	Other concerns of bias
Sequence generation and concealment	Is a sample size has been calculated and if yes for which outcome
Participants	
Total number of participants	Inclusion and exclusion criteria for the participants
Setting: Country, Date of study, Type of treatment: in-center hemodialysis or home dialysis	
Patient characteristics - Age - Sex - Heart failure - Coronary disease - Diabetes - Peripheral artery disease - Etiology of ESRD	- Dialysis vintage - Proportion of anuric patients - Type of vascular access - Duration of dialysis treatment session - Baseline ambulatory and pre-dialysis blood pressure - Baseline number of anti-hypertensive medications - Baseline Left Ventricular Mass Index
Interventions	
Number of intervention groups	Frequency of measurement
Specific intervention details: - Type of technology classified in the following categories: o Bioimpendance (Body composition monitoring) ▪ Whole body vs segmental, Single frequency, multiple frequency or spectroscopy, Type of analysis: classic analysis vs vector plot, Timing of assessment: before or after dialysis o Plasma volume monitoring ▪ Type of measurements: slope during treatment vs minimum value o Pulmonary ultrasound ▪ Method of assessment used and scoring method, Timing of assessment: before or after dialysis, interobserver reproducibility o IVC ultrasound ▪ Timing of assessment: before or after dialysis, Type of measurements performed: absolute diameter and/or respiratory variability (%), interobserver reproducibility	Frequency of treatment modifications Integrity of intervention: - Protocol used from target weight adjustments in response to measurements - Compliance to protocol and fidelity: o Adherence (delivery as prescribed), o Exposure (frequency and number), o Program modification and crossover
Outcomes (for each)	
Outcomes and time points collected and reported	Outcome definition with diagnosis criteria
Results	
Number of participants in each group	Summary data
Sample size and achieved statistical power (for each outcome)	Estimate of effect with confidence interval p- value
Missing participants	Sub-group analysis and whether they were planned in advance
Miscellaneous	
Funding source	Reference to other relevant studies
Conclusions of the authors	Comment from the reviewer
Comments from the authors	Potential conflict of interest

Section 2.1: Assumptions during data extraction

For one report(1), the distribution of patients between the intervention and the comparator group was not reported but assumed to be equal. For the same report, the rate in person-time for all-cause hospitalisations was reported but not the total number of events in each group, which is necessary to calculate the standard error as described in the *summary measures and synthesis of results* section of the present manuscript. The number of events was thus approximated by multiplying the rate by the number of participants in each group. The same approach was also used for another report.(2)

For one report(3), the mean blood pressure change from baseline was reported without standard deviation. To approximate mean blood pressure at the end of the intervention period, change from baseline was substracted from mean baseline values and standard deviations from baseline values were used as an approximation to the standard deviation of calculated blood pressure values at the end of the intervention. Finally, one of the included study(4) was a nested randomized control trial and results were presented in the report according to geographical location and diuresis status. Interventions groups and comparator groups were combined to create a single pair-wise comparison as described in Cochrane handbook section 16.5.4.(5) For continuous outcomes, results from each groups were combined using the method described in Cochrane Handbook section 7.7.3.8.(5)

Section 2.2: Additional details about statistical analysis

We analyzed data from the eligible trials using Review Manager 5.3 (The Nordic Cochrane Center, the Cochrane Collaboration). For the measure of treatment effect for all-cause mortality, results were expressed as risk ratios (RR) and pooled using a random-effect model in a Mantel-Haenszel analysis. All randomized patients for whom outcome data were not available were assumed to have not experienced the event of interest. For outcomes reported as counts such as rates of an event that can occur multiple times in a single patient (hospitalizations, cardiovascular events, hypotension episodes during dialysis, patient's symptoms during dialysis), results were reported as rate ratios. The natural logarithm of the rate ratios and calculated standard error ($SE=\sqrt{\frac{1}{Events\ in\ control\ group}+\frac{1}{Events\ in\ experimental\ group}}$) were pooled using a random-effect model in an

inverse of variance analysis.(5) A correction of 0.5 was added to each count in the case of zero events. For outcomes reported on a continuous scale (systolic and diastolic blood pressure, left ventricular mass index, medication use), the mean differences were used and pooled using a random-effect model in an inverse of variance analysis.

Appendix 3: Forest plot for sub-groups analysis and secondary outcomes.

Section 3.1: All cause mortality

Figure S3.1.1: All cause mortality according to dialysis modality

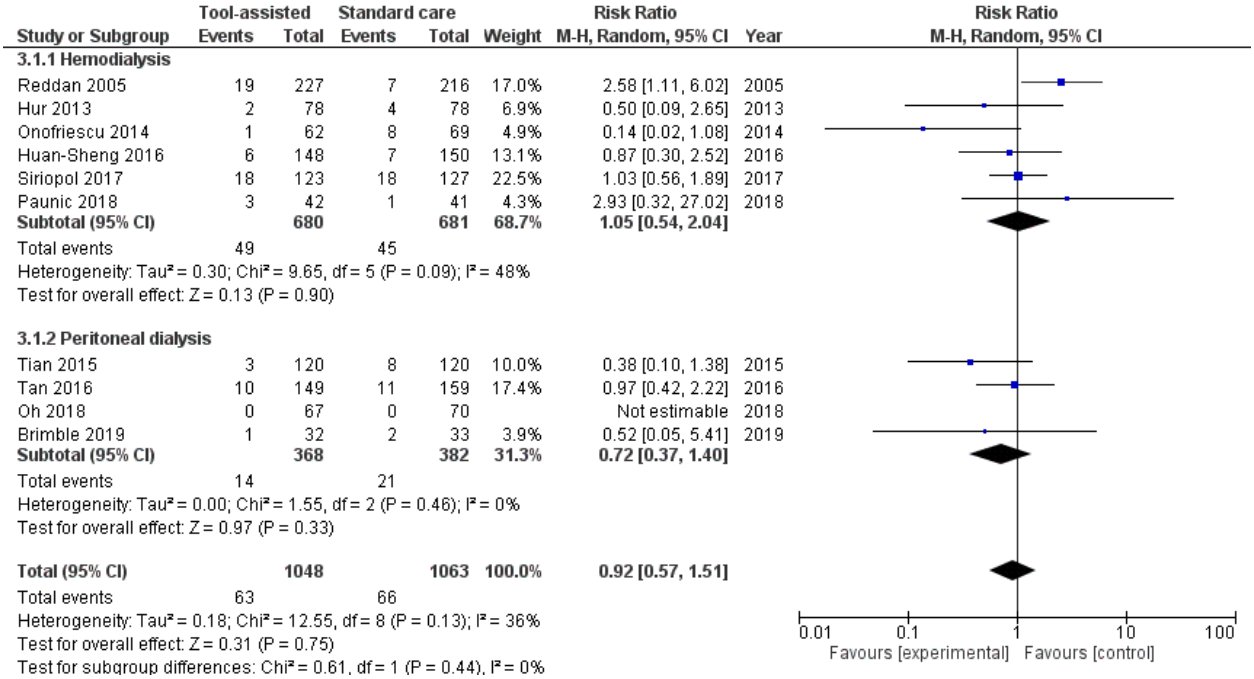


Figure S3.1.2: All cause mortality according to duration of follow-up

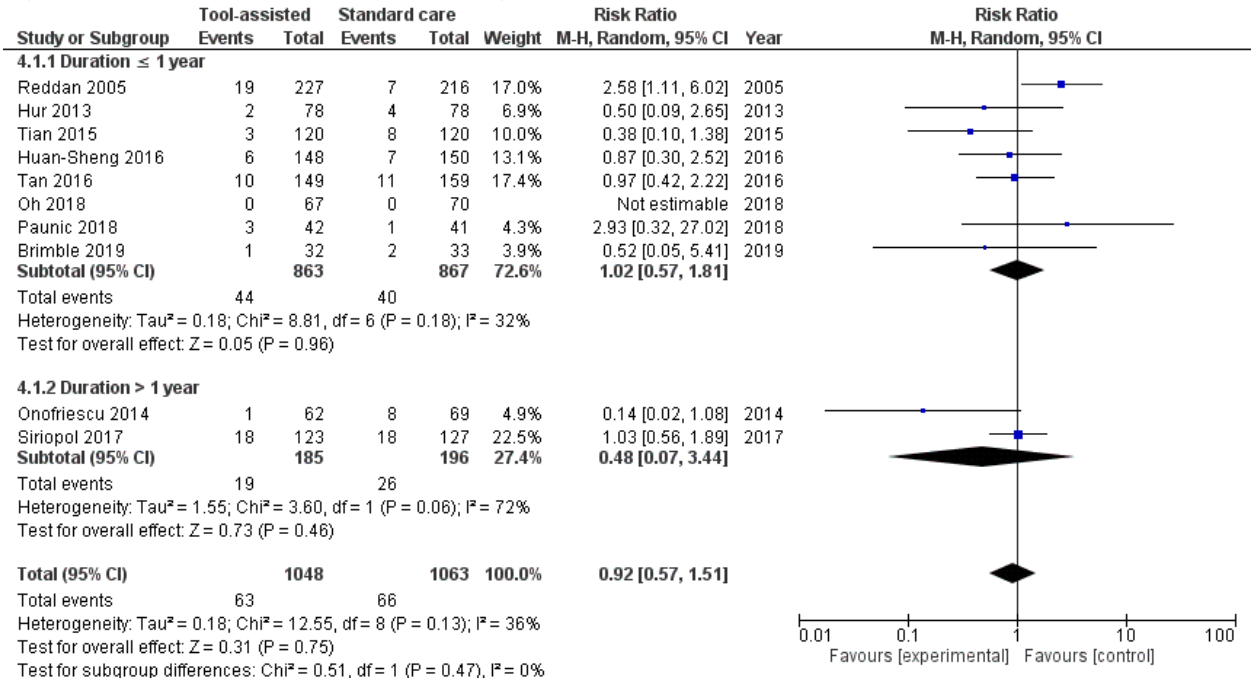


Figure S3.1.3: All cause mortality according to funding sources

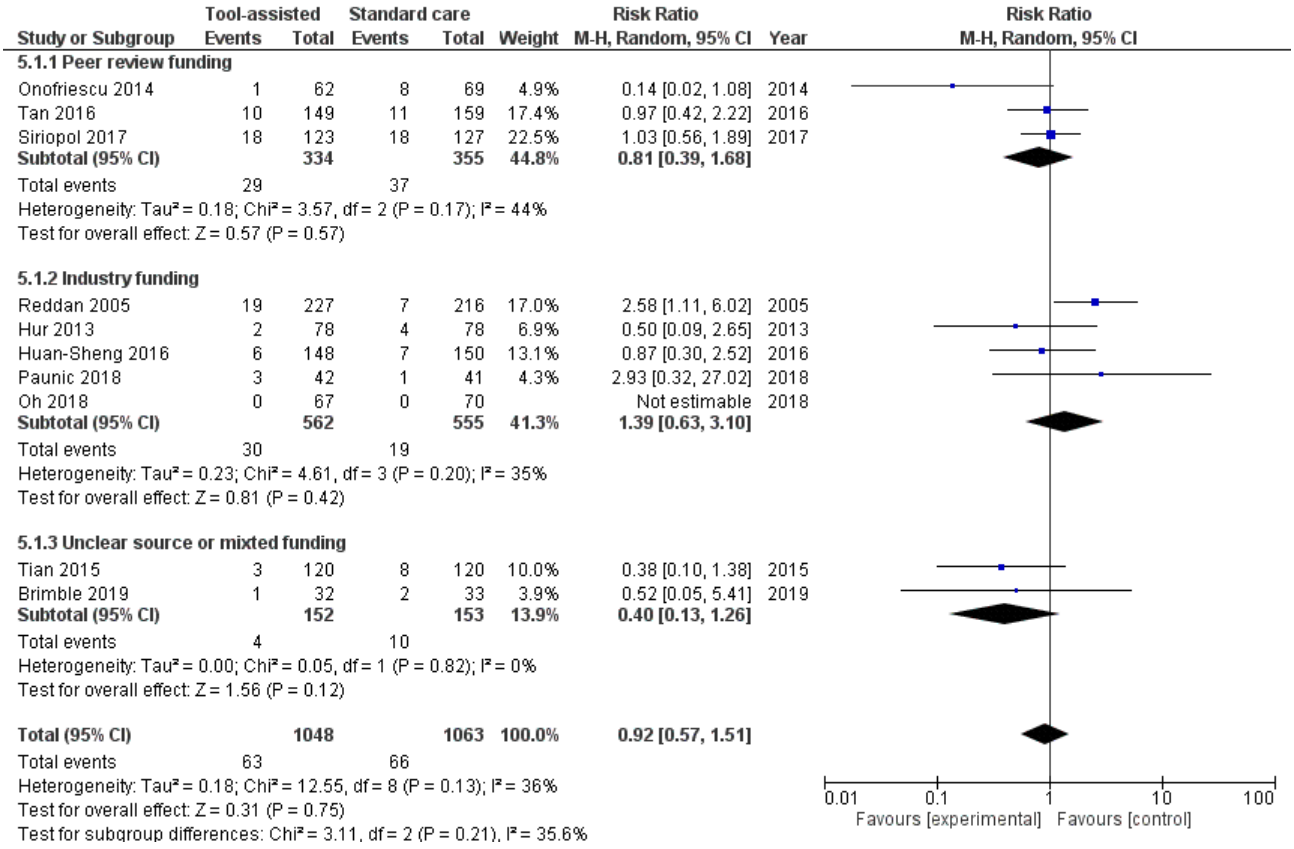


Figure S3.1.4: All cause mortality according to risk of bias

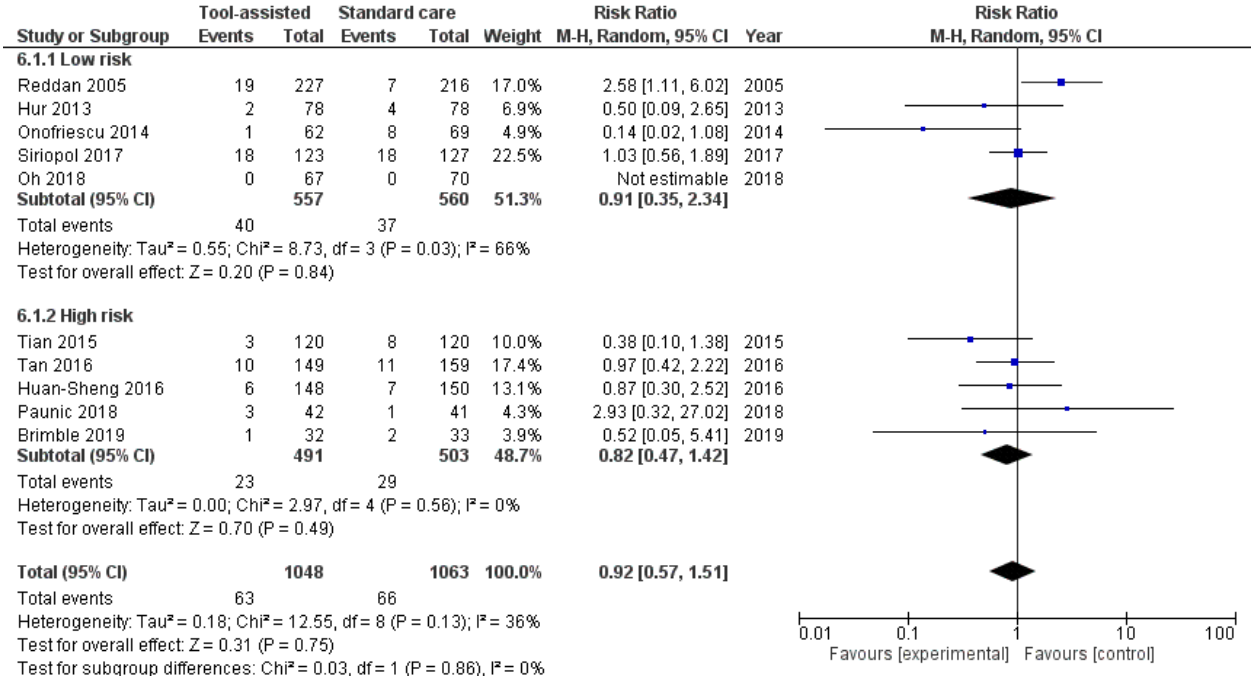
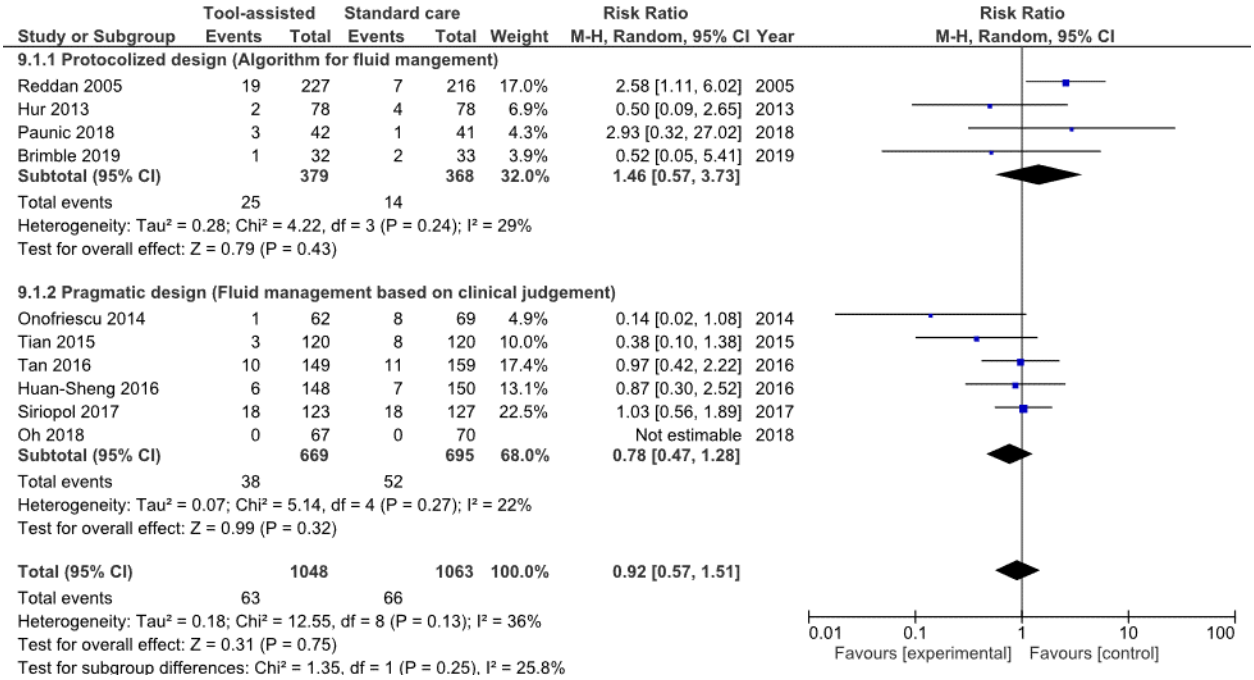


Figure S3.1.5: All cause mortality according to study design



Section 3.2: All-cause hospitalisations

Figure S3.2.1: All-cause hospitalisations according to technology used

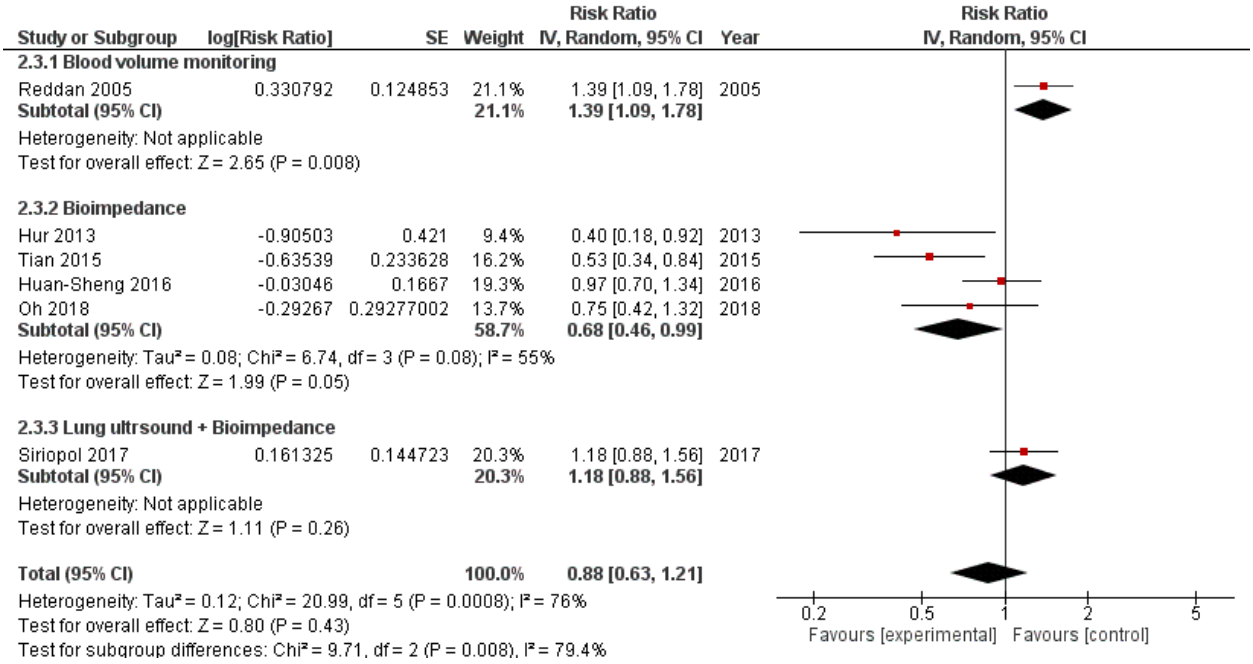


Figure S3.2.2: All-cause hospitalisations according to dialysis modality

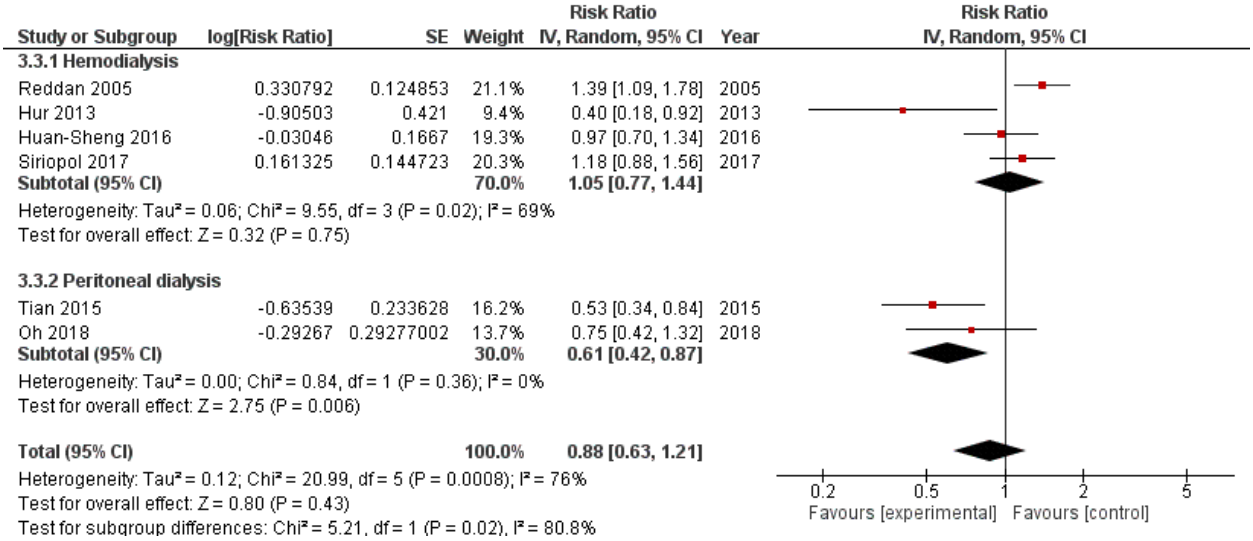


Figure S3.2.3: All-cause hospitalisations according to follow-up duration

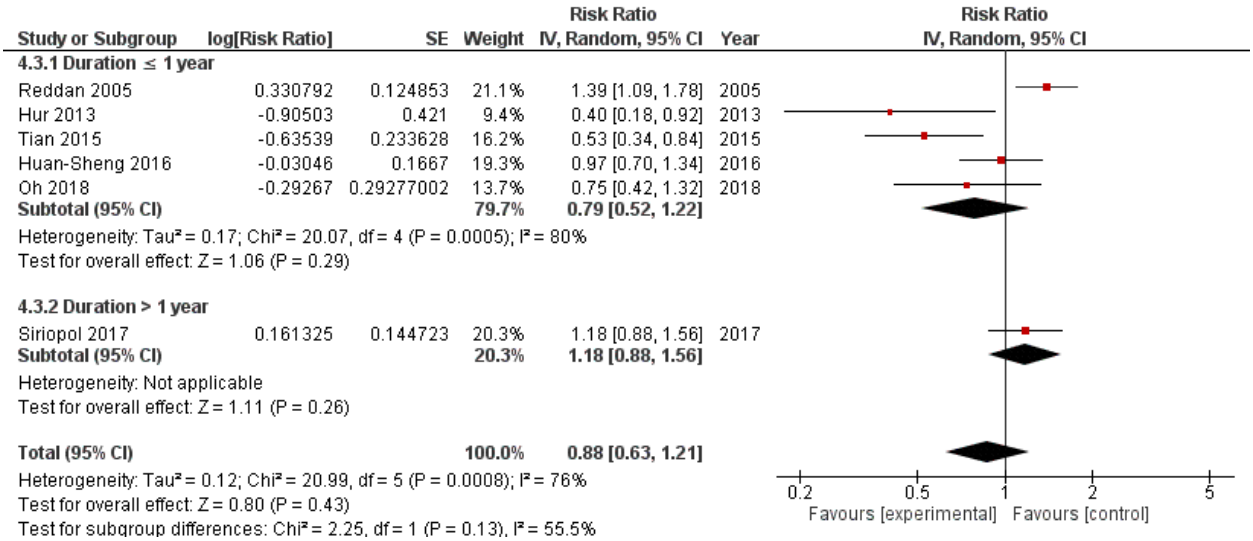


Figure S3.2.4: All-cause hospitalisations according to funding source

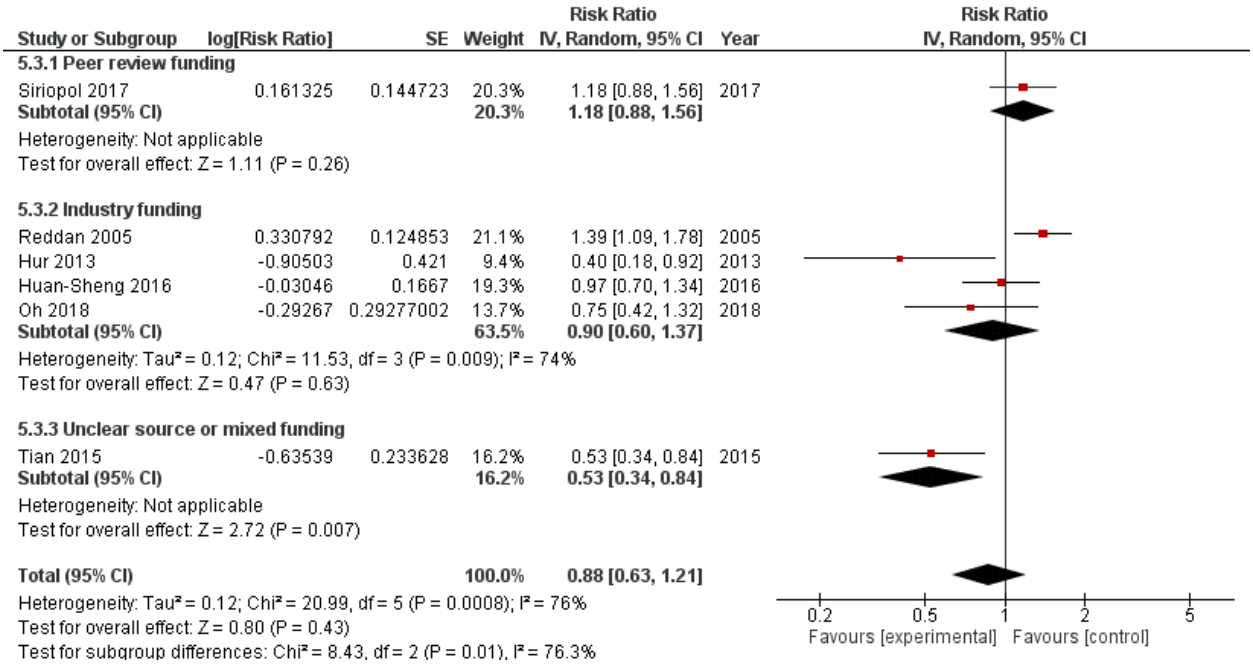


Figure S3.2.5: All-cause hospitalisations according to risk of bias

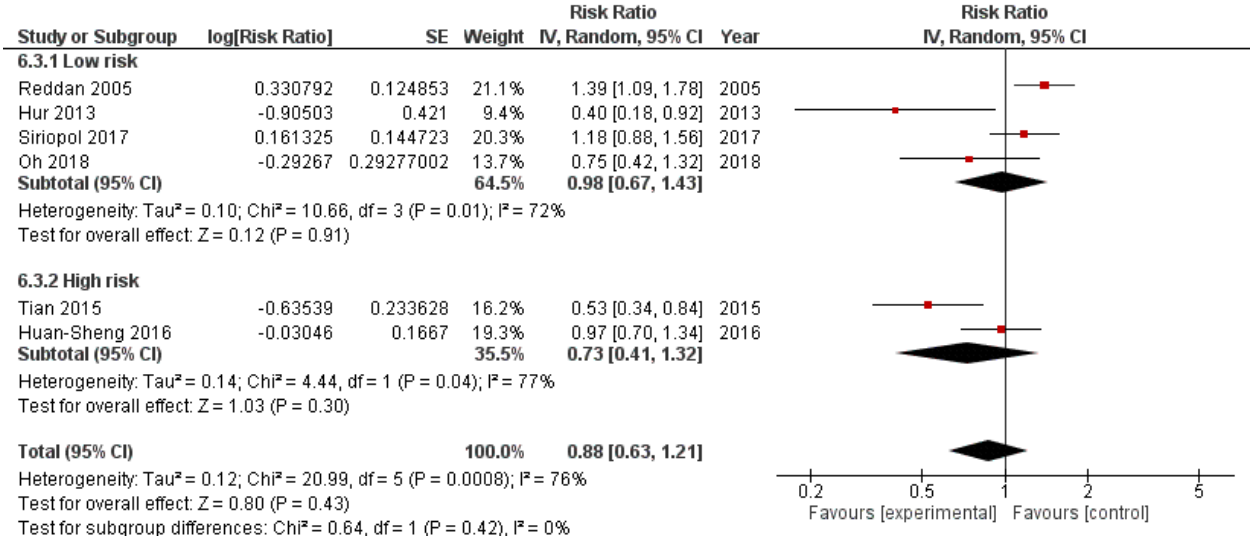
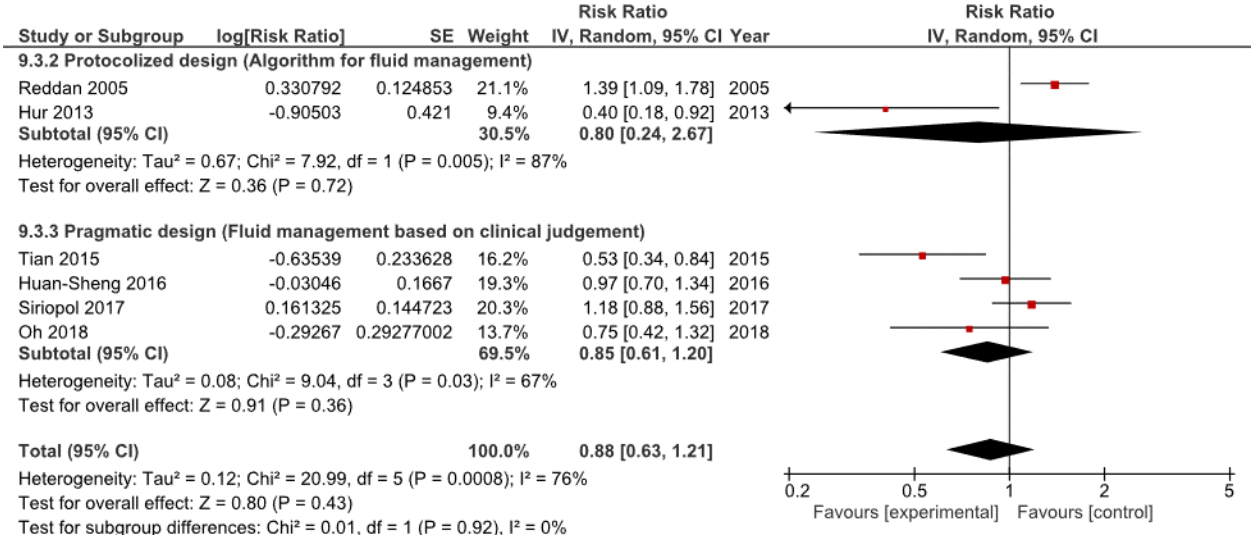


Figure S3.2.6: All-cause hospitalisations according to study design



Section 3.3: Cardiovascular events

Figure S3.3.1: Cardiovascular events according to technology used

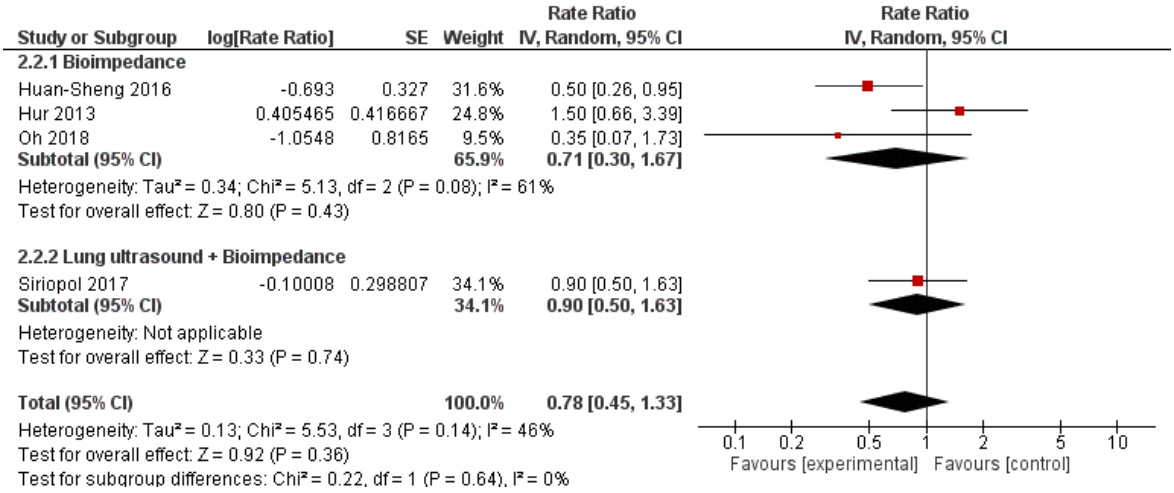


Figure 3.3.2: Cardiovascular events according to dialysis modality

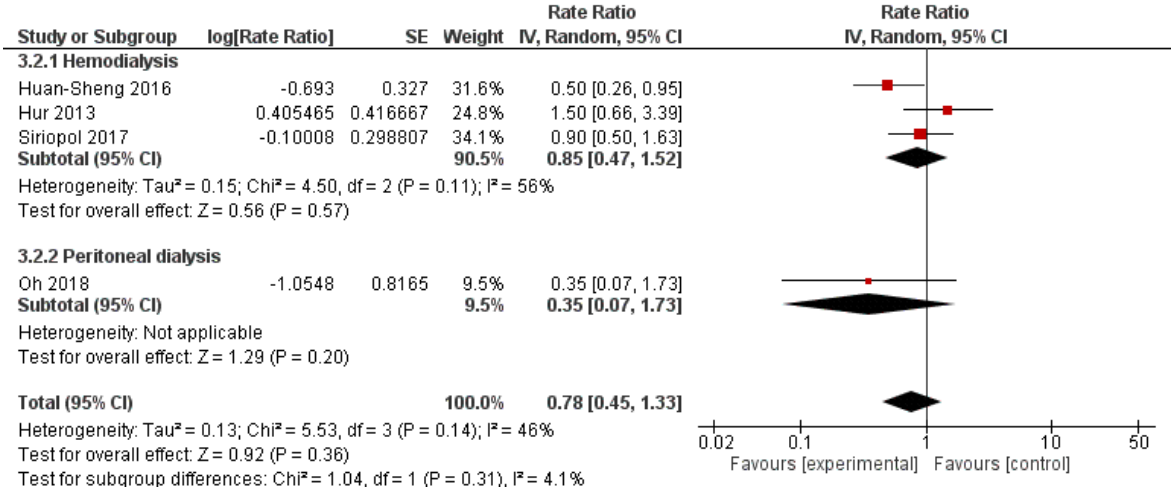


Figure 3.3.3: Cardiovascular events according to duration of intervention

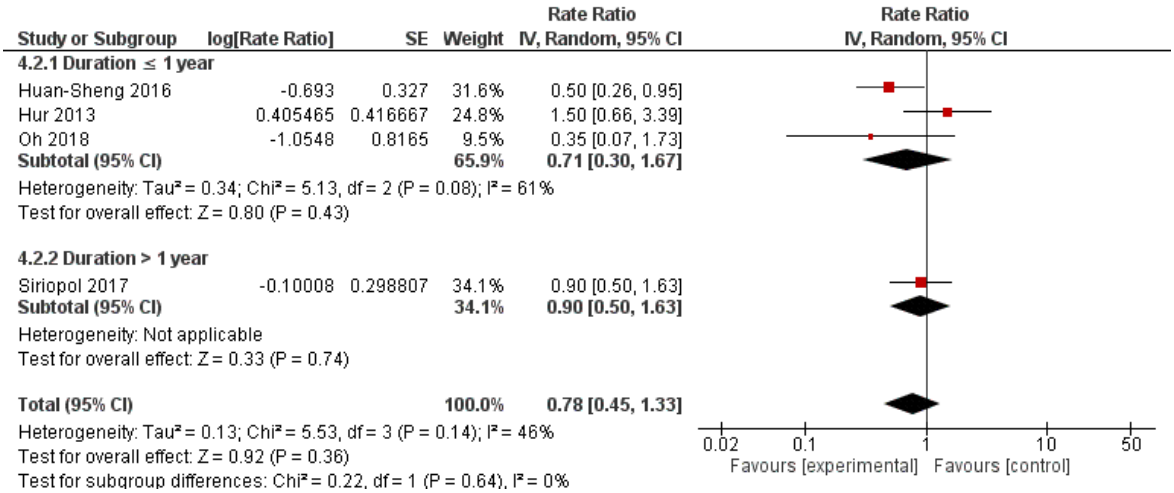


Figure S3.3.4: Cardiovascular events according to funding source

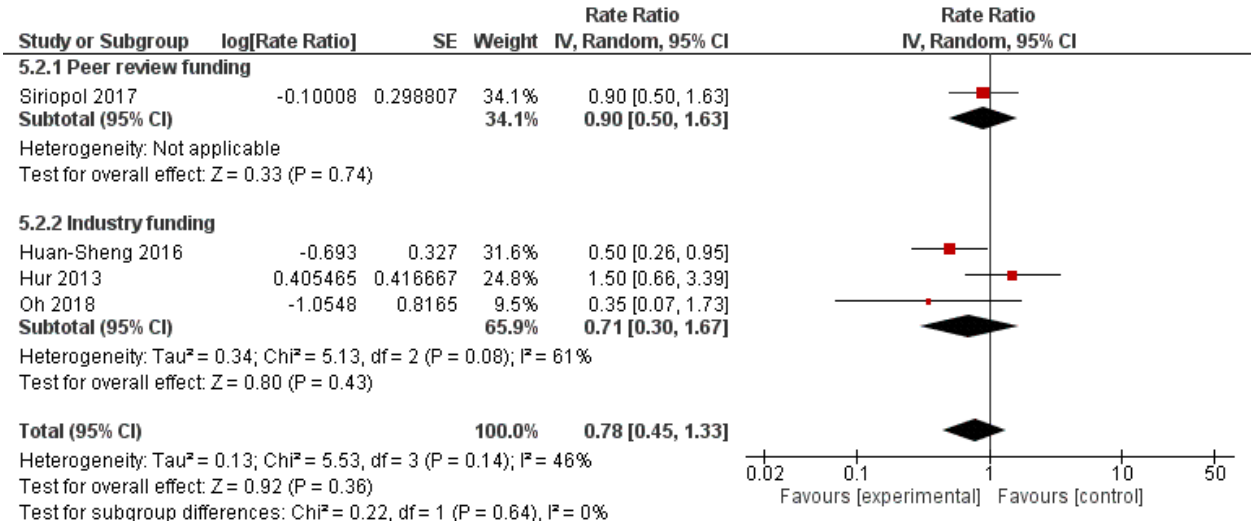


Figure S3.3.5: Cardiovascular events according to risk of bias

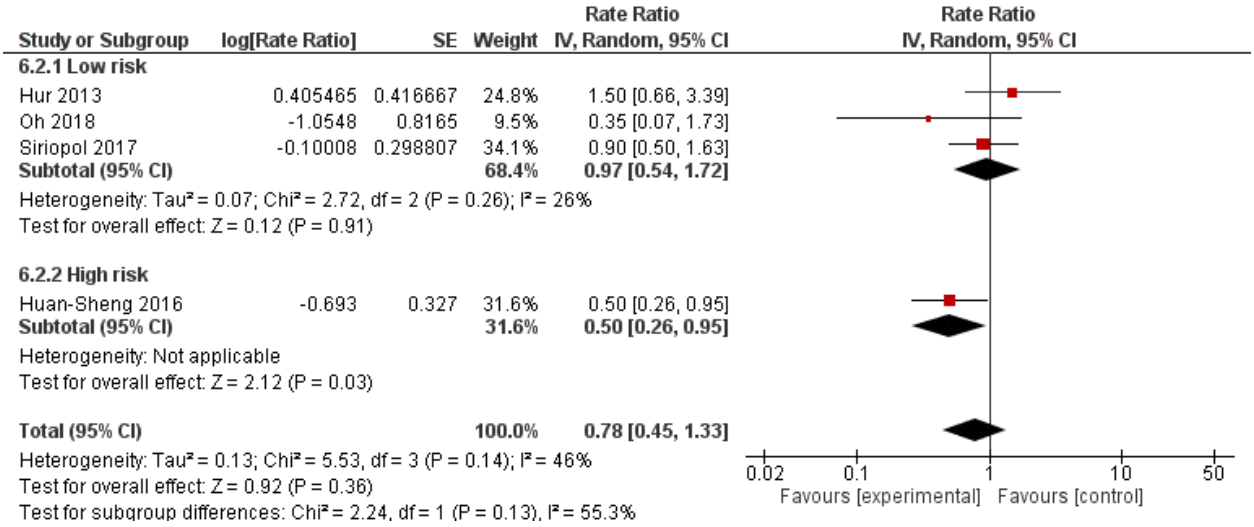
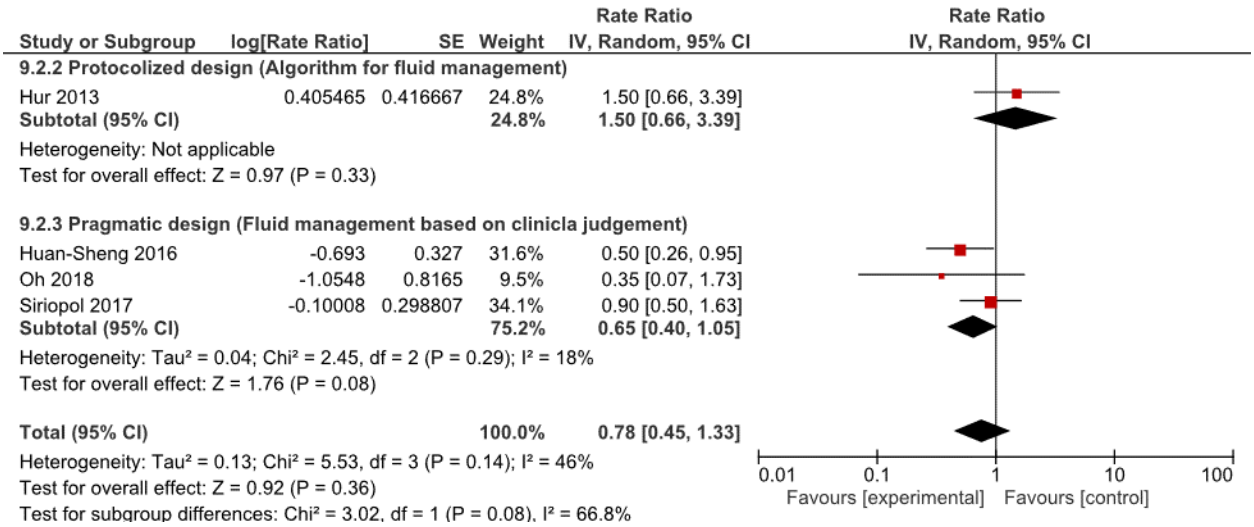


Figure S3.3.6: Cardiovascular events according to study design



Section 3.4: Rate of intra-dialytic hypotension

Figure S3.4.1: Rate of intra-dialytic hypotension according to technology used

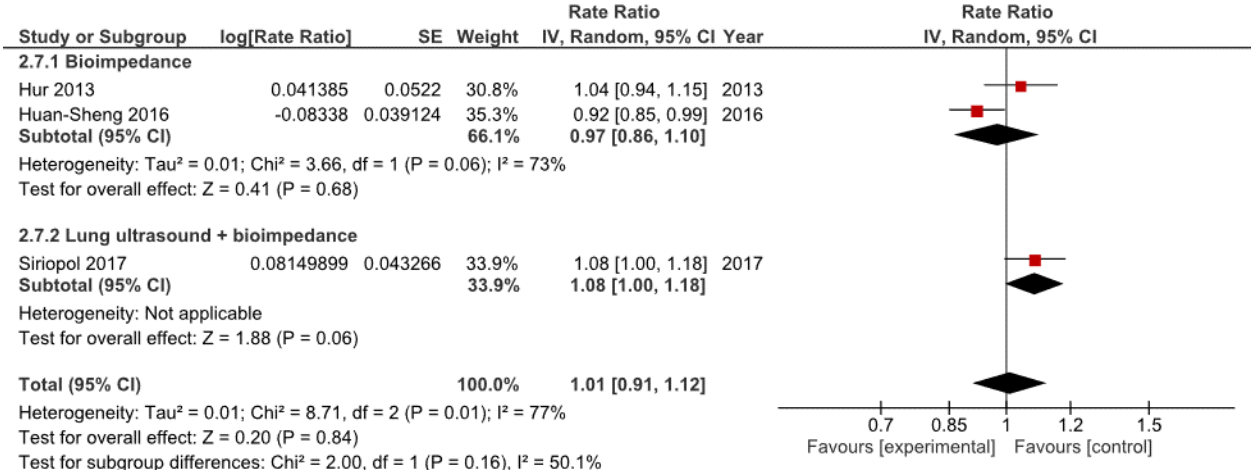


Figure S3.4.2: Rate of intra-dialytic hypotension according to duration of follow-up

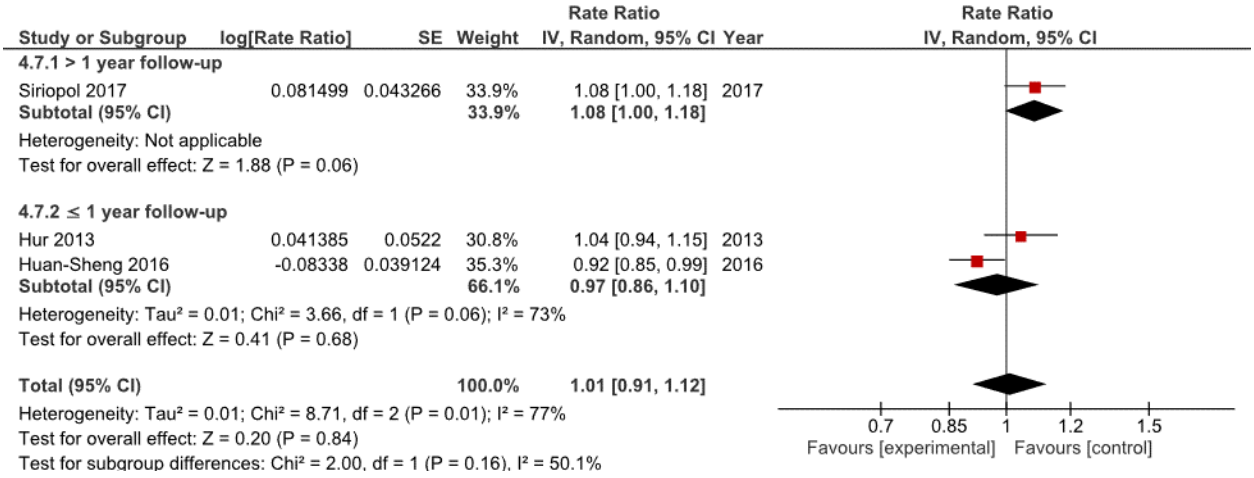


Figure S3.4.3: Rate of intra-dialytic hypotension according to source of funding

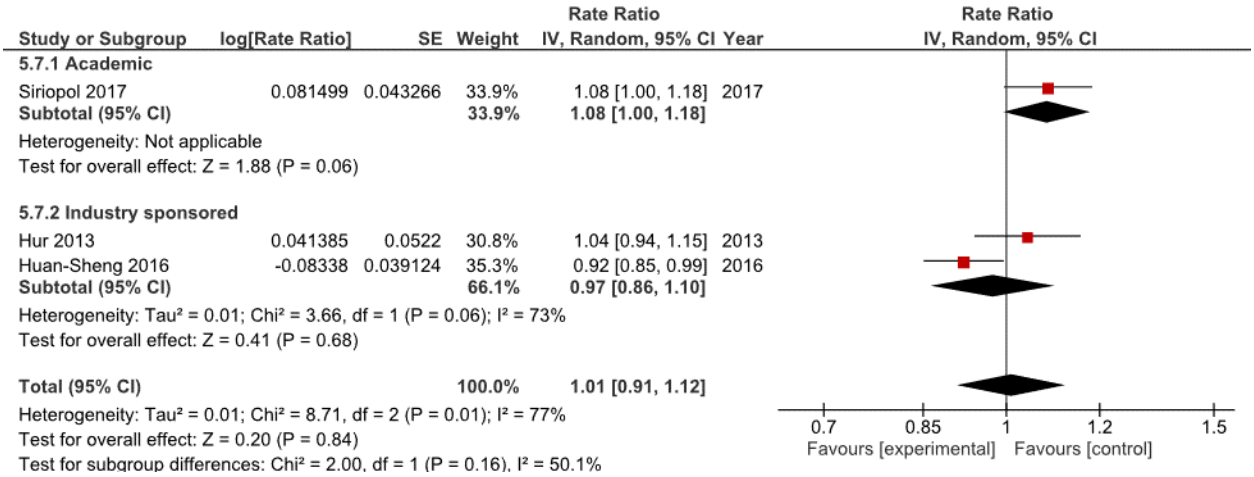


Figure S3.4.4: Rate of intra-dialytic hypotension according to risk of bias

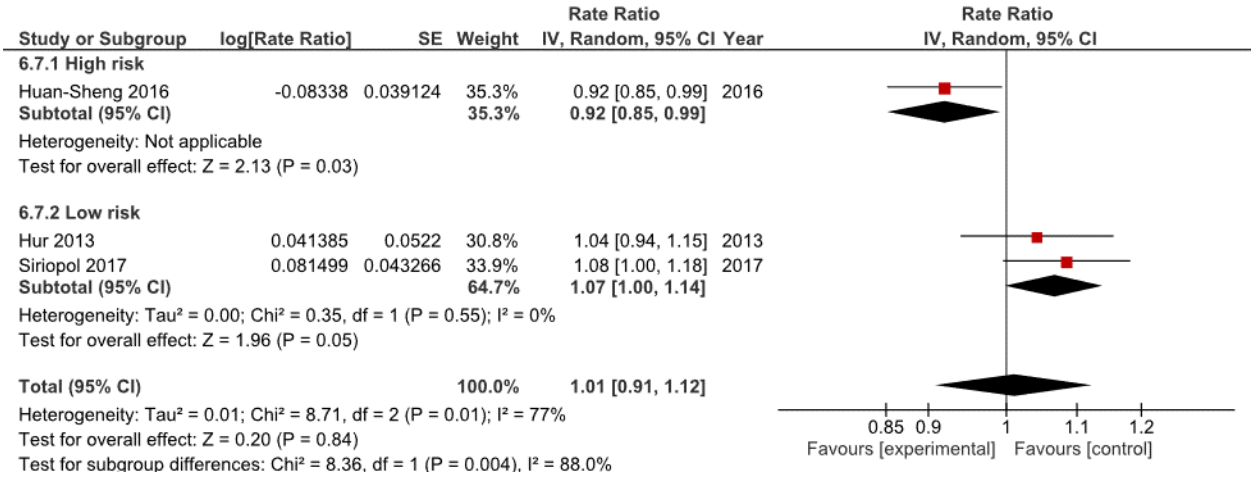
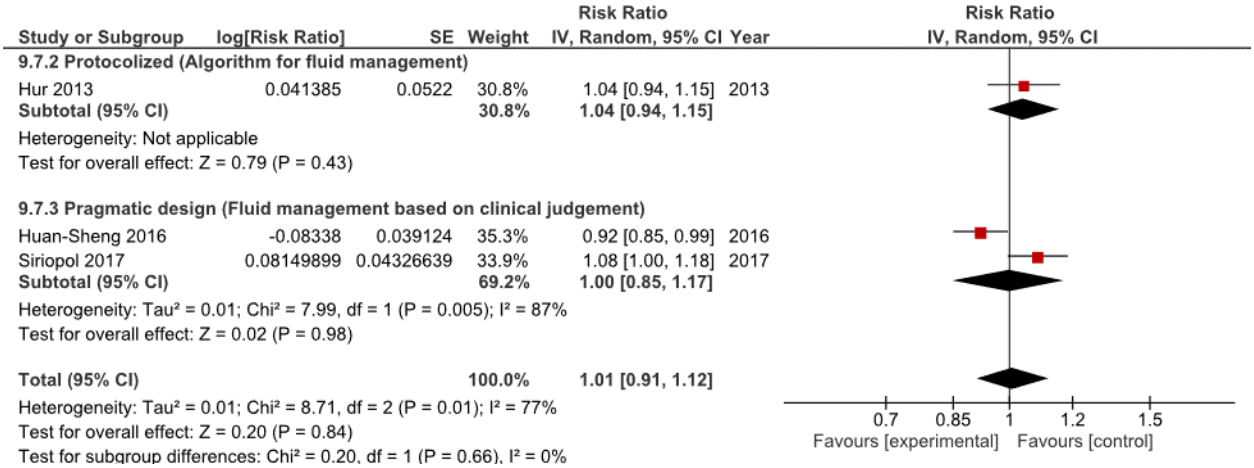
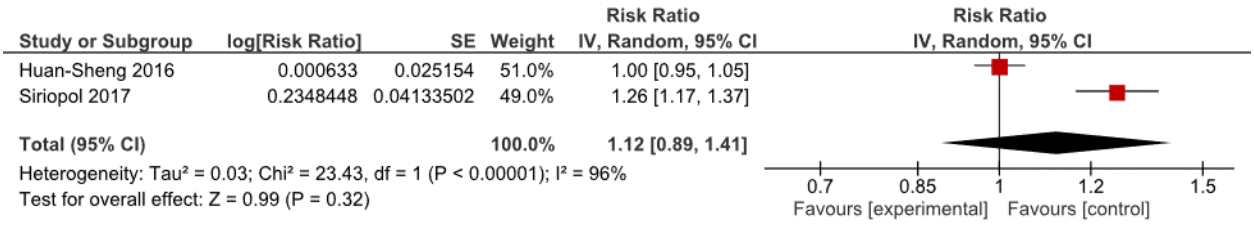


Figure S3.4.5: Rate of intra-dialytic hypotension according to study design



Section 3.5: Patient symptoms during dialysis

Figure S3.5.1: Patient symptoms during dialysis



Section 3.6: Systolic blood pressure before dialysis or at the peritoneal dialysis clinic

Figure S3.6.1: Systolic blood pressure according to dialysis modality

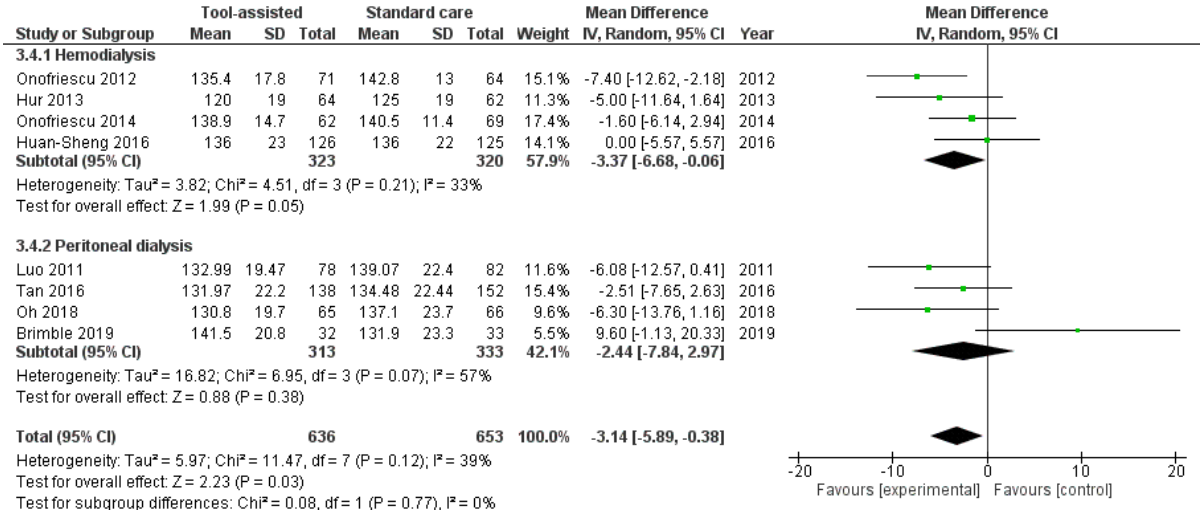


Figure S3.6.2 Systolic blood pressure according to duration of follow-up

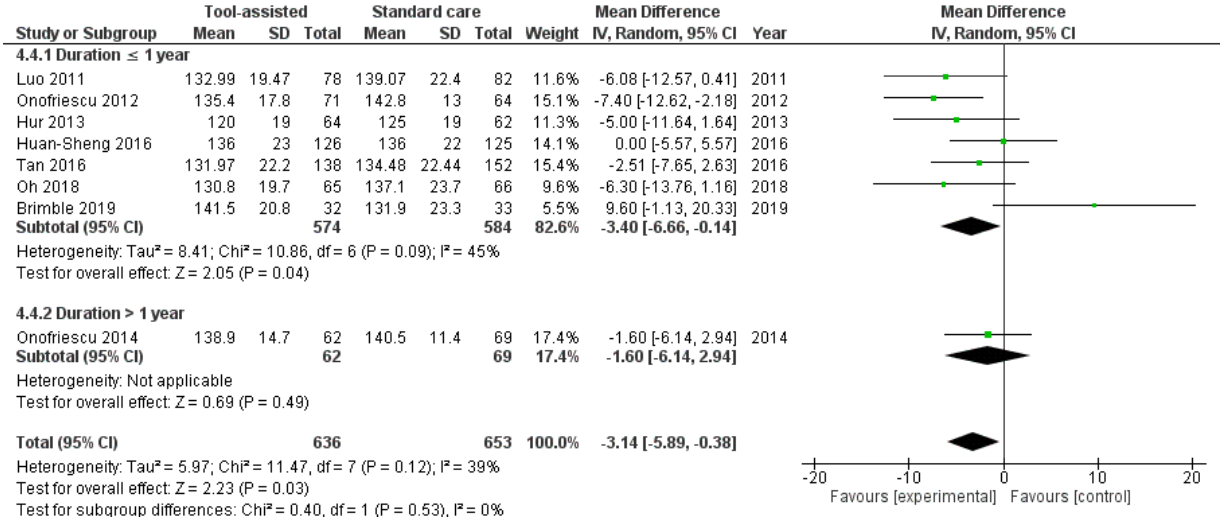


Figure S3.6.3: Systolic blood pressure according to source of funding

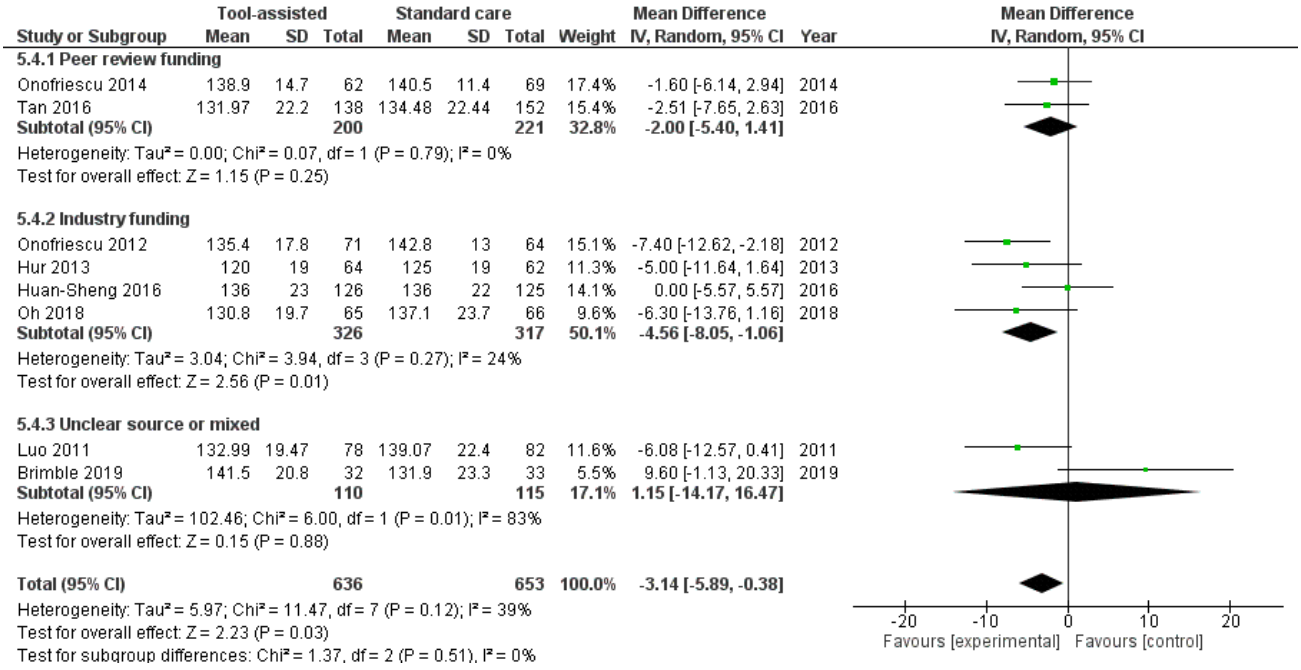


Figure S3.6.4: Systolic blood pressure according to risk of bias

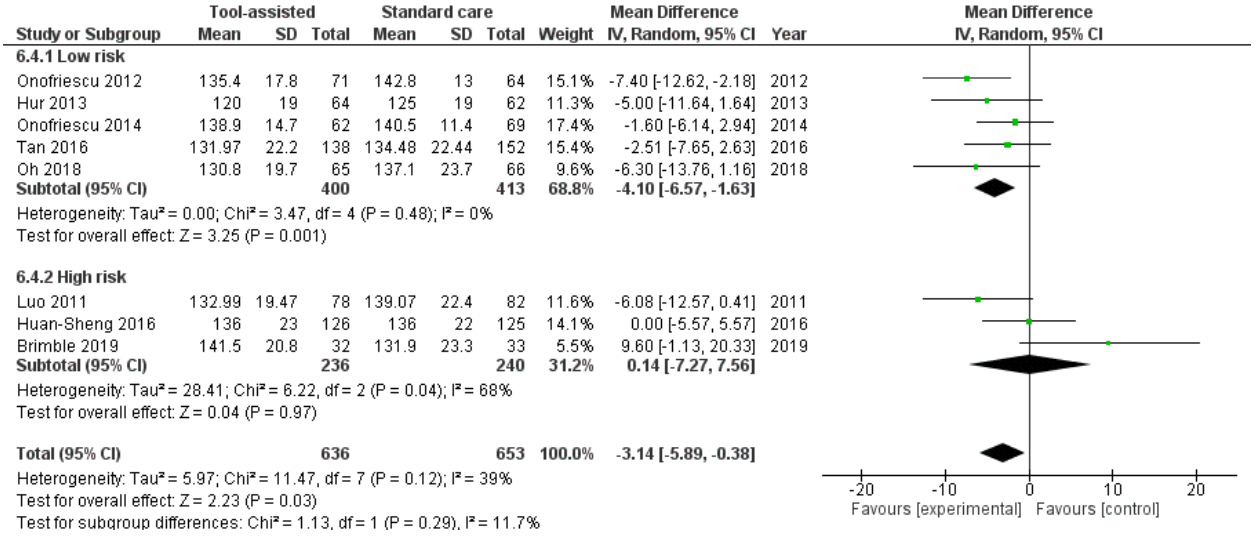


Figure 3.6.5: Systolic blood pressure according to the nature of the report used

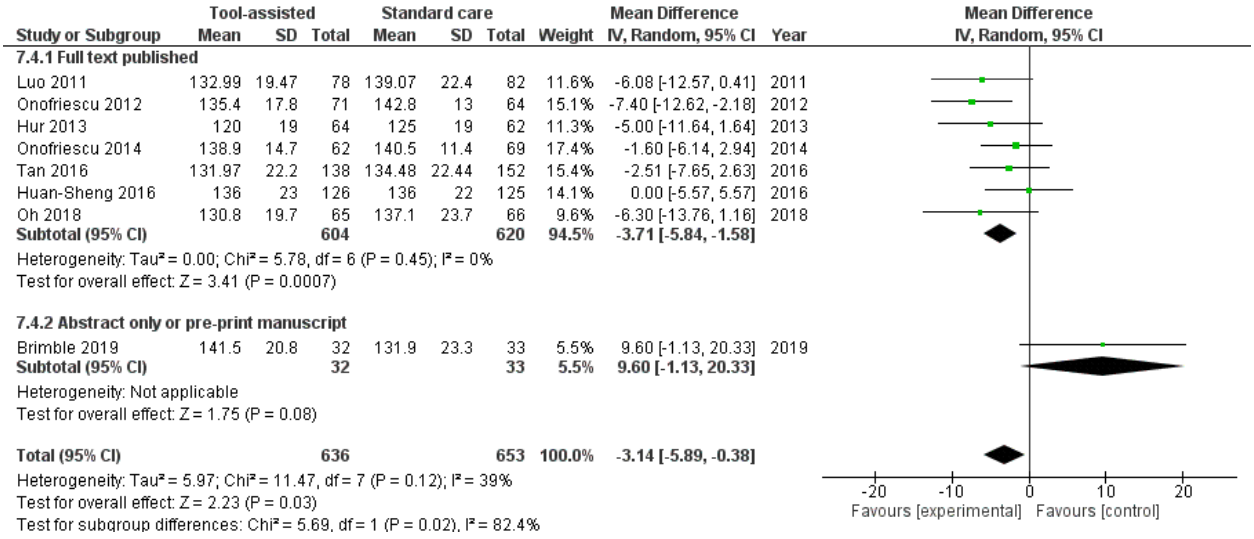
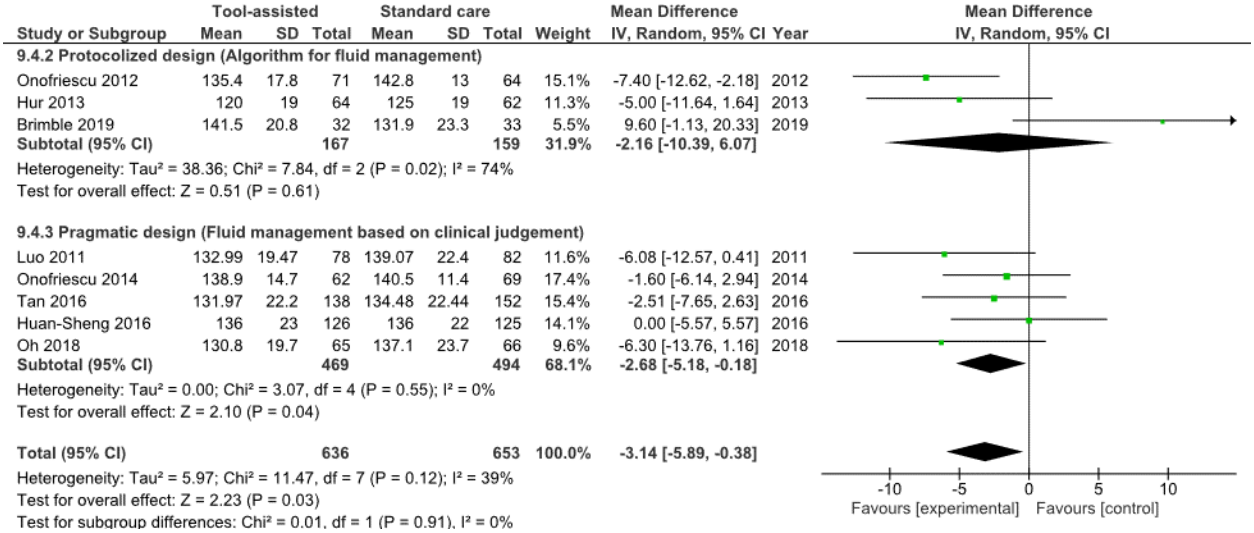


Figure 3.6.6: Systolic blood pressure according to the study design



Section 3.7: Diastolic arterial blood pressure before hemodialysis or at the peritoneal dialysis clinic

Figure S3.7.1: Diastolic arterial blood pressure according to dialysis modality

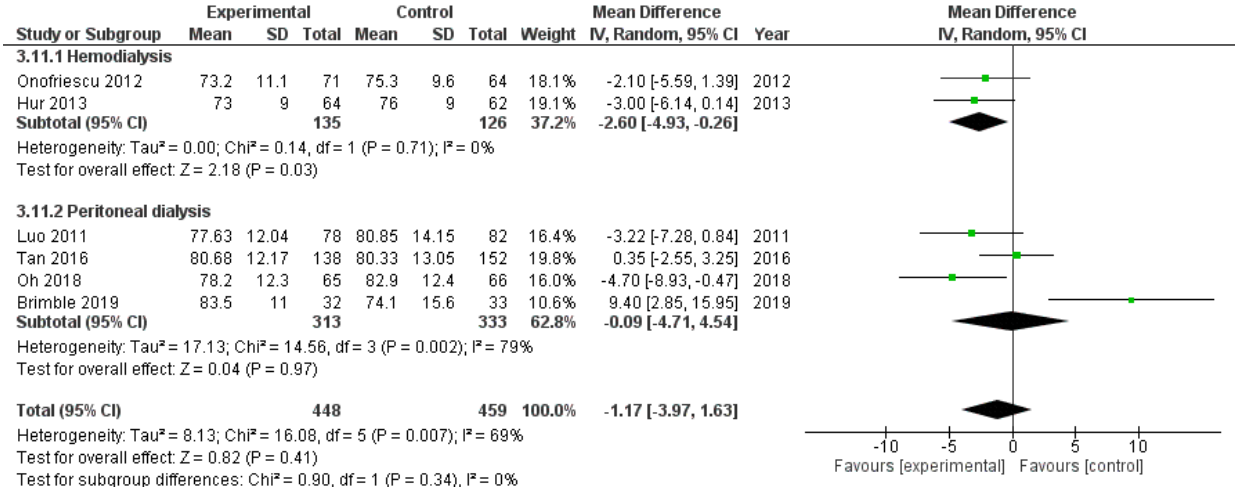


Figure S3.7.2: Diastolic arterial blood pressure according to funding source

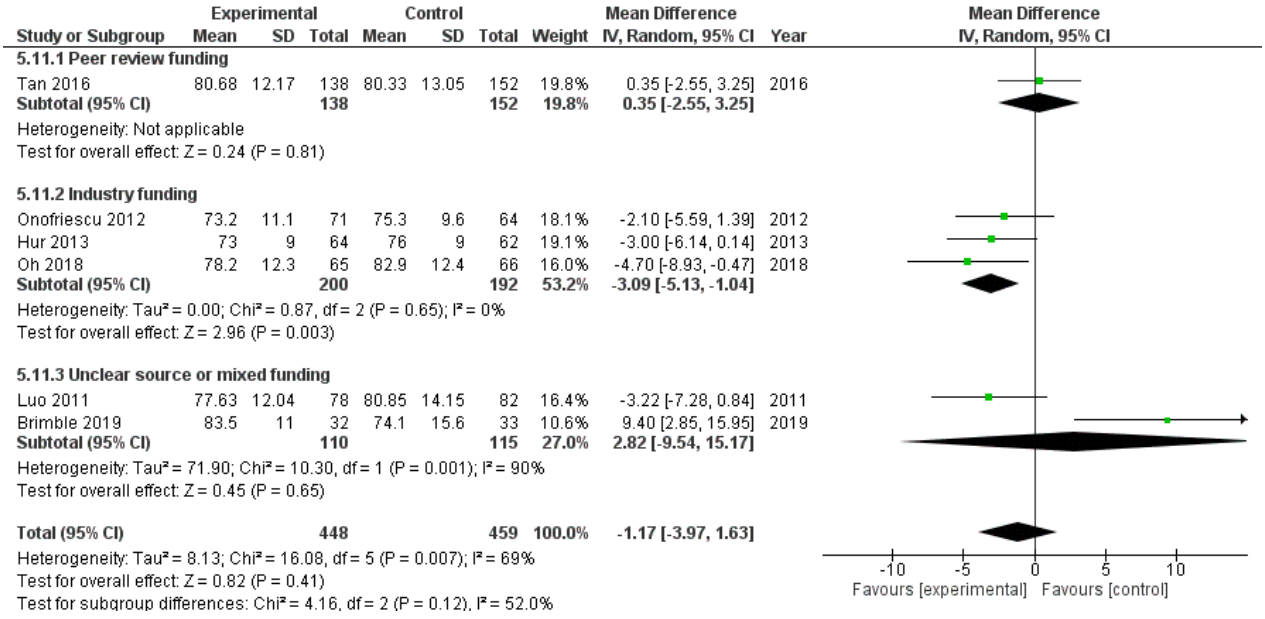


Figure S3.7.3: Diastolic arterial blood pressure according to risk of bias

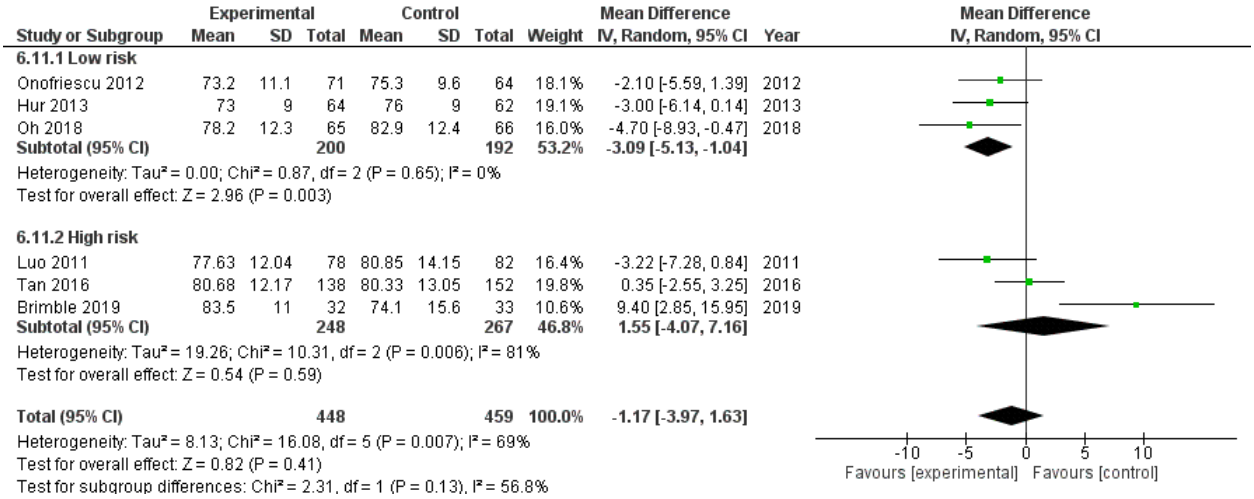
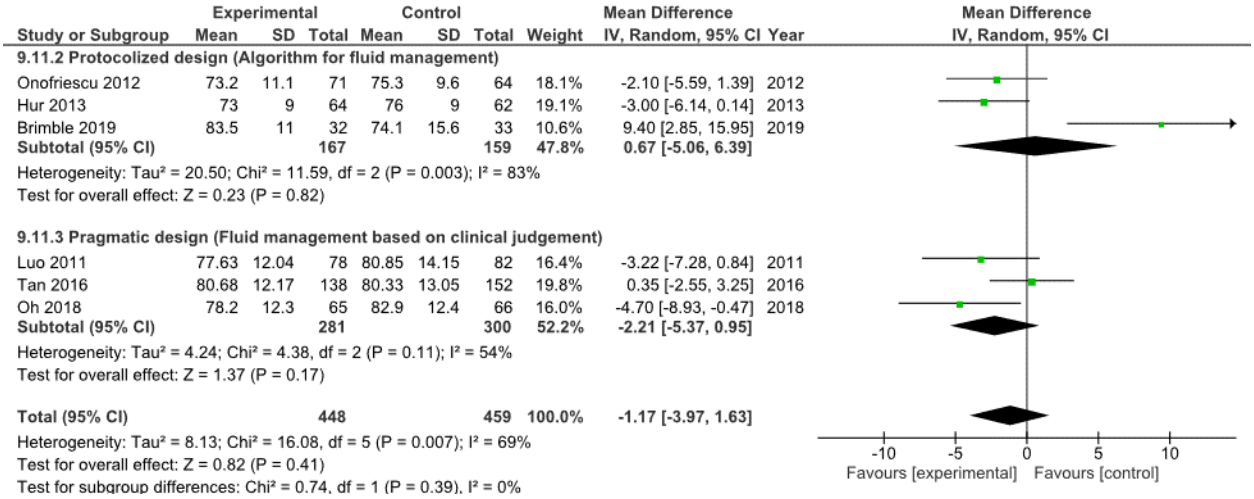
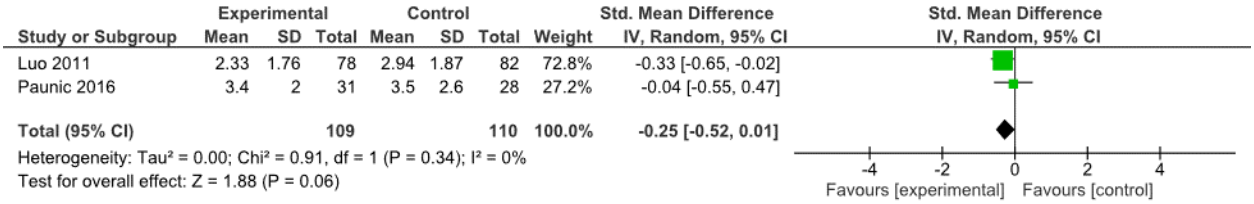


Figure S3.7.4: Diastolic arterial blood pressure according to study design



Section 3.8: Anti-hypertensive medication use in daily equivalent dose at the end of the intervention period

Figure S3.8.1: Anti-hypertensive medication use



Section 3.9: Left ventricular mass index at the end of the intervention period

Figure S3.9.1: Left ventricular mass index according to dialysis modality

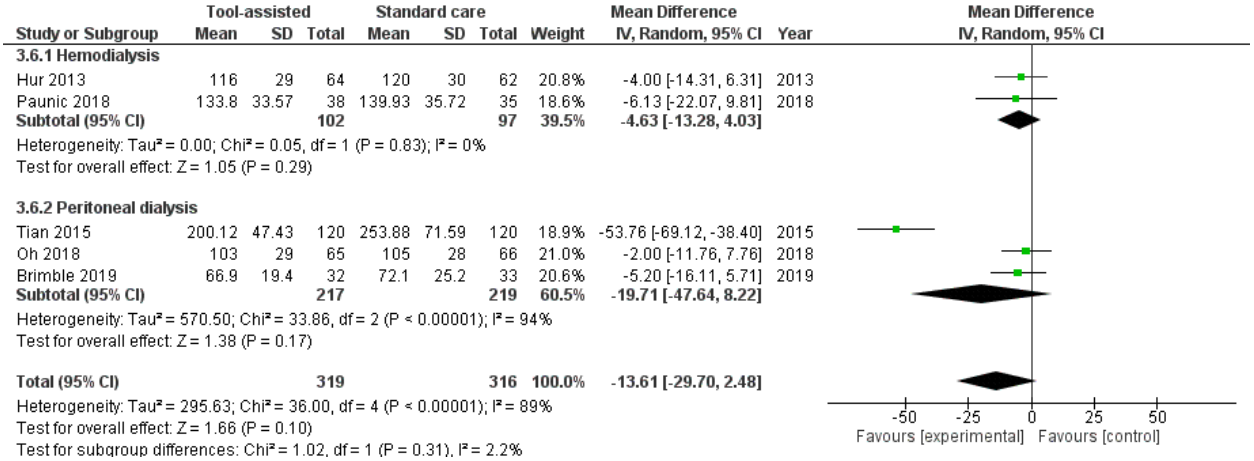


Figure S3.9.2: Left ventricular mass index according to source of funding

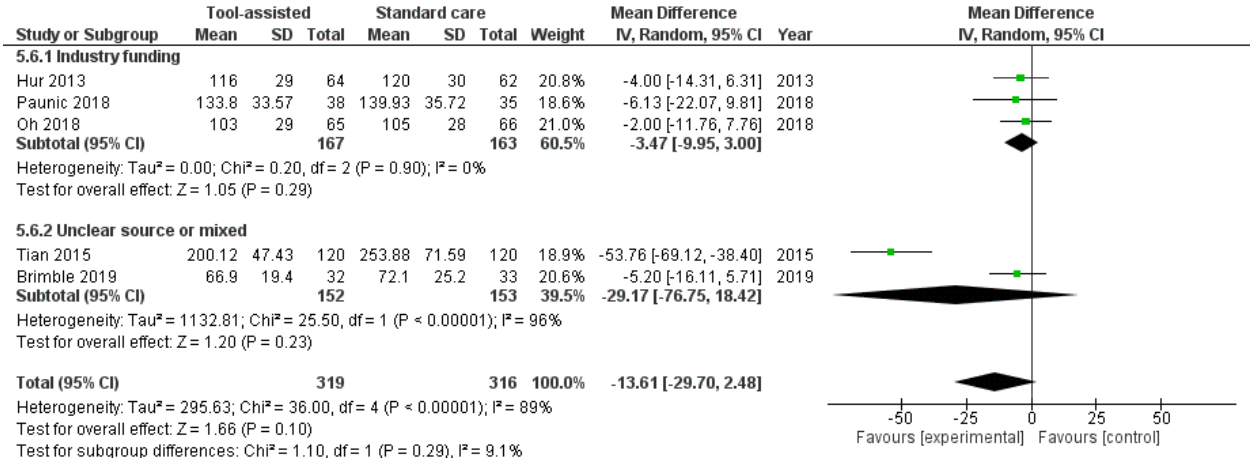


Figure S3.9.3: Left ventricular mass index according to source of risk of bias

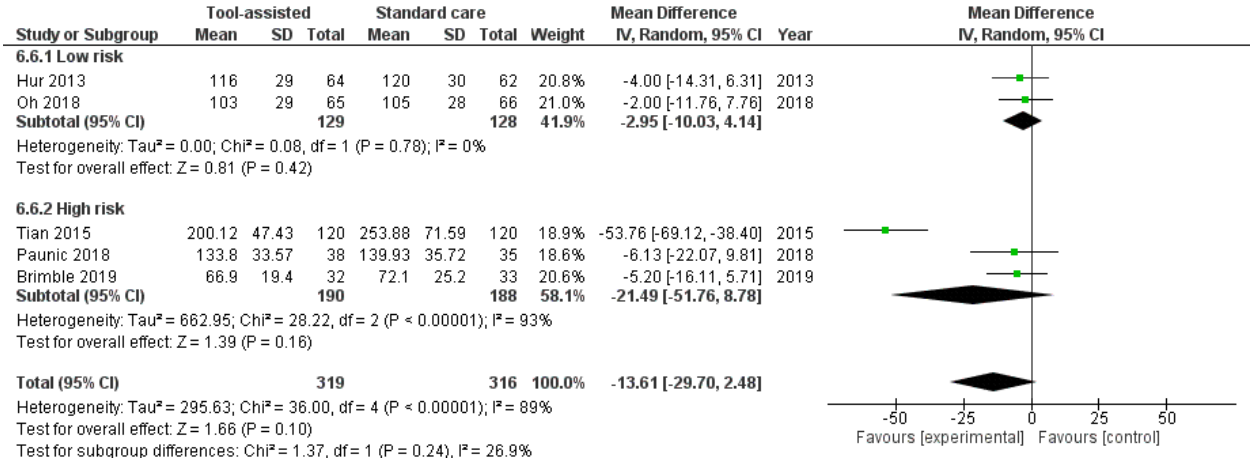
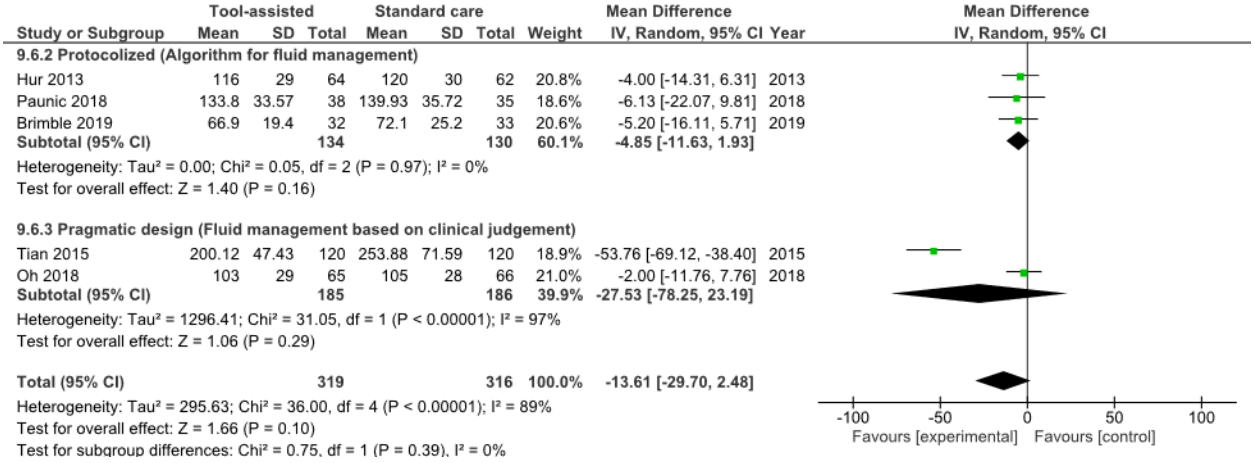
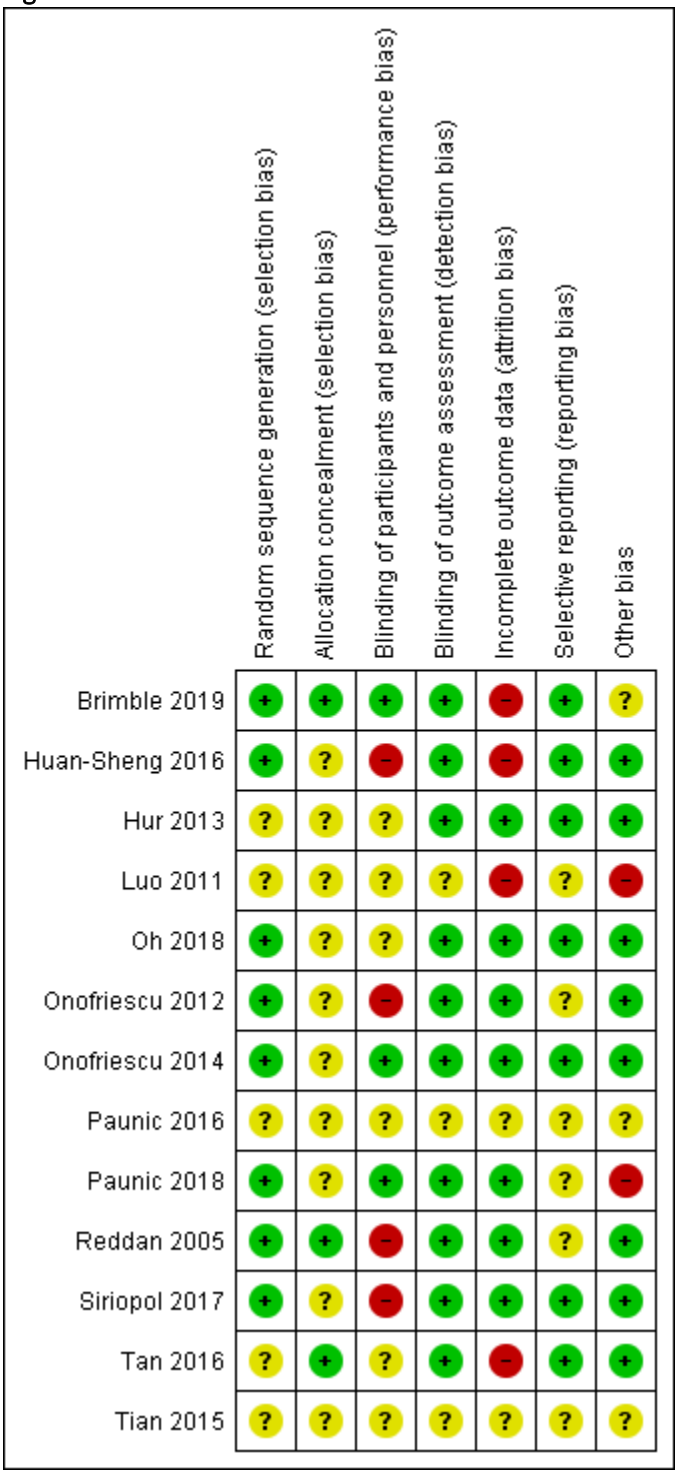


Figure S3.9.4: Left ventricular mass index according to study design



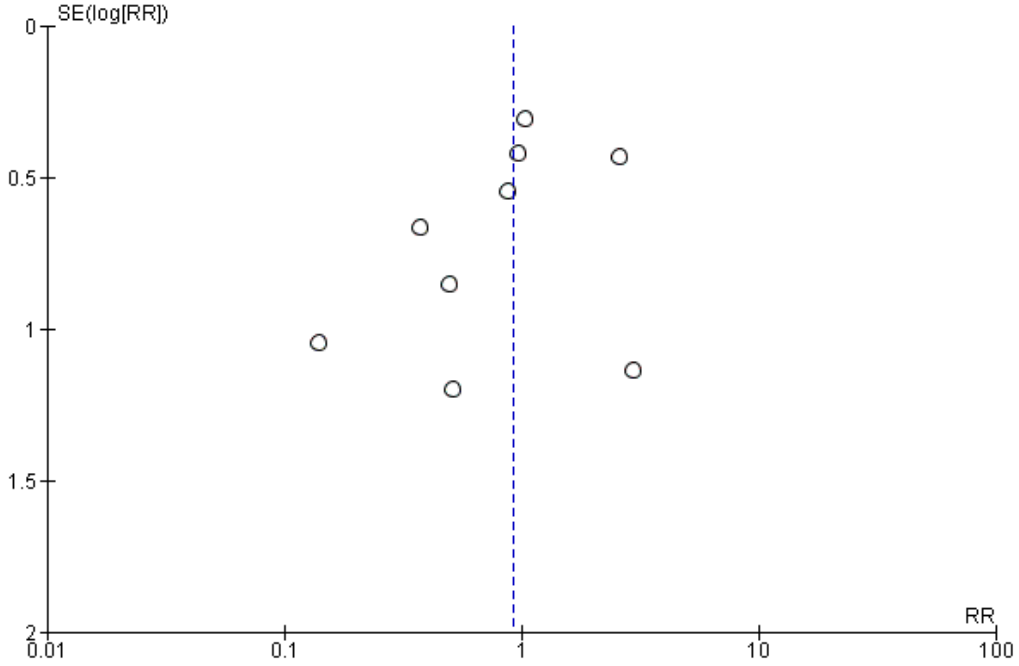
Appendix 4: Risk of bias assessment

Figure S4.1: Risk of bias assessment for the included studies



Appendix 5: Assessment of publication bias.

Figure S5.1 Funnel plot for all-cause mortality across included studies.



Appendix 6: Quality of the body of evidence assessment

Table S6.1: Evaluation of the quality of evidence for the estimated measure effect for the rate of mortality according to the GRADE methodology.

Factors	Effect on the quality of evidence	Comments
Limitations in the design and implementation	Serious	Multiples domains associated with high risk of bias in multiple studies including randomized sequence generation, allocation concealment and incomplete outcome data.
Indirectness of evidence	Minimal	The main review question was assessed in the included studies
Unexplained heterogeneity of results	Minor	Almost all statistical heterogeneity was explained in sub-group analysis according to technology type.
Imprecision of the results	Serious	As mortality was a rare event in most of the included studies, and few studies were available in each sub-group, a wide confidence interval is observed over the effect estimate.
Probability of publication bias	Minor	Insufficient information is available to determine if a publication bias is present but as most of the included studies reported no association between the intervention and mortality, this should not affect the quality of evidence on the conclusion.

Table S6.2: Evaluation of the quality of evidence for the estimated measure effect for secondary outcomes according to the GRADE methodology.

Secondary outcomes	**Cardiovascular events**	**All-cause hospitalisations**	**Intradialytic hypotension**	**Symptoms during dialysis**	**Systolic blood pressure**	**Diastolic blood pressure**	**Left ventricular mass index**	**Anti-hypertensive medications**
Limitations in the design and implementation	Serious	Serious	Serious	Serious	Serious	Serious	Serious	Serious
Indirectness of evidence	Minimal	Minimal	Minimal	Minimal	Minimal	Minimal	Minimal	Minimal
Unexplained heterogeneity of results	Serious: *(Significant statistical heterogeneity unexplained by subgroup analysis)*	Serious: *(Significant statistical heterogeneity unexplained by subgroup analysis)*	Minor: *(Significant statistical heterogeneity explained by subgroup analysis for the risk of bias)*	Serious: *(Significant statistical heterogeneity and only 2 studies available)*	Minimal: *(Minor statistical heterogeneity explained in sub-group analysis.)*	Moderate: *(Significant statistical heterogeneity partially by subgroup analysis)*	Serious: *(Significant statistical heterogeneity unexplained by subgroup analysis)*	Minimal *(No statistical heterogeneity.)*
Imprecision of the results	Serious	Serious	Moderate	Serious	Moderate	Moderate	Serious	Serious
Probability of publication bias	Minor	Minor	Minor	Minor	Minor	Minor	Minor	Minor
Quality of the body of evidence	**Very low**	**Very low**	**Moderate**	**Very Low**	**Moderate**	**Low**	**Very Low**	**Low**

Supplementary references:

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4. Tan BK, Yu Z, Fang W, Lin A, Ni Z, Qian J, Woodrow G, Jenkins SB, Wilkie ME, Davies SJ: Longitudinal bioimpedance vector plots add little value to fluid management of peritoneal dialysis patients. *Kidney int,* 89**:** 487-497, 2016
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