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The effect of Sodium Bicarbonate on blood pressure in Chronic Kidney Disease stages I-V non- Renal Replacement Therapy
A Systematic Review and Meta-Analysis

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Abstract

Despite the advances of medical science over recent decades, hypertension remains a leading cause of death and disability worldwide. Raised systolic blood pressure (SBP) is a major cause and consequence of chronic kidney disease (CKD) and reductions in SBP can delay the progression of CKD. Management strategies to reduce SBP in CKD include pharmacotherapy and dietary sodium/salt restriction. Acidosis (serum bicarbonate <22mmol/l), develops in individuals with CKD and its prevalence increases as CKD advances. Treatment of CKD acidosis can be achieved using sodium bicarbonate/citrate therapy. Concerns exist regarding the potential for the sodium load associated with the use of sodium bicarbonate/citrate to increase blood pressure, despite a lack of evidence directly supporting this. This research aims to systematically review blood pressure response to sodium bicarbonate/citrate therapy in CKD where renal replacement therapy is not used.

Using a population intervention comparison (P.I.O.) framework, a research question was developed which provided the basis for a literature search of academic and grey literature. Databases searched included: MEDLINE (OVID), EMBASE (OVID), CINHAL, AMED, COCHRANE database of systematic reviews (CDSR) and the WHO trials registry. Databases were searched for articles published to September 2017 and re-run in April 2018. Key terms included, but were not limited to: Chronic Kidney Disease, renal insufficiency, acidosis correction, alkali therapy and bicarbonate supplementation. Risk of bias was assessed using the Risk of Bias (RoB) 2.0 or Risk of Bias in Non-Randomised Studies (ROBINS) tools for RCT and NRSi publications respectively. A protocol for this review was written and published on PROSPERO.

A total of 908 studies were identified after duplicates were excluded. Following screening, a total of 6 publications, 4 Randomised Controlled Trial (RCT) and 2 Non-Randomised Studies of interventions (NRSi) were identified, providing 591 participants. All data extracted for SBP and

anti-hypertensive /diuretic medication change, was classified as 'other' outcome data i.e. not primary or secondary outcome data.

One of the RCT and both NRSi publications were evaluated as high risk of bias. Excess heterogeneity precluded a meta-analysis for blood pressure change following introduction of sodium bicarbonate/citrate. Sub-group and sensitivity analysis demonstrated that in individuals with CKD stage I-V non-renal replacement therapy, the prescription of sodium bicarbonate at a dose of 0.2-0.5mEq/kg is associated with a 0.51 mmHg reduction in SBP (95% CI 0.18-0.84). This result is clinically important since it suggests that sodium bicarbonate does not adversely affect blood pressure. When evaluated using Grading of Recommendations Assessment Development and Evaluation (GRADE) guidance, this outcome was graded as low, which suggests that the true effect is likely to be different from the estimated effect.

A meta-analysis for change in anti-hypertensive and/or diuretic medications as a surrogate for SBP change, was not possible due to a lack of statistical data. A narrative summary of included studies suggests that anti-hypertensive and/or diuretic therapies did not change following the introduction of sodium bicarbonate and exclusion of studies with a high risk of bias or due to high dose of sodium bicarbonate/citrate would not change this result.

Due to the lack of identified studies primarily evaluating the impact of sodium bicarbonate/citrate upon SBP in CKD, this systematic review highlights a gap in research knowledge. Future research is recommended to evaluate the impact of sodium bicarbonate/citrate therapy upon SBP in CKD.

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‘If we knew what we were doing, it wouldn’t be called research, would it?’
Albert Einstein

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Finally, I dedicate this this work to my parents, with love.

Glossary of terms

To ensure correct explanation of terms used in this glossary the explanation of each term has been based upon the NICE and the CDISC research terms glossaries. The exception to this is the definition of acidosis. Hyperlinks to the research glossary used for each term and the Kidney Disease Improving Global Outcomes (KDIGO) reference is at the end of this section.

Term	**Explanation**	**Source**
Acidosis	Serum bicarbonate level <22mmol/l. Results from the accumulation of hydrogen ions and/or loss of bicarbonate ions.	KDIGO 2013
Alpha error	See type I error	
Anti-hypertensive medication	Medications used to treat high blood pressure	N/A
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.	NICE
Bayesian statistics	Bayesian approaches. Approaches to data analysis that provide a posterior probability distribution for some parameter (e.g., treatment effect), derived from the observed data and a prior probability distribution for the parameter. The posterior distribution is then used as the basis for statistical inference.	CDISC
Before-and-after studies	An approach in which dependent variables are measured before and after an intervention has been delivered. Often called a pre–post study. The people in the pre- and post-intervention stages can either be the same or different.	NICE
Beta error	See type II error	
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.	NICE
Clinical significance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals. As an example, it might include a general reduction in symptoms, less pain or improved breathing. Effects identified as statistically significant are not always clinically significant, because the effect is small, or the outcome is not important.	NICE
Cochrane Collaboration	An international organisation that produces systematic reviews of the evidence from primary research relating to a particular health problem or healthcare intervention.	NICE
Cochrane handbook	A document produced by the Cochrane Collaboration to support the conduct of systematic reviews	N/A
Confidence Interval	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the	NICE

	'true' value for the population. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied). The confidence interval is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that 'based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110'. In such a case the 95% CI would be 110 to 150.	
Confounding	In a study, confounding occurs when the effect of an intervention on an outcome is distorted because of an association between the population or intervention or outcome and another factor (the 'confounding variable' or 'confounder') that can influence the outcome independently of the intervention under investigation.	NICE
Control group	A group of people in a study who do not have the intervention or test being studied. Instead, they may have the standard intervention (sometimes called 'usual care') or a dummy intervention (placebo). The results for the control group are compared with those for a group having the intervention being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the intervention group, to make it as easy as possible to detect any effects due to the intervention.	NICE
Distribution	In statistics, a group of ordered values; the frequencies or relative frequencies of all possible values of a characteristic.	CDISC
EPPI reviewer	The Evidence for Policy and Practice Information and Co-ordinating Centre software for all types of literature review, including systematic reviews, meta-analyses, 'narrative' reviews and meta-ethnographies.	EPPI website
Ethics committee	Bodies convened to protect human clinical research subjects work under	CDISC
Exclusion criteria	List of characteristics in a protocol, any one of which may exclude a potential subject from participation in a study.	CDISC
External validity	See validity	
Fishers exact test	a statistical significance test used in the analysis of contingency tables. Although in practice it is employed when sample sizes are small, it is valid for all sample sizes. It is named after its inventor, Ronald Fisher, and is one of a class of exact tests, so called because the significance of the deviation from a null hypothesis (e.g., P-value) can be calculated exactly, rather than relying on an approximation that becomes exact in the limit as the sample size grows to infinity, as with many statistical tests.	WIKI
Forest plot	A type of graph used to display the results of a meta-analysis.	NICE
Funnel plot	A visual way of showing how the results of several studies of the same treatment vary. Usually the effect of treatment in each study is plotted on a graph against the number of people involved. Ideally, the points fall into an inverted funnel shape. If they do not, publication bias or other problems are likely.	NICE

GRADE	Grading of Recommendations Assessment, Development and Evaluation. A systematic and explicit approach to grading the quality of evidence and the strength of recommendations.	NICE
Grey literature	Literature that has not been formally published in sources such as books or journal articles.	NICE
Hartung-Knapp adjustment	A statistical approach in account for uncertainty in the heterogeneity of a meta-analysis.	BMC
Heterogeneity	A term used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity.	NICE
Hierarchy of evidence	Study types organised in order of priority, based on the reliability (or lack of potential bias) of the conclusions that can be drawn from each type.	NICE
Homogeneity	A term used in meta-analyses and systematic reviews to indicate that the results of studies are similar; the opposite of heterogeneity. Study results are also regarded as homogeneous if any differences could have occurred by chance.	NICE
Hypertension	as systolic blood pressure persistently equal to or above 140mmHg and/or diastolic blood pressure equal to or above 80mmHg	WHO 2013
Inclusion criteria	The criteria in a protocol that prospective subjects must meet to be eligible for participation in a study.	CDISC
Internal validity	See validity	
Intervention	In medical terms this could be a drug treatment, surgical procedure, diagnostic test or psychological therapy	NICE
MeSH	Medical Subject Headings. The US National Library of Medicine's controlled vocabulary thesaurus used for indexing articles from biomedical journals for databases such as MEDLINE.	NICE
Meta-analysis	A method often used in systematic reviews to combine results from several studies of the same test, treatment or other intervention to estimate the overall effect of the treatment.	NICE
NICE guidance	Evidence-based recommendations produced by the National Institute for Health and Care Excellence (NICE)	NICE
'Other' outcome	See also outcomes. Outcome measures which are stated in a protocol or manuscript which are not the primary or secondary outcomes of the trial/study	
Outcome	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Depending on the intervention, outcomes could include changes in knowledge and behaviour related to health or in people's health and wellbeing, the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, symptoms or situation.	NICE
Outliers	Values outside of an expected range.	CDISC

P value	The p value is a statistical measure that indicates whether or not an effect is statistically significant. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 1% probability that the results occurred by chance), the result is seen as highly significant. However, a statistically significant difference is not necessarily clinically significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.	NICE
P.I.C.O	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).	NICE
Placebo	A fake (or dummy) treatment given to patients in the control group of a clinical trial. It is indistinguishable from the actual treatment (which is given to patients in the experimental group). The aim is to determine what effect the experimental treatment has had - over and above any placebo effect caused because someone has had (or thinks they have had) care or attention.	NICE
Prevalence	How common a disease or condition is within a population, either at a point in time or over a given period of time (it includes new and existing cases). It is different from incidence.	NICE
Primary outcome	The primary outcome is the main question to be answered and drives any statistical planning for the trial (e.g., calculation of the sample size to provide the appropriate power for statistical testing).	CDISC
Prospective study	A research study in which the health or other characteristic of patients is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.	NICE
Protocol	A plan or set of steps that defines how something will be done. Before carrying out a research study, for example, the research protocol sets out what question is to be answered and how information will be collected and analysed.	NICE
Publication bias	Publication bias occurs when researchers publish the results of studies showing that a treatment works well and do not publish those results showing it did not have any effect. If this happens, analysis of the published results will not give an accurate idea of how well the treatment works. This type of bias can be assessed by a funnel plot.	NICE
Randomisation	Assigning people in a research study to different groups without taking any similarities or differences between them into account. For example, it could involve using a random numbers table or a computer-generated random sequence. It means that each individual (or each group in the case of cluster randomisation) has the same chance of having each intervention.	NICE
Randomised controlled trial	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment or other intervention. One group (the experimental group) has the intervention being tested, the other (the comparison or control group) has an alternative	NICE

	intervention, a dummy intervention (placebo) or no intervention at all. The groups are followed up to see how effective the experimental intervention was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.	
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.	NICE
Sample	People in a study recruited from part of the study's target population. If they are recruited in an unbiased way, the results from the sample can be generalised to the target population as a whole.	NICE
Sensitivity analysis	A means of exploring uncertainty in the results of economic evaluations. There may be uncertainty because data are missing, estimates are imprecise or there is controversy about methodology. Sensitivity analysis can also be used to see how applicable results are to other settings. The analysis is repeated using different assumptions to examine the effect of these assumptions on the results.	NICE
Secondary outcome	A secondary variable. Data on secondary outcomes are used to evaluate additional effects of the intervention.	CDISC
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance. See P value.	NICE
Stratification	Grouping defined by important prognostic factors measured at baseline.	CDISC
Surrogate marker	A measurement of a drug's biological activity that substitutes for a clinical endpoint	CDISC
Treatment effect	An effect attributed to a treatment in a clinical trial. In most clinical trials the treatment effect of interest is a comparison (or contrast) of two or more treatments.	CDISC
Type 1 error	Error made when a null hypothesis is rejected but is actually true. Synonym: false positive.	CDISC
Type 2 error	Error made when an alternative hypothesis is rejected when it is actually true. Synonym: false negative.	CDISC
Validity	Whether a test or study actually measures what it aims to measure. Internal validity shows whether a study or test is appropriate for the question, for example, whether a study of exercise among gym members measures the amount of exercise people do at the gym, not simply whether people join. External validity is the degree to which the results of a study hold true in non-study situations, for example, in routine NHS practice. It may also be referred to as the generalisability of study results to non-study populations.	NICE

Hyperlinks/References

https://www.cdisc.org/standards/glossary
https://www.nice.org.uk/glossary
Kidney Disease: Improving Global Outcomes (KDIGO) CKD work group (2013) 'KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease'. *Kidney International Supplements* 3 (1), 1–163.

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1 Introduction

1.1 Hypertension (HTN)

Hypertension is defined as systolic blood pressure persistently equal to or above 140mmHg and/or diastolic blood pressure equal to or above 80mmHg (WHO 2013). Dubbed the 'silent killer' due to a lack of symptoms until the onset of clinical complications, hypertension is a modifiable risk factor in the development of cardiovascular disease (CVD) and chronic kidney disease (CKD) (Chobanian 2009). In the UK, it is estimated that 16 million adults are hypertensive and at a population level, hypertension is the biggest cause of premature death and disability in England; approximately half of all CVD deaths could be prevented with adequate treatment of hypertension (NHS Digital 2016). Systematic review and meta-analysis evidence suggest that the aetiology of CVD relates more to systolic than diastolic blood pressure (Rapsomaniki et al. 2014). Furthermore, observational data suggests that CVD risk elevates progressively as systolic blood pressure (SBP) rises above 115mmHg (Lewington et al. 2002) and SBP >130mmHg has been implicated in the development of CKD (de Goeij et al. 2011).

It is widely recognised that dietary salt (sodium) reduction is essential to the prevention and management of hypertension. Epidemiological data supports a linear association between increasing sodium intake and increasing blood pressure, particularly SBP (Elliott et al. 1996). The average daily salt intake for a UK adult is 8g/day (Public Health England 2016). This compares favourably with many other developed populations e.g. USA yet falls short of the World Health Organisation (WHO) target 5g of per day (WHO 2013). Systematic review evidence demonstrates that for populations like the UK, reducing salt consumption by 4.4g/day (from a baseline of 9-12 g/day), reduces SBP by 4.18mmHg (He, Li and MacGregor 2013). To contextualise the benefits of such dietary change and associated reduction of SBP,

statistical modelling predicts that for the same population a 3 g/d reduction could reduce the incidence of stroke by 13% and ischemic heart disease by 10% (He and MacGregor 2003).

1.2 Chronic Kidney Disease (CKD)

CKD describes abnormalities of kidney function or structure (NICE 2017). In the UK, 1.8 million people have diagnosed CKD and a further 1 million are considered to have undiagnosed CKD (Aitken et al. 2014). The focus of clinical care in CKD is to slow disease progression, reduce its impact upon other physiological systems and manage symptoms. Hypertension has been shown to increase the rate of CKD progression and to compound this issue, the prevalence of hypertension increases with advancing CKD (Judd and Calhoun 2015). To limit the progression of CKD global guidance recommends blood pressure treatment targets of <140/90mmHg or <130/80mmHg in the presence of proteinuria (Kidney Disease: Improving Global Outcomes (KDIGO) 2013). This guidance is supported by observational evidence from CKD IV-V individuals where a 10 mmHg increase in SBP resulted in an accelerated decline in renal function and an earlier start of RRT compared to those achieving a target SBP of <130mmHg (de Goeij et al. 2011). There is increasing evidence to suggest that Individuals with CKD are more likely to die of CVD than develop stage V disease (Schiffrin, Lipman and Mann 2007). Thus, appropriate management of hypertension reduces CKD progression and CVD related complications.

Dietary salt restriction has a central role in the management of hypertension in CKD. The WHO suggest that dietary sodium intake is proportionately linked with progression of CKD, secondary to hypertension and other renal risk factors including proteinuria and aldosterone secretion (WHO 2012). Furthermore, systematic review evidence demonstrates that salt restriction in CKD reduces blood pressure and proteinuria (McMahon et al. 2015). This evidence is important since if such reductions could be maintained long term, they may translate into clinically significant reductions in CKD incidence, progression and cardiovascular

events. Despite the additional risks associated with excess salt consumption in CKD, dietary salt recommendations parallel those of the 'normal' population at 5g salt per day (2g sodium)/day (KDIGO 2013).

1.3 Acidosis

Clinical acidosis is an often-neglected protagonist of CKD, associated with accelerated progression of CKD and poorer health outcomes (Chen and Abramowitz 2014). Acidosis is characterised by serum bicarbonate levels <22mmol/l, presents in approximately 30% of patients with advancing CKD and treatment with low cost, oral sodium bicarbonate has been shown to improve health outcomes (Loniewski and Wesson 2014) . There are no UK recommendations for treatment of acidosis in pre-dialysis CKD. International guidance recommends supplementation with sodium bicarbonate, if serum bicarbonate is <22mmol/l in CKD stage IV, unless contraindicated due concerns regarding exacerbation of hypertension, secondary to sodium loading (KDIGO 2013). However, the grading of evidence for this recommendation is level B and reflects that research evidence in this area is limited and inconclusive.

Oral sodium bicarbonate supplementation for the management of CKD related acidosis, is commonly started at a dose of 1500mg/day, rising to 4800mg/day (Joint Formulary Committee 2018) providing 20-60% of recommended daily sodium intake. The need to restrict dietary sodium to adjust for such pharmacological dosing is unlikely to be achievable, despite significant dietetic support. Consequently, the clinical use of sodium bicarbonate in CKD is potentially under-utilised due to perceived concerns regarding sodium loading and consequent hypertension. Whilst evidence supports a direct relationship between sodium consumption and hypertension in CKD (WHO 2012), there is also evidence which suggests that correction of acidosis with sodium bicarbonate, actually decreases blood pressure in CKD (Husted, Nolph

and Maher 1975). This raises the possibility that some sodium salts may have differing effects upon blood pressure, depending on their anion base and/or acidosis correction reduces blood pressure in CKD.

1.4 CKD, Hypertension, acidosis and future research

Clinical management of hypertension and acidosis helps to reduce CKD progression and mortality. The kidneys have a central role in the treatment of hypertension, since management strategies target the Renin-Angiotensin-Aldosterone-System (RAAS) e.g. dietary salt (sodium) reduction, anti-hypertensive medication and diuretics. However, despite availability of these therapies' hypertension remains a significant cause of CKD and associated mortality. There are limited numbers of anti-hypertensive drugs in development (Burnier, Vuignier and Wuerzner 2014), thus further clinical research is needed to identify novel or targeted ways to use existing treatments improve blood pressure control and health outcomes.

Clinical research endeavours to provide high quality information for the practice of evidence-based medicine (EBM). An area of increasing research interest for EBM is the use of stratified medicine. Stratified medicine endeavours to identify groups of individuals likely to respond to a defined treatment regime and KDIGO recommends application of this strategy in CKD (KDIGO 2013). The management of CKD Hypertension and acidosis may benefit from this approach, since for some individuals the risk of sodium loading with sodium bicarbonate to correct acidosis may be too great to justify its use. Conversely, there may be a stratum of patients where the benefit of acidosis correction outweighs the detriment of sodium loading. Therefore, review of the current evidence would inform research development in this area.

2 Background

2.1 Hypertension

2.1.1 Prevalence of hypertension and impact of health outcomes

Hypertension (blood pressure ≥ 140mmHg/90mmHg) is a significant global health issue and accounts for 9.4 million deaths, worldwide each year (WHO 2013). In England, the prevalence of adult hypertension is reported to be 25% (NHS Digital 2016) and is comparable to data from the United States (US), which suggests that 29% US adult population has hypertension (Nwankwo et al. 2013). Observational data from the Chronic Renal Insufficiency Cohort (CRIC) study, a large (n=3162) multi-centre study conducted in the US, suggests that for adults with stage III-IV kidney disease the prevalence of hypertension is 86%, three times greater than the normal population (Lash et al. 2009). Furthermore, the CRIC study also demonstrated that blood pressure progressively deteriorates as renal function declines: when mean systolic blood pressure (SBP) rose from 123.5mmHg to 130.5mmHg estimated glomerular filtration rate (eGFR) declined from >60ml/min to <30ml/min ($p = 0.0001$). Such a dramatic increase in prevalence of hypertension within the CKD population, may be partly explained by the population; hypertension is a major cause of CKD and consequently, is more prevalent in the CKD population. However, the associated loss of functional capacity which occurs with progressive kidney disease is also a recognised cause of hypertension.

2.1.2 Aetiology of hypertension in CKD

The aetiology of hypertension is multifaceted and is thought to result from the interaction of genetic, environmental and behavioural factors (Bolívar 2013). The kidneys have a major role in the regulation of blood pressure primarily through their effect on salt and water balance, exerted through the Renin-Angiotensin-Aldosterone-System (RASS). The RAAS is a hormonal feedback system, which regulates blood volume and vascular resistance to control arterial

blood pressure and cardiac output. The mechanism through which these actions are achieved is the regulation of plasma sodium. Sodium is the most significant cation distributed though out the extra-cellular fluid (ECF) and the major osmotic determinant of ECF volume and blood pressure. The kidneys maintain the osmolality of ECF volume via RAAS regulation of urinary sodium. Please see appendix 2 for further details regarding the action of the RASS to maintain blood pressure. Dysregulation or disruption to one or more processes within the RAAS system can cause abnormalities in the renal handling of sodium, which alter blood pressure and can result in hypertension (Manrique et al. 2009). Factors which are known to disrupt the RAAS include: excess sodium/salt consumption, salt sensitivity, abnormal kidney function and increased sympathetic activity (which is influenced by genetics, obesity, stress, lifestyle) (Bolívar 2013). The mechanisms for the accelerated rise in blood pressure associated specifically with CKD are not completely understood and are thought to include: increasing salt sensitivity, development of resistant hypertension, adaptations of sodium storage and alterations in circadian patterns of blood pressure (Judd and Calhoun 2015). Consequently, the interdependence of hypertension and CKD increases the complexity of clinical management for this patient group and justifies the need for further research.

2.1.3 Salt sensitivity

The relationship between CKD, blood pressure and sodium balance is complex. A difference in blood pressure response to salt consumption, supporting the identification of a salt sensitive phenotype, has been noted when comparing non-CKD hypertensive and normotensive subjects (de-Brito Ashurst et al. 2013). This is important since it helps identify patients who would benefit from targeted treatment to manage blood pressure. It is likely that individuals with CKD are more salt sensitive than the normal population (Mallamaci and Tripepi 2014), which could provide some explanation for the rapid development of hypertension as CKD progresses. Salt sensitivity has been defined as ‘a physiological trait by which the blood

pressure of some members of the population exhibits changes parallel to changes in salt intake' (Elijovich et al., 2016:e7). There is ongoing research evaluating how salt sensitivity disrupts normal sodium homeostasis to induce hypertension. It is possible that a combination of many factors including: renal malfunction, endothelial dysfunction and a non-osmotic accumulation of sodium in the skin interstitium contribute to this phenomenon (Choi, Park and Ha 2015). In their review of evidence, Meneton et al. (2005) discuss the changes in the renal handling of sodium which occur to increase salt sensitivity associated with age or CKD. They propose that GFR falls by 40% between the age of 30 and 80 years due to the loss of functional units i.e. nephrons, and the progressive development of glomerulosclerosis. Unless salt intake is proportionally reduced, sodium balance is maintained by a fractional increase in the excretion of sodium via the remaining functioning nephrons. The consequence of this physiological change is the development of hypertension in CKD and the age-related rise in blood pressure which is seen in populations consuming >3g salt per day. Clinically identifying salt sensitive individuals is challenging since there is a reliance on measuring blood pressure response to salt loading which is time and labour consuming. In addition, the absence of specifically agreed procedural guidance and appropriate reference ranges means that the diagnosis of salt sensitivity is subjective, which increases variability and accuracy of any 'salt sensitive' diagnosis. Thus, whilst it may not be possible to clinically identify individuals with CKD and salt sensitivity due to resource limitations, there is sufficient evidence to support general recommendations for salt restriction throughout the CKD population to manage hypertension and disease progression.

2.2 Acidosis and CKD

2.2.1 Acidosis, anion gap and blood pressure

One of the primary goals of CKD management is to slow disease progression and for many individuals with CKD rigorous control of blood pressure represents one aspect of clinical management. In 30-35% of individuals with CKD, correction of acidosis represents an additional management strategy to delay disease progression (Chen and Abramowitz 2014). Acidosis is defined by a serum bicarbonate of <22mmol/l (KDIGO 2013) and results from the accumulation of organic acids, hydrogen ions or the loss of bicarbonate ions. It has been suggested that 7% of individuals with CKD stage II are acidotic, rising to 37% in stage IV CKD (Goraya et al. 2017). A serum anion gap is defined as the sum of serum chloride and bicarbonate concentrations subtracted from serum sodium concentration (Kraut and Kurtz 2005). With respect to CKD, changes to serum anion gap can be a surrogate for metabolic acidosis which falls into two distinct types: hyperchloremic acidosis with a normal anion gap and metabolic acidosis with an increased anion gap (Kraut and Madias 2013). In the case of a normal anion gap metabolic acidosis, a reduction in serum bicarbonate is compensated by an increase in serum chloride ions to maintain electrolyte neutrality; consequently, the anion gap remains unchanged and normal Whereas in an increased anion gap metabolic acidosis, there is an increase in unmeasured anions derived from organic acids retained due to CKD, which are not compensated for by an increase in serum chloride.

Observational data demonstrates that in non-CKD populations a high anion gap (low serum bicarbonate) is associated with an increasing prevalence of hypertension (Taylor, Forman and Farwell 2007). A review of the National Health and Nutrition Examination Survey (NHANES) data demonstrated that, after adjusting for age, gender, race, BMI, creatinine, albumin, sodium and chloride, systolic blood pressure increased by 0.46 mmHg for each mEq/L decrease in bicarbonate (95% CI: 0.23 to 0.69 mm Hg). After multivariable adjustment, participants in

the highest quintile of bicarbonate (mean: 26.8 mEq/L) had systolic blood pressure 2.73 mmHg lower than participants in the lowest quintile of bicarbonate (mean: 20.2 mEq/L) (95% CI: 1.26 to 4.20 mm Hg; p<0.01) (Raphael 2016). In support of this finding, a prospective case-controlled study of 695 non-obese American nurses, conducted over a 6-year period, demonstrated that nurses who had a low serum bicarbonate at the point of recruitment to the study were more likely to develop hypertension (Mandel et al. 2013). When adjustments for body mass index, family history of hypertension, plasma creatinine, and dietary and lifestyle factors were made, the outcome showed that higher plasma bicarbonate was associated with lower odds of developing hypertension across serum bicarbonate quintiles (p <0.04). Subjects in the highest quintile of plasma bicarbonate had 31% lower chance of developing hypertension (OR = 0.69; 95% confidence interval = 0.48–0.99) compared with the lowest quintile.

With respect to CKD populations there is limited evidence that a high anion-gap or a hyperchloremic acidosis is associated with an increase in blood pressure. It is unclear if this is related to an absolute absence of evidence or the existence of too many confounders in late CKD to enable any research conclusions. Given the limited human evidence to evaluate the impact of low serum bicarbonate (acidosis) or a high anion gap upon blood pressure, it is necessary to consider evidence from animal studies. Studies of 2/3 nephrectomised rates suggest that the decline of renal function associated with acidosis is mediated by acid retention induced kidney endothelin and aldosterone production (Wesson and Simoni 2010). This is of significant interest since rat studies have also shown that increasing aldosterone levels contributes to hypertension and renal injury (Greene, Kren and Hostetter 1996). With respect to human studies the evidence suggests that in the presence of subclinical and metabolic acidosis, hydrogen ion retention causes an increase in plasma endothelin and aldosterone levels (Wesson et al. 2011). Whilst evidence and physiological understanding of

RAAS suggests that increasing circulating aldosterone induces hypertension, there is no available evidence to confirm that that the increase in aldosterone associated with acidosis, causes an increase in systolic blood pressure in CKD. Additional research in this area is warranted.

2.2.2 Treatment of acidosis in CKD.

There is limited guidance available for the management of acidosis in non-renal replacement CKD. International guidance (KDIGO 2013) recommends the use of sodium bicarbonate or sodium citrate for the management CKD acidosis, whilst highlighting concerns regarding possible sodium loading and disruption to blood pressure and fluid retention. However, KGIDO also highlights the lack of large and long-term trials to support this recommendation and suggests that clinicians should be aware of the potential controversy associated with a recommendation based on limited evidence. The benefit of sodium bicarbonate or its precursor sodium citrate in slowing progression of CKD has been demonstrated in human and rat studies (Abramowitz et al. 2013; Ori et al. 2015). However, there is also growing evidence to support alternative methods of managing CKD acidosis, which include the use of low acid diets (Goraya et al. 2013). In its simplest sense, a low acid diet restricts foods such as high-protein foods which produce dietary acid and encourages consumption of foods capable of generating bicarbonate ions from naturally occurring citrate e.g. fruit and vegetables. To reduce dietary acid consumption in their studies of low acid diets, one study provided financial aid to ensure that 50% of food intake within a study participants household was derived from fruit and vegetables (Goraya et al. 2013). Recent data from this group demonstrates that such dietary changes treated CKD acidosis and resulted in significant reductions in blood pressure, antihypertensive and/or diuretic medications (Goraya et al. 2017). It is difficult to evaluate if these clinical changes were a direct result of correcting acidosis or due to a reduction of body weight, reduction of salt intake, promotion of potassium intake or a combination of these

factors. Loniewski (2012) suggests that a low acid diet supplemented with sodium bicarbonate may be the best approach to treatment.

2.3 Sodium supplements and blood pressure

2.3.1 Sodium bicarbonate and blood pressure

The BNF (Joint Formulary Committee 2018) recommended dose for sodium bicarbonate supplementation for treatment of acidosis in CKD is 4.8g daily. This provides 57mmol sodium and 57mmol bicarbonate, which equates to 63% of daily recommended sodium intake in CKD. However, in prescribing sodium bicarbonate there is conflict between the negative impact of the sodium load upon the development of hypertension (Yaqoob 2013) and the positive impact of sodium bicarbonate supplementation on disease progression in acidotic CKD (Kovesdy 2012). Research directly evaluating the impact of sodium bicarbonate on blood pressure in CKD, to guide the clinical treatment of acidosis is limited in both quality and quantity.

2.3.1.1 Evidence evaluating the impact of sodium bicarbonate upon blood pressure in CKD subjects

A non-randomised intervention crossover study from 1975 comparing the tolerance of sodium chloride versus sodium bicarbonate in human subjects with stage 5 CKD, demonstrated that sodium bicarbonate therapy did not increase blood pressure whilst an equivalent dose of sodium chloride increased blood pressure ($p<0.05$) and sodium excretion was significantly greater when consuming sodium bicarbonate compared to sodium chloride ($p<0.02$) (Husted, Nolph and Maher 1975). A lack of randomisation reduces confidence in this result. In addition, whilst small p values minimise the possibility of the findings occurring by chance, it is possible that due the small population size (n=10) the study will be underpowered to detect a result.

The publication suggested that sodium bicarbonate would not result in clinically significant sodium retention when compared to sodium chloride intake, due to increased urinary losses. The null hypothesis was therefore rejected and introduced the possibility of a type I or α error. Unfortunately, no power calculations are available for this study. However, it should be noted that this paper was rigorous in its scientific approach for its era and evaluation by current standards may inevitably introduce doubt regarding outcomes observed.

More recently, four non-randomised prospective before, after studies assessing the impact of sodium bicarbonate therapy in CKD, measured blood pressure as a secondary or 'other' outcome (Abramowitz et al. 2013; Chen et al. 2016; Ori et al. 2015; Verove et al. 2002). For all four studies, the data collected demonstrated that sodium bicarbonate therapy did not have a detrimental effect on blood pressure. As with the studies cited previously, participant numbers were small, ranging from 13 to 20 subjects, and information regarding subject selection or anti-hypertensive medication was not always available. The latter is important since changes in antihypertensive therapy may mask any negative impact sodium loading could have upon blood pressure and limits clinical interpretation of reported outcomes. However, these results are important to evaluate since they are counter-intuitive to our understanding of the role of sodium in the management of hypertension in CKD.

Abramowitz et al. (2013) in a prospective before, after study noted that individuals could be divided into two differing groups, dependant on the presence of oedema. Individuals with oedema did not show the same dose dependant rise in serum bicarbonate compared to individuals without oedema. There was a 94% (95% CI=43%–99%) less likelihood of patients with oedema on study entry achieving a ≥3 mEq/L increment in serum bicarbonate, compared with patients without oedema. This is interesting since it suggests that physiologically, sodium

bicarbonate requirements may be different depending on CKD pathology and raises the possibility that treatment with sodium bicarbonate may be stratified to maximise outcomes.

Clinically, stratification endeavours to identify groups or sub-groups of individuals likely to respond to a defined treatment regime. International guidance recommends application of this strategy in CKD management (KDIGO 2013). The presence of oedema may represent a patient subgroup that clinicians are hesitant to treat with sodium bicarbonate due to concerns relating to additional fluid retention and deterioration of BP. As such, the treatment of hypertension and acidosis in CKD may benefit from a stratified approach since, for some individuals, the risk of sodium loading through supplementation with sodium bicarbonate may limit its use.

Looking for evidence beyond human studies to evaluate the impact of sodium bicarbonate supplementation upon blood pressure produces potentially conflicting results. In a study of acidotic mass nephrectomised rats, sodium bicarbonate and sodium chloride significantly increased blood pressure, whereas calcium carbonate lowered blood pressure (Phisitkul et al. 2008). Furthermore, from the results documented sodium chloride appeared to cause a greater rise in blood pressure than sodium bicarbonate; unfortunately, the significance of blood pressure changes between these two study groups was not statistically evaluated.

2.3.1.2 Evidence evaluating the impact of sodium bicarbonate upon blood pressure in non-CKD subjects

Interestingly, data from a crossover study of non-CKD subjects, also testing the hypothesis that sodium chloride and sodium bicarbonate have divergent effects on blood pressure (Luft et al. 1990), had similar findings to Husted, Nolph and Maher (1975). In this study, dietary salt was restricted in both study groups and sodium chloride supplementation did not increase blood pressure in either the normotensive or hypertensive group, whereas an equimolar amount

sodium in the form of sodium bicarbonate reduced blood pressure, by 5mmHg, in the hypertensive group only ($p < 0.05$). The results of this study suggest that sodium bicarbonate supplementation or dietary chloride restriction reduces SBP in hypertensive individuals. This study also documents a lack of blood pressure response to sodium chloride which conflicts with a large body of observational and intervention trial evidence suggesting that sodium chloride supplementation increases blood pressure. It is possible that the total daily intake of sodium chloride was modest (8.2g/d) and possibly insufficient to induce a response over the 7-day intervention period or the 4 day wash out period, was inadequate to deplete the complex human sodium storage mechanisms described by Titze et al. (2013). In addition, the degree of significance relating to blood pressure reduction due to bicarbonate supplementation was small ($p<0.05$). It is difficult to evaluate if the results represent a true effect or a type II (β) error due to small population numbers ($n = 20$).

2.3.2 Sodium chloride, chloride and BP

There is an overwhelming body of evidence which demonstrates that that increasing sodium chloride (salt) consumption increases blood pressure at a population level (WHO 2013). Moreover, reductions in sodium chloride (salt) intake are associated with significant reductions in blood pressure in both CKD and non-CKD populations (He, Li and MacGregor 2013; McMahon et al. 2015). Physiologically increasing sodium consumption intuitively increases blood pressure through activation of the RAAS. However, over recent years, the influence of chloride in the development of salt sensitivity and hypertension has become an area of research interest. In their review of the evidence, McCallum, Lip and Padmanabhan (2015) suggest that chloride is an independent mediator of hypertension. This is supported by an earlier review publication evaluating rat studies, where the authors state that selective dietary sodium loading in the absence of chloride does not induce hypertension (Kotchen 2005). If

proven, this could help to alleviate concerns associated with the use of sodium bicarbonate and development of hypertension in the acidotic CKD population.

2.4 Summary

From the evidence reviewed, it is possible that sodium bicarbonate supplementation does not increase blood pressure to the extent predicted from the associated sodium load. To determine this and inform future research in this area, a rigorous, comprehensive systematic review is required.

2.5 Aims of this systematic review

This research aims to systematically review the evidence regarding the impact of sodium bicarbonate supplementation on blood pressure in CKD I-IV, to inform the course of future research and improve clinical practice. If statistical data allows, a meta-analysis will be undertaken to evaluate the impact of sodium bicarbonate supplementation on blood pressure in CKD stages I-IV.

3 Methodology

3.1 Introduction

The impact of correcting acidosis with sodium bicarbonate upon blood pressure in Chronic Kidney Disease (CKD) represents an unmet research need, which this research aims to evaluate. From an epistemological perspective, this research sits within the positivist paradigm and necessitates a structured, defined, quantitative methodology. A focused research question was developed to provide the foundation for a literature review. To improve scientific validity, this appraisal took the form of a systematic review. 'A systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria to answer a specific research question' (Chandler et al. 2017: 1.1). The explicit, systematic methods aim to minimize bias and provide more reliable findings from which conclusions can be drawn and decisions made. To simplify, a systematic review identifies and evaluates evidence using pre-published or pre-specified criteria to investigate a research question. The National Institute for Health Research recommends that all clinical trials should start with a systematic review of the existing research evidence (NIHR 2017). This strategy helps to reduce research waste by ensuring that the research question cannot be answered by existing research evidence. Systematic reviews are also an ethical use of research resources since they synthesize data available in the public domain. This lack of patient/public involvement alters the level of governance and financial investment required to support the research. A systematic review also has ethical challenges which include: the source of data included in the review and the conduct of the review. These challenges may be overcome using a pre-published protocol and extraction of ethical approval information for included studies.

Well conducted systematic reviews of well conducted studies, are highly valued research outputs and form the pinnacle of the research hierarchy (Murad et al. 2016). It has been suggested that systematic reviews have three principle elements which support such

significant contribution to research knowledge (Mulrow 1994)

- Systematic reviews efficiently integrate existing information to provide data for rational decision-making.
- Meta-analysis can increase power and precision of estimates of treatment effects.
- Explicit methodologies applied during a systematic review can limit bias.

The efficient 'integration of existing information' element above provides a succinct insight into the value of a systematic review. Policy makers, researchers and clinicians are often required to make value judgements upon existing publications, often with differing outcomes and subtle differences in populations or methodology. Using explicit methods, a systematic review can account for these differences and synthesis data to produce a meaningful result. A meta-analysis is a quantitative, formal approach to statistically assess the results of previous research (Haidich 2010). A meta-analysis aims to statistically combine similar outcomes from different reviews, to produce a more statistically powerful answer to a research question. This is achieved through calculation of the effect size for each study, which is then used to calculate the overall treatment effect. An explicit methodology ensures that every possible source of relevant data is included and potential bias in the conduct of the systematic review is identified and addressed, to strengthen confidence in the review outcome. A bias is 'a systematic error, or deviation from the truth, in results or inferences' (Higgins et al. 2017:8.3). To reduce bias in a systematic review a homogenous approach is favoured i.e. inclusion of evidence exclusively from Randomized Controlled Trials (RCT). In this instance, due to a limited availability of RCT evidence in the scoping review, it was necessary to consider a heterogeneous approach. This resulted in synthesis of evidence from non-randomised studies of interventions (NRSi) and RCT. NRSi were only included where there was a control arm.

Inclusion of NRSi in a meta-analysis is an emerging science, with significant concerns regarding risk of bias due to lack of randomisation (selection bias) and the possibility that an NRSi amplifies elements of bias when compared to an RCT (Deeks et al. 2003). To support the synthesis of NRSi evidence in a systematic review, guidance has been published and appraisal tools have been validated (Deeks et al. 2003). Assessing study bias in this manner, attempts to minimise bias which arises from evaluating an NRSi with an RCT tool, which will inevitably distort results. The tools considered for use in this review were the Downs and Black checklist (Downs and Black 1998) for Randomised and Non-Randomised studies and the Risk of Bias 2.0 tool (RoB 2.0) (Higgins et al. 2016) with the Risk Of Bias In Non-randomised Studies (ROBINS)tool (Sterne et al. 2014). Other tools were considered i.e. the Ottawa scale (Wells et al. 2010) and the Joanna Briggs Institute (Tufanaru et al. 2017), however, they were not selected since it was felt important to limit any bias which may occur from using different methods to evaluate bias in each study type. The Downs and Black checklist offers the ability to appraise bias in both study types, using a single checklist. The RoB 2.0 and ROBINS tools requires the use of two checklists, which assess bias in 4 common domains post intervention and differ in their assessment of bias pre- and during intervention. The differences in the RoB and ROBINS tools reflect their purpose since evaluation of bias in the process of allocation and its impact on confounding variables, will vary significantly when an RCT is compared to a NRSi. The Downs and Black checklist is a valid, well used and established tool, which evaluates internal and external validity, using a point scoring system. The Downs and Black tool was published in 1998, consequently there are many publications which is discuss its functionality. Recently, O'Connor et al. (2015) documented concerns regarding the scoring system since it does not have the sensitivity to differentiate between degrees of bias. In addition, a European Union Health Technology Assessment working group (eunethta 2015) recommended against the use of the Downs and Black checklist, due to concerns relating to assessment of baseline comparability which impact evaluation of internal validity. The RoB

and ROBINS tool are more recent developments for the evaluation of bias based which supersede existing tools (RoB 1.0 & ACROBAT-NRSi) produced by the Cochrane Bias Methods Group and the Cochrane Non-Randomised Studies Methods Group. Both tools focus on evaluating bias in internal validity due to concerns that confusion arises when using a tool that aims to evaluate internal and external validity (Higgins et al. 2011). These tools use signalling questions to guide the evaluation of bias in specified domains e.g. selection bias, publication bias. The overall risk of bias is derived from the bias judgments for each domain. Due to published concerns regarding use of the Downs and Black checklist, the more recently development RoB 2.0 and ROBINS-1 tools were selected for use in this review. Including NRSI in systematic review also introduces heterogeneity due to inclusion of differing study types, with differing levels of internal validity. A meta-analysis of RCT and NRSi data was conducted and is presented separately, to minimise the impact of bias which may result from this approach.

Whilst there are significant advantages to undertaking a systematic review, the disadvantages must be recognised and where possible accounted for in a review protocol to improve the scientific credibility of the outcomes. The most significant limitations of systematic reviews are highlighted in table 1:

Table 1: A table to highlight and explain the limitations of a systematic review

Limitation	Explanation
Dependence on the quality of pre-published research	This influences the quality and outcome of a systematic review.
Publication bias	It is suggested that a disproportionally large amount of positive or significant results are published (Sedgwick 2015). Thus, any review dependent on an amalgam of published data, may have an inappropriately positive conclusion.
Lack of data published regarding outcomes of interest	Conducting a systematic review where data regarding secondary or other outcomes is extracted and synthesised, may have a significant impact on validity since power calculations and/or confounders controlled for may only related specifically to the primary outcome.
Quality of systematic review methodology	This impact data identification, extraction and synthesis. To improve confidence in methodology and consequently results guidance documents e.g. PRISMA-P (Shamseer et al. 2015) should be used.
Study heterogeneity	This may be clinical, methodological or statistical. Identified statistical heterogeneity may preclude a meta-analysis. Heterogeneity not accounted for may mis-inform the outcome.
Quality of reports disseminating results	The quality of any study type has the potential to be undervalued by poor quality reporting and publication. To counteract this, some publishers require publications to use specific structure e.g. PRISMA guidance.

Murad et al. (2016) challenge traditional concepts regarding systematic reviews: arguing that inevitable heterogeneity and methodological or statistical impression, devalue confidence in systematic review outputs and they should not be considered as part of the research hierarchy. More specifically Murad et al. (2016) describe a systematic review as a lens through which evidence is viewed. Despite these concerns systematic reviews remain a fundamental element of many research programmes. Furthermore, recognising the strengths and weaknesses of this methodology may facilitate the formulation of a credible review protocol.

3.2 Method

3.2.1 Research Design

3.2.1.1 Protocol and registration

This systematic review was conducted using an ethically approved (see appendix 1), pre-published protocol which was agreed by the research team and registered with PROSPERO. The protocol was written using PRISMA-P guidance and can be accessed using the following link: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=58933

A copy of the PRISMA-P checklist evaluating where PRISMA-P guidance has been considered when producing the protocol maybe seen in appendix 3. There are significant research benefits to a pre-published protocol for a systematic review and its importance can be compared to the priori methods registered for an intervention trial. Publishing and registering a systematic review protocol with an organisation such as PROSPERO introduces a level of waste management, through a reduction in research duplication; offers confidence in a review methodology and helps to reduce the potential impact of arbitrary decision making, which is often associated with a generic critical appraisal publication (Shamseer et al. 2015). Furthermore, a protocol acts as a reference point to identify selective outcome reporting for any users of the review report. Finally, the use of PRISMA-P guidance supports the development of a robust protocol and helps to ensure confidence in the integrity of the research output (Shamseer et al. 2015). This protocol was validated using a scoping search. The scoping search also confirmed that there were no published systematic reviews which evaluated the impact of sodium bicarbonate on blood pressure in CKD.

3.2.1.2 Research Team

The review team personnel and roles are detailed in table 2 below:

Table 2: Research Team Personnel

Team member	Job title	Explicit role
Beverley Beynon-Cobb (BBC)	Masters by Research Student (CU), 1st reviewer	Scoping searches protocol production under guidance of review team, searches, screening data extraction, bias analysis, data analysis, statistical analysis, report production.
Dr Rizwan Hamer (RH)	Consultant Nephrologist (UHCW), 2nd reviewer	Data extraction, bias analysis. Support and guidance.
Dr Bernice Tighe (BT)	Senior Lecturer (CU), Primary Supervisor, 3rd reviewer	Support and guidance. Arbitration of discrepancies identified in data extraction which could not be resolved via discussion between BBC and RH.
Dr Deborah Lycett (DL)	Senior Lecturer (CU), Second Supervisor	Support and guidance.

3.2.2 Research question

Do sodium bicarbonate salts increase blood pressure in chronic kidney disease stage I-V non-renal replacement therapy (RRT)?

The research question was determined using the **P**opulation **I**ntervention **O**utcome (PIO) model. A P.I.O or **P**opulation **I**ntervention **C**omparator **O**utcome (P.I.C.O) format enables a focused research question to be formed from a clinical observation and supports the systematic planning of a literature review. In this instance the more traditional P.I.C.O format was not used due to the lack of comparator identified in the scoping search. Furthermore, from the scoping search it was evident that whilst studies were predominately using sodium bicarbonate, there were a small number using sodium citrate (citrate is a precursor to bicarbonate). The research question uses the wording 'bicarbonate salts' to reflect this anomaly. Dialysis therapy (RRT) alters fluid balance and uses dialysate containing bicarbonate, adding blood pressure variables, which are difficult to account for in a systematic review. The research question addressed this issue by focusing the population as CKD stages I-V non RRT.

3.2.3 Eligibility criteria

The search criteria for including studies in this review was determined using the PIO model above, adapted to include study design and is summarised in table 3 below:

Table 3: Search criteria determined using a Population Intervention Outcome Study design (PIOS) model

Criteria	Inclusion	Exclusion	Justification
Population	Human. Chronic Kidney Disease stage I-V non-RRT, no age, gender or ethnicity limits.	Renal Replacement Therapy (RRT) Acute Kidney Injury Non-CKD. Healthy individuals.	Physiological process of acidosis applies irrespective of age, gender and ethnicity. RRT corrects acidosis and adds SBP variables.
Intervention	Sodium Bicarbonate or Sodium Citrate Supplementation	Studies not using Sodium Bicarbonate or Sodium Citrate	Sodium citrate is a precursor to bicarbonate, occasionally used in clinical practice where sodium bicarbonate is not tolerated and provides and equivalent sodium load.
Outcome	Change in systolic blood pressure or dosage of anti-hypertensive medications and/or diuretics		Sodium alters systolic not diastolic blood pressure. Changes in blood pressure maybe absent in studies due to use of anti-hypertensive and/or diuretic agents.
Study design	Randomised controlled Trials (RCT) and non-randomised intervention trials (NRSi).	Studies where there is no control arm.	To reduce bias.
Setting	No restrictions.		To improve data collection, setting is unlikely to influence outcome.
Language	No restrictions.		To improve data collection.
Time frame	No restrictions for dates of publication or study duration. Studies published up to April 2018	Studies published after April 2018	To improve data collection.
Publication status	Peer reviewed, and non-peer reviewed publications		To reduce publication bias.

3.2.4 Information sources

The following electronic databases were searched: MEDLINE (OVID), EMBASE (OVID), CINHAL, AMED, COCHRANE database of systematic reviews (CDSR) and the WHO trials registry database for articles published to September 2017 and re-run in April 2018. The electronic databases searched represent a deviation from the review protocol. The protocol stated that SCOPUS, OpenSIGL, OpenGrey, Greylit. The OpenSigle data base has been merged with OpenGrey, furthermore in January 2017 the Greylit database was closed. Therefore, OpenGrey was the only grey literature database searched. However, on use no suitable publications were identified. In addition, following advice of the faculty librarian, the SCOPUS and TRIP databases were not searched, since it would provide no additional search coverage to the databases already searched.

3.2.5 Search Strategy

The generic search strategy was initially constructed using the PIO format and developed using the scoping search. During the scoping search, it was identified that blood pressure change was a secondary or 'other' outcome for most studies, consequently changes to blood pressure were not explicitly mentioned in title, abstract or key words. Therefore, blood pressure or related search terms were not included in the review search strategy to avoid over restriction of the literature search. The search was constructed using search terms to represent the population and intervention elements of the research question. A copy of the generic search strategy used can be seen in table 4 below. This strategy was amended to include adaptations for index terms, key words and Boolean operators specific to each database searched. The search was re-run prior to meta-analysis and did not identify any additional publications.

Table 4: The generic search strategy

Patient/Population/Problem	Intervention/exposure	Not
CKD	Bicarbonate	Acute kidney injury
Chronic kidney disease	Bicarbonate supplementation	Acute kidney disease
Kidney disease	Oral bicarbonate	Acute kidney failure
Chronic renal insufficiency	Bicarbonate therap*	Acute renal failure
Renal insufficiency	Bicarbonate buffer	Pregnancy / pregnan*
Chronic renal failure	Sodium bicarbonate	Neonat*/neonate MH
Renal failure	NaHCO3	Intensive therapy unit
Kidney failure	Sodium citrate	Intensive care unit
Chronic Renal disease	Na citrate	Critical care
Renal Disease	Baking soda	Dialysis solutions
Renal function	Acidosis treatment	Dialysate
Glomerular filtration rate	Acidosis correction	Renal dialysis
GFR	Alkali therapy	Renal replacement therapy
Creatinine clearance		Dialysis
Renal disease progression		Hemodialysis/haemodialysis
Kidney disease progression		Peritoneal dialysis
Pre-dialysis		Hemofiltration/haemofiltration
Acidosis		Contrast
Metabolic acidosis		Renal stones or kidney stones
Renal tubular acidosis		Oxalate/oxalosis = oxal* hyperoxaluria MH
Acid-base imbalance		Cystinuria
Chronic metabolic acidosis		Cystinosis MH Cystin*
Acid-base equilibrium		nephrocalcinosis
		Calculus/calculi calcul*

3.2.6 Management software used to support this review included:

- Refworks and Papers3 bibliographic software: repositories for completed searches from the bibliographic databases available from: https://www.refworks.com and https://www.readcube.com/papers/mac respectively.
- EPPI reviewer 4: a web-based system to support data management and analysis in systematic literature reviews, available from: http://eppi.ioe.ac.uk/cms/Default.aspx?alias=eppi.ioe.ac.uk/cms/er4
- Risk of bias tools: excel spreadsheets for RoB 2.0 available for free download from https://sites.google.com/site/riskofbiastool/

3.2.6.1 Data management paper tools

Data extraction: a paper tool was produced for this review using the Cochrane Community template see appendix 4 for the URL details. This tool was used to detail the coding applied to the EPPI reviewer 4 software and support data extraction.

Risk of bias: ROBINS-1 paper tool available from https://sites.google.com/site/riskofbiastool/welcome/home to assess bias in NRSi. A spreadsheet was created using the paper tool due to stability issues using the access database tool available from the risk of bias website.

3.2.7 Study selection process

- References identified during the literature search phase were saved directly into RefWorks or Papers and uploaded into EPPI reviewer 4.
- Title then abstracts were screened and irrelevant references excluded. Reasons for exclusion were coded in EPPI reviewer 4.
- Duplicate reports were identified using the appropriate functions in EPPI reviewer 4 and the publication with the most data available was used.
- Full text PDF documents following initial screening were located and saved into EPPI reviewer 4.
- Full text reports were examined using the selection criteria above.

- All full text reports considered relevant were included in the synthesis and meta-analysis.
- Reasons for exclusion at this stage were coded in EPPI reviewer 4.

3.2.8 Data Collection

Two reviewers (BBC and RH) extracted data for this review. BBC extracted data using the paper tool created for this review, then uploaded the information to EPPI reviewer. RH extracted data directly into EPPI reviewer. Differences in data extraction were identified using a report function in EPPI reviewer. Identified differences were discussed and agreed to finalise data documentation.

3.3 Data items extracted

The following items were extracted from the located studies:

1. Treatment characteristics: name, route, dosage and frequency of intervention and duration of treatment.
2. Control type.
3. Patient characteristics: age, gender, ethnicity, stage of renal disease (eGFR or serum creatinine, or creatinine clearance) SBP, serum bicarbonate.
4. Trial characteristics: design, size, duration, source of funding, publication status. Attrition rates and causes, intention to treat analysis.
5. Outcome data as defined below

3.3.1 Missing data

Where required, study authors were contacted via email and requested to provide missing data. Three abstracts were excluded due to a lack of full trial data following author contact. Two authors responded to clarify items for data extraction following review of two full publications.

3.3.2 Outcomes

The following outcomes were evaluated:

3.3.2.1 Primary Outcomes

1. Change in mean systolic blood pressure from baseline to end of intervention.
2. Change in antihypertensive use from baseline to end of intervention.
3. Change in diuretic use from baseline to end of intervention.

Whilst the first primary outcome is a quantifiable aim of the systematic review, changes in anti-hypertensive and diuretic therapy were also chosen since they are clinical surrogates of blood pressure change.

3.3.2.2 Secondary Outcomes

1. Change in mean serum bicarbonate.
2. Dose sodium bicarbonate used.

These secondary outcomes were selected since a change in mean serum bicarbonate can be a marker of treatment adherence and dose response to sodium-based alkali therapy. Evaluating the dose of sodium bicarbonate will support identification of SBP changes due differencing treatment prescription.

3.3.2.3 Adverse effects

1. Attrition due to hypertension
2. Attrition due to oedema

It was necessary to document the above, since exit of any trial due to these adverse effects may impact the outcome data.

3.3.3 Risk of Bias in Individual Studies

Risk of bias was assessed independently by BBC and RH using the following assessment tools:

- **RoB 2.0 tool:** to assess risk of bias in randomized trials (Higgins et al. 2016)
- **ROBINS-1 tool:** to assess Risk Of Bias In Non-randomized Studies - of Interventions (Sterne et al. 2016)

EPPI reviewer 4 has the function to produce risk of bias figures based upon pre-configured code sets determined during the software's development using the Cochrane risk of bias tool (The Cochrane Collaboration 2011). The Cochrane risk of bias tool comprises of five domains for bias assessment; each domain has three judgement options from which one judgement is selected. The EPPI risk of bias code set can be amended with simple text changes and addition of domain sets. However, it is not possible to amend the number of bias judgements options specified per domain. Consequently, EPPI will only support a risk of bias tool which has three judgement options per risk of bias domain. The RoB 2.0 tool has three risk judgements options per domain, these are entitled 'low', 'high' and 'some concerns', thus its answer format is compatible with EPPI coding. The ROBINS-1 tool has four judgements options per domain: 'Low', 'moderate', 'serious' and 'critical' and is not compatible with EPPI coding. To meet the coding requirements of EPPI reviewer, the 'serious' and 'critical' judgement in the ROBINS-1 tool were combined to form a single 'high-risk' judgement. Furthermore, the term 'moderate' risk was documented as 'some concerns' in EPPI reviewer 4, to ensure consistency of reporting: see table 5. Whilst amending any tool potentially undervalues its application, the coding requirements of EPPI left no alterative if a risk of bias figure was to be generated. ROBINS-1 guidance (Sterne et al. 2016) recommends against including studies assessed as 'Critical risk' of bias in any meta-analysis, and advocates caution for studies assessed as 'Serious risk' of bias. Whilst a meta-analysis was attempted, it is recognised that it is of limited use, since all the NRSi evaluated were a 'serious' risk of bias and a subgroup analyses was not possible.

Table 5: Explanation of the risk of bias judgement

Tool	**Risk of bias judgment/Explanation**			
R.o.B 2.0	**Low**	**Some concerns**	**High**	
	The study is judged to be at low risk of bias for all domains for this result.	The study is judged to be at some concerns in at least one domain for this result.	The study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.	
ROBINS	**Low**	**Moderate**	**Serious**	**Critical**
	the study is comparable to a well-performed randomized trial with regard to this domain	the study is sound with regard to this domain, but cannot be considered comparable to a well-performed randomized trial	the study has some important problems in this domain	the study is too problematic in this domain to provide any useful evidence on the effects of intervention

Key: Low risk of bias

Some concerns

High risk of bias

3.3.4 Data synthesis

A meta-analysis was performed for the primary outcome of mean blood pressure change and the secondary outcome of serum bicarbonate change since no statistical data was identified to support a meta-analysis of the other primary outcomes. Meta-analysis reports were produced for RCT and NRSi independently. Reports were generated in EPPI reviewer to support a descriptive synthesis for outcomes relating to anti-hypertensive and diuretic medication changes following administration of sodium bicarbonate, dose of sodium bicarbonate used and attrition due to hypertension or oedema. In addition, reports were also generated for information regarding study characteristics.

3.3.5 Statistical measures

3.3.5.1 Descriptive statistics:

Characteristics of included studies: where studies did not state the total population value for age and serum bicarbonate, it was calculated from intervention and control group data, using Cohens formula and a weighted average. For the formulae and completed calculations please see appendix 5. Standardised mean differences, with a standard error were used for continuous data outcomes of mean systolic blood pressure and serum bicarbonate change. Where the mean differences and errors were not stated, they were calculated from extracted data provided using the following tool:

https://www.medcalc.org/calc/comparison_of_means.php

3.3.5.2 Meta-analysis statistics

A meta-analysis was performed using the random effects model available in EPPI reviewer 4, which applies the Der Simonian-Laird random effects calculation. A random effects model was chosen due to the inherent heterogeneity introduced into the review through inclusion of studies with different stages of CKD, variable doses of sodium bicarbonate/citrate and length of treatment intervention. A fixed effects model assumes that differences between the included studies are due to chance and there is no heterogeneity. The summary estimate of a fixed effects meta-analysis is a weighted average of the same treatment effect, common to all included studies i.e. the 'true effect'. In a random effects model, the within study and between study variance i.e. heterogeneity is considered. Thus, the estimate of treatment effect in a random effects model, is an estimation of the average not the common treatment effect. The original and most commonly used random-effects model is the DerSimonian and Laird model (Kelley and Kelley 2012). The DerSimonian and Laird model, as with other models for calculating random effects can be criticised for potential lack of precision in calculating

between study variance also known as Tau (τ), particularly in a random effects meta-analysis with small numbers of studies. Due to the potential uncertainty in the accuracy of the overall effect calculated using this method, a Knapp and Hartung modification was applied (IntHout, Joannidis and Borm 2014). Hartung-Knapp adjustment calculates the between study variance differently to DerSimonian and Laird. Firstly, it estimates the between-study variance and treating it as a fixed value. Then additional calculations to calculate the average effect, are made using quantiles as opposed to the normal distribution curve used by DerSimonian and Laird. Consequently, a Hartung-Knap adjustment often presents with wider confidence intervals for the overall effect, which reflects the uncertainty in this statistical variance (Jackson et al. 2017).

3.3.5.3 Assessment of heterogeneity

Assessment of statistical heterogeneity i.e. the presence of variation in true effect sizes underlying the included studies (Higgins 2008) was calculated using the standardised formulae run by EPPI reviewer for the following statistical functions:

- **Chi^2** : a test for significance of heterogeneity, but it does not specifically qualify it. In this analysis, a value of 0.05 was used to identify statistical significance i.e. p >0.05 suggested a lack of heterogeneity.
- **I^2 :** I^2 descriptive statistic used to represent the percentage of the total variation in point estimates between studies. Values of 25%, 50% and 75% were used to quantify heterogeneity as low, medium and high.

3.3.5.4 Sensitivity analysis and Sub-group analysis

It can be argued that heterogeneity is inevitable when conducting a meta-analysis and the ability to understand the cause of heterogeneity, is of significant value to any meta-analysis output (Higgins 2008). The rationale for understanding the cause of heterogeneity is to support the identification of any sources of uncertainty so they can be accounted for using sensitivity and sub-group analysis. A sensitivity analysis was performed omitting studies with a

high risk of bias identified using the RoB or ROBINS-1 tool. This was only applicable to the RCT analysis, due to low numbers of NRSi. No unpublished data was identified in the search so a sensitivity analysis to exclude such data was not possible. A sub-group analysis was conducted to evaluate the following potential causes of clinical heterogenicity identified in the protocol: presence of acidosis at baseline and dose of sodium bicarbonate/citrate prescribed. In addition, despite other potential causes of heterogenicity were identified these include: stage of CKD and duration of treatment. A sub-group analysis was conducted by stage of CKD and represents a deviation from protocol. It was not possible to conduct this sub-group for duration of treatment due to large differences in this data set. The specific reasons to support each sub-group analysis are documented in table 6 below:

Table 6: Rationale for sub-group analysis

Source of heterogenicity	**Explanation**
Stage of CKD	Acidosis and blood pressure worsen with advancing CKD. Clinically sodium bicarbonate is used in stage IV CKD. A sub group analysis aimed to include stages IV-V non-RRT only.
Presence of acidosis	Clinically acidosis is defined as a serum bicarbonate <22mmkol/l and sodium bicarbonate/citrate are used in this patient group. A sub-group analysis was repeated including studies which only included acidotic participants.
Dose of sodium bicarbonate	The BNF (Joint Formulary Committee 2018) recommends administration of 4.5g sodium bicarbonate/d in ureamic acidosis. For a standardised, 70kg adult this equates to 0.83mEq/kg. A subgroup analysis was performed excluding studies with a sodium bicarbonate dose above this threshold. One study (De-Brito et al. 2009) did not contain specific data regarding mean dosage of sodium bicarbonate per kg body weight, thus it was calculated using the mean dose and mean weight data provided using the Taylor Expansion equation: see appendix 5 for this data set.

3.3.6 Meta-bias

The potential for publication bias was reduced through: inclusion of search strategies to identify unpublished research; absence of limitations on language and date of publication; use of a risk of bias tool which included selective outcome reporting as a domain of bias assessment and identified studies with multiple publications of the same data. Unfortunately, there were insufficient studies available i.e. <10, to evaluate the presence of publication bias using a funnel plot as specified in the protocol (The Cochrane Collaboration 2011). With respect to reporting bias, unpublished studies in the form of abstracts were identified, yet the authors were unable to provide full study results and only two studies pre-published protocols (de-Brito Ashurst et al. 2013; Bellasi et al. 2016), thus evaluating reporting bias was not possible.

3.3.7 Confidence in cumulative evidence

The quality of evidence for all primary outcomes and sensitivity analysis for the outcome of systolic blood pressure change with sodium bicarbonate, was rated using the Grading of Recommendations Assessment, Development and Evaluation working group (GRADE) guidance (Guyatt et al. 2011) and software. Each outcome was assigned a-priori ranking which can then be upgraded or downgraded for study limitations, inconsistency of results, indirectness of evidence, imprecision and reporting bias and a summary of findings table was produced.

4 Results

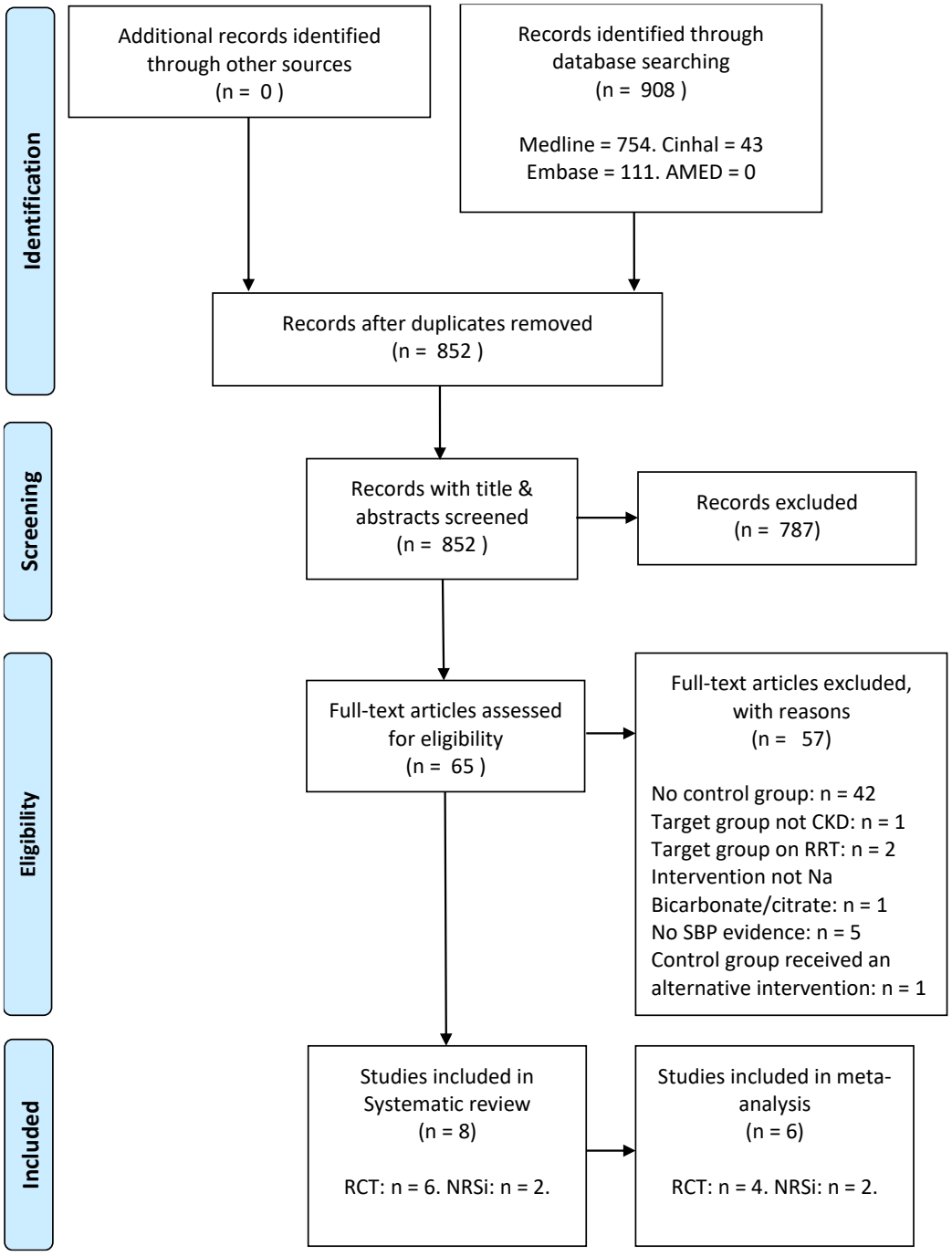
4.1 Introduction

The purpose of this systematic review was to evaluate the impact of sodium bicarbonate/citrate upon systolic blood pressure (SBP) in Chronic Kidney Disease (CKD) stages I-V non-Renal Replacement Therapy (RRT) patients. The first section of this chapter presents the literature search results and describes the studies included in this systematic review. The second section presents the results for the quality assessment of included studies. The final section details the meta-analysis including sub-group analysis for each outcome defined in Chapter 3. Where there was insufficient data to support application of statistical measures, a descriptive analysis is presented. Any discussions related to the results presented in this chapter will be documented in Chapter 5.

4.2 Search Results

The searches were conducted as per description in methods, in August and September 2017 then re-run in April 2018 for completeness. For full documentation evidencing search strings see appendix 6. No grey literature evidence was identified. A total of 908 publications were identified and screened. Authors were contacted to clarify missing data, consequently three publications were excluded due to a lack of data. Six publications met the inclusion criteria for this review. Two authors, Professor Di Iorio (Bellasi et al. 2016) and Professor Wesson (Goraya et al. 2012) responded to clarify items for data extraction. A flow chart describing the identification and screening of studies is presented in figure 1.

Figure 1: A flow diagram depicting the flow of information throughout this systematic review



Key: CKD = Chronic Kidney Disease. SBP = Systolic Blood Pressure. RRT = Renal Replacement Therapy. RCT = Randomised Controlled Trial. NRSi = Non- Randomised Study of Interventions

Articles identified were published between 2006 and 2016, all publications were written in English. The stages of CKD ranged from I to V non-RRT. All studies were conducted in outpatient clinics. The age range of participants was 40.5 to 65.5 years, no studies of childhood CKD which met the inclusion criteria were identified. 48% of participants were female. Three trials did not provide data regarding ethnicity (Bellasi et al. 2016; Jeong, Kwon and Kim 2014; Mathur et al. 2006). The primary alkali salt used was sodium bicarbonate with only one study using sodium citrate (Phisitkul et al. 2010). Duration of interventions was 4 weeks to 2 years. One study (Mathur et al. 2006) used a placebo for the control group, the remaining studies compared the intervention to standard care. The characteristics of included studies may be seen in table 7. All data extracted is described as 'other outcome data' i.e. not primary or secondary outcome data.

Table 7: Characteristics of included studies

Publication	Study type	No. Participants	CKD stage	Mean Age (SD)	Gender	Ethnicity (authors classification)	Mean serum bicarbonate	Intervention Type	Duration of intervention (weeks)
Bellassi et al. (2016)	RCT	145	III-IV	65.5 +/- 12.4	Male 57% Female 43%	Not stated	24.2 +/-2.7	SB	52
de-Brito Ashurst at al. (2009)	RCT	134	IV	54.8 +/- 2.5	Male 51.5% Female 48.5%	Asian/Black 48%	19.9 +/- 1.9	SB	104
Goraya et al. (2012)	RCT	133*	I-II	50.7 +/- 8.5	Male 47% Female 53%	Black 49% Hispanic 28% White 22%	26.1 +/- 0.7	SB	4
Jeong, Kwon and Kim (2014)	NRSi	80	IV-V	54.6 +/- 13.1	Male 55% Female 45%	Not stated	18.7 +/- 4.0	SB	52
Mathur et al. (2006)	RCT	40	IV-V	40.5 +/-3.2	Male 25/40 Female 15/40	Not stated	19.4 +/- 4.7	SB	12
Phisitkul et al. (2010)	NRSi	59	III-IV	54.3 +/- 5.8	Male 48% Female 52%	Black 54% Hispanic 27% White 19%	20.6 +/-1.0	SC	104

Key: SB = Sodium bicarbonate SC = Sodium Citrate RCT = Randomized Controlled Trial NRSi = Non- Randomized Study of interventions

*The study had three arms, control, sodium bicarbonate and low acid diets. Only data from two arms (i.e. sodium bicarbonate/citrate and control) was extracted.

4.3 Methodological quality of included studies

The internal validity of the included trials was evaluated as previously described. Four studies were using the RoB 2.0 tool (fig.2) and two studies using the ROBINS tool (fig.3).

4.3.1 Bias assessment using the RoB 2.0 tool for RCT publications

Figure 2: *Evaluation of Risk of bias in RCT publications using the RoB 2.0 tool*

Publication	Randomisation process bias	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of reported result	Overall Risk of Bias
Bellassi et al. (2016)	+	+	+	+	+	+
de-Brito Ashurst et al. (2009)	+	+	+	+	+	+
Goraya et al. (2012)	+	?	+	+	+	?
Mathur et al. (2006)	?	?	?	+	?	-

Key			
	+ Low risk of bias	? Some concerns	- High risk of bias

4.3.1.1 Evaluation of each domain of bias using the RoB tool

4.3.1.1.1 Randomisation bias

Except for one study (Mathur et al. 2006), all publications clearly stated that the study was randomised, which was supported by the absence of baseline imbalances. There was variation in the degree of descriptive text within publications describing the process of randomisation e.g. sequence generation, this did not ultimately affect the bias judgement. Mathur et al. (2006) did not describe the process of randomisation or statistically evaluate baseline imbalances. This is a concern and returned a judgment of some concerns.

4.3.1.1.2 Deviations from intended interventions

Publications identified as having 'some concerns', related to a lack information with in the study publication. One study (Goraya et al. 2012) provided very limited information regarding anti-hypertensive and or diuretic therapy co-interventions. One publication (Mathur et al. 2006) did not contain enough information to answer five of six questions in this domain. Both publications were classified as 'some concerns'.

4.3.1.1.3 Missing outcome data

One study (Mathur et al. 2006) was identified as having 'some concerns' in this domain. The numbers in the intervention and control groups are stated at baseline, however there is no documentation regarding withdrawals or participant numbers at the end of the study period. Remaining studies were of 'low risk of bias' for this domain.

4.3.1.1.4 Measurement of the outcome

No concerns were identified in this domain.

4.3.1.1.5 Selection of reported result

Concerns were identified with the Mathur et al. (2006) publication due to a lack of protocol or clear information regarding outcomes evaluated and ambiguity as to the purpose of the investigation. Furthermore, there is no published evaluation of baseline differences. These discrepancies suggest that multiple analysis of the data could have occurred to justify a publishable result.

4.3.1.1.6 Overall risk of bias

As may be seen in fig 2. two studies were considered low risk of bias (Bellasi et al. 2016; de-Brito Ashurst et al. 2009), one of moderate risk (Goraya et al. 2012) and one of high risk of bias (Mathur et al. 2006).

4.3.2 Bias assessment using the ROBINS tool for NRSi publications

Figure 3: Evaluation of Risk of bias in NRSi publications using the ROBINS tool

Publication	Confounding	Selection of participants	Classifications of interventions	Deviations from intended interventions	Missing outcome data	Measurement of outcome	Selective reporting	ROB
Jeong, Kwon and Kim (2014)	-	?	+	?	-	?	+	-
Phisitkul et al. (2010)	-	?	+	+	+	?	+	-

Key:	+ Low risk of bias	? Some concerns	- High risk of bias

4.3.2.1 Evaluation of each domain of bias using the ROBINS tool

4.3.2.1.1 Bias due to confounding

For both studies included (Jeong, Kwon and Kim 2014; Phisitkul et al. 2010) dietary acid and salt intake were possible confounders which were not considered. Furthermore, a lack of regression analysis compounded this oversight. One study (Phisitkul et al. 2010) excluded subjects from the intervention arm of the if they were unable to afford the use of sodium citrate. These subjects then received sodium bicarbonate or were enrolled onto the control

arm. This potentially introduces a socio-economic confounder. Both studies returned a judgement of 'serious' concerns.

4.3.2.1.2 Bias in selection of participants into the study

There was a lack of detailed information regarding this domain for both publications. Participants in the Phistikul et al. (2010) study received six months of blood pressure treatment using a management protocol, prior to starting the study treatment. The publication lacks clarity regarding when patients were allocated to their treatment group i.e. before or after the blood pressure management intervention. Furthermore, the allocation to treatment group based upon ability to afford sodium citrate is a concern. In both publications baseline clinical parameters were similar in the intervention and control groups, reducing the potential for selection bias. A response of a moderate risk of bias was documented for both studies.

4.3.2.1.3 Bias in classification of interventions:

There were no concerns identified in this area.

4.3.2.1.4 Bias due to deviations from intended interventions

The Phistikul et al. (2010) study was at low risk of bias. Jeong, Kwon and Kim (2014) did not publish enough information for evaluation and returned a judgement of moderate risk of bias.

4.3.2.1.5 Bias due to missing data

Phisitkul et al. (2010) had a data return of 100% and was judged as low risk of bias. The data tables in the Jeong, Kwon and Kim (2014) study documented that 7 patients with stage 5 CKD were not accounted for at the end of the study, this is not qualified with descriptive text. Consequently, a judgement of serious concerns was documented.

4.3.2.1.6 Bias in measurement of outcomes

Both studies were judged as moderate risk of bias, since the study participants and research teams were not blinded to the intervention.

4.3.2.1.7 Bias in selection of reported result

Both studies were judged as a low risk of bias.

4.4 Primary Outcome Results

4.4.1 Primary outcome 1: Change in mean SBP from baseline to end of intervention.

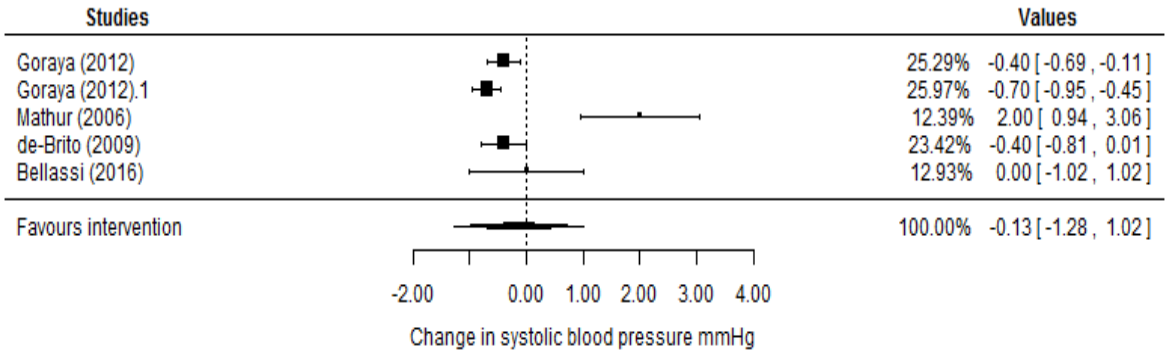
This outcome was evaluated using meta-analysis. A sensitivity analysis was conducted eliminating studies with a high risk of bias and sub-group analysis to identify any sources of clinical variance i.e. heterogeneity. Data for mean change in SBP was extracted from all studies included and can be seen in Appendix 7.

4.4.1.1 RCT analysis: Change in mean SBP from baseline to end of intervention.

Four RCTs (524 participants) were included in the meta-analysis (fig.4). One trial (Goraya et al. 2012) published data for CKD stages I and II separately within the same publication, the meta-analysis presents this as two separate data points. The duration of studies included was 4-104 weeks. Dose of sodium bicarbonate was 0.2 +/- 0.1 mEq/kg to 1.2mEq/kg. The combined point estimate crosses the line of null effect and heterogeneity is significant (I^2 84%), which precludes any meaningful conclusion.

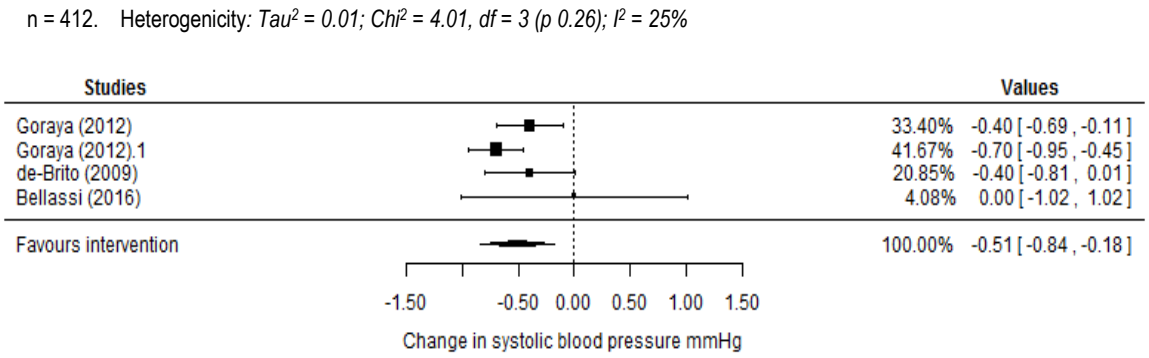
Figure 4: A forest plot of the continuous outcome measure change in mean SBP from beginning to end of intervention with sodium bicarbonate for RCTs.

n = 524. Heterogenicity: $Tau^2 = 0.24$; $Chi^2 = 25.39$, $df = 4$ ($p<0.0001$); $I^2 = 84\%$



Visual evaluation of the forest plot suggests the presence of statistical heterogeneity due to 'within' and 'between' study variance. Within study variance, is reflected in wider confidence intervals on two data points (Bellasi et al. 2016; Mathur et al. 2006). The presence of between study variance is suggested by the vertically irregular data points for all included studies which is reflected in the study weighting: the studies with the most extreme data point contributed least to the overall effect (Bellasi et al. 2016; Mathur et al. 2006). Risk of bias evaluation for RCT publications as seen in figure 2, highlights the variation in methodological quality. Consequently, a sensitivity analysis was performed excluding the study with a high risk of bias (Mathur et al. 2006) and is detailed in figure 5. In addition, it was not possible to interpret the funnel plot to assess publication bias, due to the limited numbers of studies included in the analysis. The funnel plot produced by the software package maybe seen in appendix 8.

Figure 5: A sensitivity analysis for the outcome change in mean SBP from beginning to end of sodium bicarbonate therapy, for low and moderate risk of bias studies



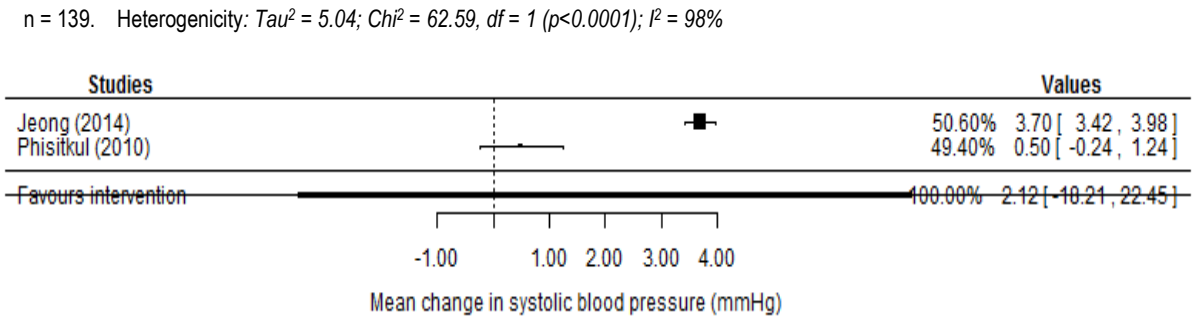
The sensitivity analysis considerably reduced heterogeneity measured using Chi^2 and I^2 statistics. The composite point estimate and confidence interval data point sit to the left of the line of null effect, favouring intervention. This suggests that SBP is reduced by 0.51 mmHg CI 95% (-0.84, -0.18) in individuals with CKD, prescribed sodium bicarbonate. Whilst this is not a clinically meaningful reduction in SBP, it is clinically important since it demonstrates that sodium bicarbonate does not increase blood pressure in CKD. The sensitivity analysis did not account for other sources of heterogeneity e.g. clinical differences between studies which will be assessed through sub-group analysis.

4.4.1.2 NRSi analysis: Change in mean SBP from baseline to end of intervention.

Two studies, providing 139 participants were included in this meta-analysis (fig. 6). Trial duration was 52-104 weeks and dose of sodium bicarbonate/citrate was 0.58 +/- 0.42 mEq/kg to 1.0mEq/kg. Participants had CKD III-V non-RRT and baseline serum bicarbonate was 18.7 +/- 4.0 to 20.6+/-1.0 mmol/l i.e. participants were clinically acidotic. Heterogeneity was significant and precludes formation of conclusions. Visual evaluation of the forest plot suggests the presence of 'within' study variance relating to the wide confidence intervals of the Phistikul et al. (2010) data points and 'between' study variance illustrated by the vertically irregular data

points of included studies. The studies had an equal contribution to the overall effect. Performing a sensitivity or sub-group analysis was not possible due to the limited number of studies.

Figure 6: A forest plot of the continuous outcome measure change in mean SBP from beginning to end of intervention with sodium bicarbonate for NRSi



4.4.2 Primary outcome 2 and 3: change in antihypertensive and diuretic use from baseline to end of intervention.

There was insufficient data to conduct a meta-analysis for these outcomes. A descriptive summary of all data extracted for these outcomes is presented in table 8. The total number of participants was 524. Only two RCT publications (de-Brito Ashurst et al. 2009; Mathur et al. 2006) provided numerical data detailing changes to anti-hypertensive medications. de-Brito Ashurst et al. (2009) evaluated the numerical data statistically and no significant difference in the prescription of anti-hypertensive or diuretic medication was identified. Statistical evaluation of data extracted from the Mathur et al. (2006) publication, using Fishers exact test as per methods for this review (see appendix 9) also found no significant difference in prescription of anti-hypertensives or diuretics for this study. Jeong, Kwon and Kim (2014) only provided numerical data for diuretic change in the CKD stage V study group. Evaluation of this

data using fishers exact test suggested no statistical difference between the use of diuretics in the control and intervention groups. Two authors (Bellasi et al. 2016; Goraya et al. 2012) were contacted to clarify information regarding anti-hypertensive medications and/or diuretics. The authors stated that there were no significant differences in the prescription of anti-hypertensives or diuretics between the intervention and control groups for their respective studies. Thus, no publication identified a significant change in the prescription of anti-hypertensive or diuretic therapy following the introduction of sodium bicarbonate or sodium citrate. With respect to potential heterogeneity between study groups, there were variations in clinical characteristics (see table 8), these included stage of CKD, dose and duration of sodium bicarbonate/citrate intervention and presence of acidosis).

Table 8: A summary of data extracted detailing change in antihypertensive and diuretic use from baseline to end of intervention.

Publication Trial design No. participants	**CKD Stage**	**Serum bicarbonate mmol/l**	**Sodium bicarbonate mEq/kg bw**	**Change in anti-hypertensive therapy with Sodium bicarbonate**	**Change in diuretic therapy with Sodium bicarbonate**
Bellassi et al. (2016) RCT 145	III-IV	24.2 +/-2.7	0.5	**No** Data: none published Personal communication with author: no changes were made to anti-hypertensive drugs in this sub group	**No** Data: none published Personal communication with author: no changes were made to diuretic drugs in this sub group
de-Brito Ashurst et al. (2009) RCT 134	V	19.9 +/- 1.9	0.2	**No** Data: Increase in antihypertensive therapy: HCO3 group: 61% Control group: 48% **p 0.17 = not significant.**	**No** Data: Increase in loop diuretics throughout the study: Control = 30% HCO3 = 39% **p 0.5 = not significant.**
Mathur et al. (2006) RCT 40	IV-V	19.4 +/- 4.7	1.2	**No** Data: 3/20 patients needed increase in anti-hypertensives in the treatment group **p 0.231 = not significant.**	**No** Data: 2/20 patients needed increase in diuretics in the treatment group **p 0.437 = not significant.**
Goraya et al. (2012) RCT 133	I-II	26.1 +/- 0.7	0.5	**No** Data: none published Personal communication with author: there were no differences in anti-hypertensive drugs between the control and bicarbonate study groups.	**No** Data: none published Personal communication with author: there were no differences in diuretic drugs between the control and bicarbonate study groups.
Jeong, Kwon and Kim (2014) NRSi 80	IV-V	18.7 +/- 4.0	0.58	**No** Data**:** none published. Statement: 'no differences between the numbers and types of anti-hypertensives during the study between the two groups'.	**No** Data: CKD stage 5 'Loop diuretic use increased similarly by 75 and 82% in the control and treatment group, respectively' **p 0.110 = not significant.**
Phisitkul et al. (2010) NRSi 59	III-IV	20.6 +/-1.0	1.0	**No** Data: none published Statement: 'There was no difference in the distribution of **non-ACE drugs** or diuretics among subjects in the two groups'. Personal communication with author: there were no differences between the doses of ACE in the two groups	**No** Data: none published Statement: 'There was no difference in the distribution of non- ACE drugs or **diuretics** among subjects in the two groups'.

4.5 Secondary Outcome Results

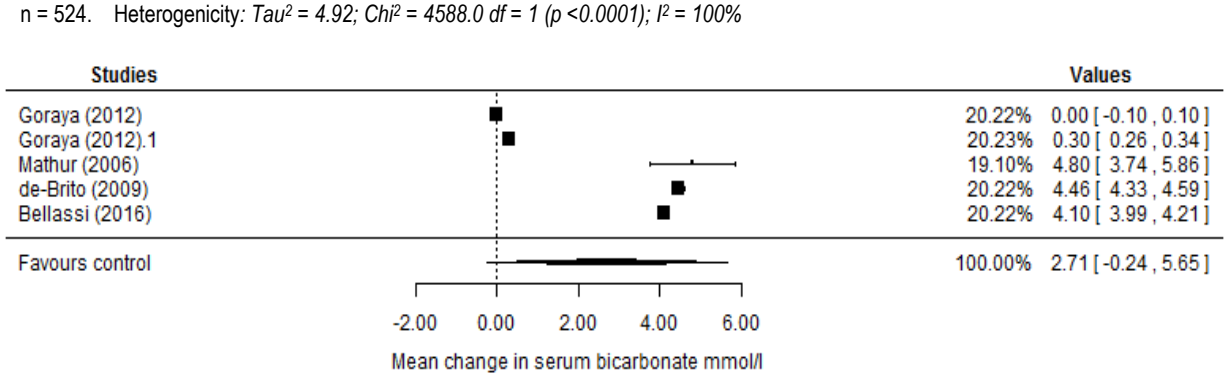
4.5.1 Secondary outcome 1: Change in mean serum bicarbonate

This outcome was evaluated using meta-analysis which included four RCTs and two NRSi. Data for mean change in serum bicarbonate was extracted from all studies included and can be seen in appendix 10.

4.5.1.1 RCT analysis: Change in mean serum bicarbonate from baseline to end of intervention.

The total number of participants was 524. Trial duration was 4-104 weeks and dose of sodium bicarbonate 0.2mEq/kg to 1.2mEq/kg. Goraya et al. (2012) published data for CKD stages I and II separately: the meta-analysis presents this as two separate data points. Heterogeneity is high, as denoted by I^2 and Chi^2 values and precludes any conclusions. Visual evaluation of the forest plot (see fig. 7) highlights that the diamond-shaped point estimate and confidence interval data point crosses the line of null effect, whilst vertically irregular data points suggest the presence of 'between' study variance. Only one study (Mathur et al. 2006) suggests a level of within study variance. All studies contributed a similar weighting to the meta-analysis.

Figure 7: A forest plot analysis representation of mean change in serum bicarbonate from beginning to end of intervention with sodium bicarbonate for RCT studies



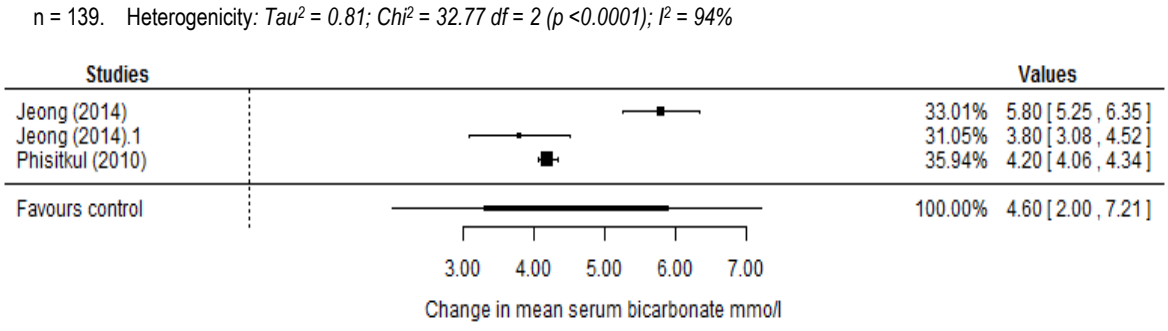
4.5.1.1.1 Sensitivity analysis

A sensitivity analysis was conducted excluding one study (Mathur et al. 2006) due to its high risk of bias. Chi^2 and I^2. This did not reduce heterogeneity or modify the result. See appendix 11 for the forest plot output.

4.5.1.1.2 NRSi analysis: Change in mean serum bicarbonate from baseline to end of intervention.

Two trials (139 participants) were included in this meta-analysis (fig.8). Trial duration was 52-104 weeks and dose of sodium bicarbonate was 0.58+/- 0.42mEq/kg to 1.0mEq/kg. Participants had CKD III-V non-RRT and baseline serum bicarbonate was 18.7 +/-4.0 to 20.6+/-1.0 mmol/l i.e. all participants were clinically acidotic. One trial (Jeong, Kwon and Kim 2014) published data for CKD stages 4 and 5 separately which presents as two data points in the forest plot. Heterogeneity was significant and precludes the formation of conclusions, despite the composite diamond point estimate and confidence intervals sitting to the right of the null effects line. Visual evaluation of the forest plot (fig.8) suggests the presence of 'within' and 'between' study variance. Performing a sensitivity or sub-group analysis was not possible to the limited number of studies. Both studies were of high risk of bias.

Figure 8: A forest plot analysis representation of mean change in serum bicarbonate from beginning to end of intervention with sodium bicarbonate for NRSi studies



4.5.2 Secondary outcome 2: Dose of sodium alkali

The details of the sodium-based alkali prescription for each study are documented in table 9. Only one publication (Phisitkul et al. 2010) prescribed sodium citrate. All studies used an oral form of sodium bicarbonate or citrate and the dose was divided throughout the day. Bellassi et al. (2016) titrated the dose down once a serum bicarbonate of 28mmol/l was reached. De Brito-Ashurst et al. (2009) detailed the total daily dose only, the dose expressed as mEq/kg bw was determined using calculations stated in methods. The dose of sodium bicarbonate across studies was 0.2 +/-0.1 to 1.2mEq/kg and duration of intervention was 4 to 104 weeks. The dose of sodium bicarbonate/citrate did not appear to be related to the stage of CKD or mean serum bicarbonate at baseline.

4.6 Adverse events

The adverse events of interest were hypertension and oedema. Three studies reported the occurrence of these adverse events (de-Brito Ashurst et al. 2009; Jeong, Kwon and Kim 2014; Mathur et al. 2006) and their occurrence was not significantly different between the control and intervention groups. The adverse event of hypertension is an outcome for this review and has been evaluated in more details in section 4.4.1.

Table 9: Dose of sodium bicarbonate/citrate used and adverse events documented in the studies identified

Publication **Trial design** **No. participants total/intervention group**	**Dose sodium bicarbonate/citrate mEq/kg bw** **Duration of intervention**	**CKD stage**	**Mean serum bicarbonate mmol/l**	**Adverse events**
Bellassi et al. (2016) RCT 145/71	Sodium bicarbonate 0.5 52 weeks	III-IV	24.2 +/-2.7	None stated
de-Brito Ashurst at al. (2009) RCT 134/67	Sodium bicarbonate 0.2 +/-0.1 104 weeks	IV	19.9 +/- 1.9	48% control and 61% HCO3 group had worsening BP needing change in treatment (NS). Loop diuretic treatment increased by 30% in control group and 39% in bicarbonate group (NS)
Goraya et al. (2012) RCT 133/66	Sodium bicarbonate 0.5 4 weeks n = CKD I 26 & CKD II 40	I & II	26.1 +/- 0.7	None stated
Mathur et al. (2006) RCT 40/20	Sodium bicarbonate 1.2 12 weeks	IV & V	18.7 +/- 4.0	3/20 in treatment group HTN (NS) 2/20 in treatment group OEDEMA (NS)
Jeong, Kwon and Kim (2014) NRSi 80/40	Sodium bicarbonate 0.58 +/- 0.42 52weeks	IV & V	19.4 +/- 4.7	There was a significant difference in CKD 5 body weight due to fluid.
Phisitkul et al. (2010) NRSi 59/30	Sodium citrate 1.0 104 weeks	III & IV	20.6 +/-1.0	None stated

4.7 Sub-group analysis

Sub-group analysis aiming to exclude the following sources of clinical heterogeneity were conducted: stage of CKD, presence of clinical acidosis (serum bicarbonate <22mmol/l) at baseline, dose of sodium bicarbonate, duration of intervention and changes to anti-hypertensive and/or diuretic medications. Due to large variation in the duration of intervention, a sub-group analysis evaluating this data set was not possible. No studies identified a difference in anti-hypertensive or diuretic use between control and intervention groups, therefore, a sub-group analysis was not conducted to evaluate this source of heterogeneity. Sub-group analysis by stage of CKD IV-V non-RRT and the presence of clinical acidosis at baseline resulted in an analysis which included the same studies; heterogeneity remained high (I^2 94%, Chi^2 <0.0001) and precluded the formation of a meaningful result, see appendix 12.

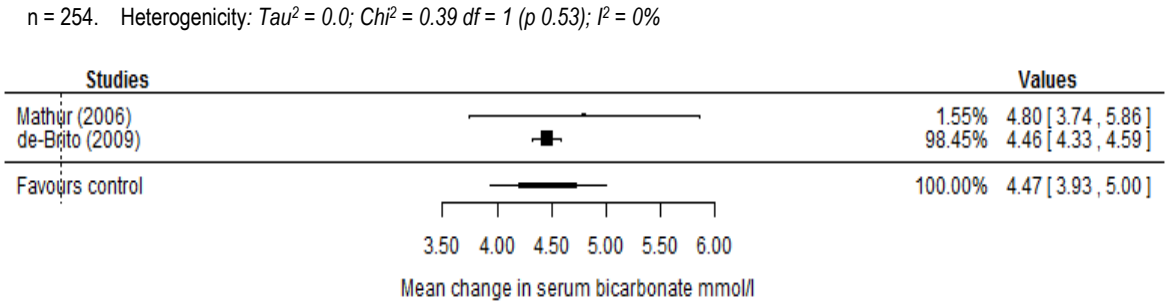
4.7.1 Subgroup analysis: Change in mean SBP from baseline to end of intervention excluding high dose with sodium bicarbonate.

The sub-group analysis excluding studies with a dose greater than the BNF threshold of 0.83mEq/kg/bw excluded one study (Mathur et al. 2006). This resulted in the inclusion of the same studies and generation of the same forest plot as the sensitivity analysis (fig.5). The dose range of sodium bicarbonate used in this sub-group analysis was 0.2 – 0.5 mEq/kg bw. The forest plot suggests that a dose of sodium bicarbonate <0.5mEq/kg bw is associated with a reduction in SBP in CKD I-V non-RRT CKD.

4.7.2 Subgroup analysis: Change in mean SBP from baseline to end of intervention including presence of acidosis or CKD stage IV-V non-RRT

A sub-group analysis by presence of acidosis at baseline or CKD stages IV-V non-RRT, included two studies (de-Brito Ashurst et al. 2009; Mathur et al. 2006) and produced the forest plot presented in figure 9. Heterogenicity reduced to I^2 0% and Chi^2 p0.53. The confidence intervals for the Mathur et al. (2006) data points are large, and the study only contributes 1.55% of data, compared to 98.45% from the de Brito-Ashurst et al. (2009) publication. Therefore, the result produced is largely a reflection of one study (de-Brito Ashurst et al. 2009), which accounts for the notable reduction in heterogeneity. The composite diamond-shaped point estimate and confidence interval which sits to the right of the null line and suggests that sodium bicarbonate increases serum bicarbonate in acidotic or stage IV-V CKD non-RRT.

Figure 9: A sub-group analysis of change in serum bicarbonate by presence of acidosis at baseline or by stage IV-V CKD non-RRT



4.8 Confidence in cumulative evidence using **G**rading of **R**ecommendations **A**ssessment, **D**evelopment and **E**valuation working group (GRADE)

The quality of evidence for all primary outcomes and the sensitivity analysis for the outcome of systolic blood pressure change with sodium bicarbonate, was rated using GRADE (Guyatt et al. 2011). Each outcome was evaluated for certainty in the following domains: study limitations, inconsistency of results, indirectness of evidence, imprecision and reporting bias and a summary of findings table was produced see table 10. Overall, evaluating certainty within each domain resulted in a downgrading of the evidence produced. With exception to the sensitivity/sub-group analysis to exclude high dose sodium bicarbonate, all outcomes evaluated were rated as having very low certainty. This means that the true effect is probably markedly different from the estimated effect for these outcomes. The main reasons for such downgrade in certainly are detailed in table 10 and relate to: risk of bias, lack of primary or secondary outcome data, and heterogeneity. The outcome of change in SBP sensitivity and subgroup analysis excluding high dose sodium bicarbonate was downgraded to level of low certainty. A low level of certainty suggests that the true effect might be markedly different from the estimated effect. This is to be expected since whilst the sensitivity analysis excluded studies with a high risk of bias and reduced heterogeneity, the issue of the 'other outcome data' which the study is not powered to detect, was not resolved and partly accounts for the evaluation.

Table 10: A Summary of findings table produced using GRADE

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sodium bicarbonate**	**usual care/placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	
4	randomised trials	serious [a]	serious [b]	very serious [c]	serious [d]	all plausible residual confounding would suggest spurious effect, while no effect was observed	244	248	-	SMD **0.13 SD lower** (1.28 lower to 1.02 higher)	⨁◯◯◯ **VERY LOW**
3	randomised trials	not serious [e]	serious [f]	serious [g]	serious [h]	all plausible residual confounding would reduce the demonstrated effect	204	208	-	SMD **0.51 SD lower** (0.84 lower to 0.18 lower)	⨁⨁◯◯ **LOW**
4	randomised trials	serious [a]	serious [i]	very serious [i]	serious [h]	all plausible residual confounding would suggest spurious effect, while no effect was observed	There was a variation in the amount of the of information available for this outcome. Overall, no study detected a change in anti-hypertensive medication therapy following introduction of sodium bicarbonate when compared to the control arm (usual care or placebo).				⨁◯◯◯ **VERY LOW**
4	randomised trials	serious [a]	serious [i]	very serious [i]	serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	There was a variation in the amount of information available for this outcome. Overall, no study detected a change in diuretic therapy following introduction of sodium bicarbonate when compared to the control arm (usual care or placebo).				⨁◯◯◯ **VERY LOW**

CI: Confidence interval; **SMD:** Standardised mean difference

5 Discussion

5.1 Summary of results

The purpose of this review was to investigate if sodium bicarbonate salts increase systolic blood pressure (SBP) in chronic kidney disease (CKD) stage I-V non-renal replacement therapy (RRT). The primary outcomes for this review were: changes in mean SBP, antihypertensive and/or diuretic use following introduction of sodium bicarbonate/citrate. Secondary outcomes were evaluation of change in mean serum bicarbonate following introduction sodium bicarbonate/citrate and evaluation of the dose of sodium bicarbonate used. This systematic review identified six published studies, four randomised controlled trials (RCT) and two non-randomised studies of intervention (NRSi), which fulfilled the selection criteria. The RCT meta-analysis for SBP change following introduction of sodium bicarbonate was not possible due to excessive heterogeneity. The sensitivity and subgroup meta-analyses excluding high dose sodium bicarbonate, excluded the same study (Mathur et al. 2009) and suggests that SBP was reduced in individuals with CKD stage I-V non-RRT prescribed sodium bicarbonate 0.2-0.5mEq/kg bw/d. The sensitivity and sub-group analysis were graded as 'low' when evaluated using Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool suggesting that confidence in the effect estimate is limited and the true effect may be substantially different from the estimate of the effect. In addition, the results of this systematic review suggest that sodium bicarbonate/citrate supplementation does not change antihypertensive medication and/or diuretic prescription.

To discuss these findings and other outcome of this review in depth, this chapter is divided into four sections: the first section discusses the consistency of findings in relation to existing literature; the second section considers the strengths and limitations of the review; the third

section discusses the confidence in the results evaluated using GRADE. The final section considers the conclusions of the review, implications for clinical practice and future research.

5.2 Consistency of findings

5.2.1 *Risk of bias*

An inherent challenge for the conduct of any systematic review is the identification and evaluation of bias to reduce the risk of an erroneous result. Bias may result from the included studies and/or the systematic review process. The inclusion of two study types i.e. RCT and NRSi in this analysis, required a considered approach to evaluating bias to reflect the study design being assessed. Evidence suggests that NRSi may overestimate or produce different estimations of effect when compared to an RCT (Odgaard-Jensen et al. 2011). Thus, it was important to recognise that results may differ depending on the study being evaluated, this was achieved using separate meta-analysis and risk of bias evaluation for RCT and NRSi.

The RCT risk of bias assessment (fig. 2) highlighted significant variability in the quality of studies included in this review. Two studies (Bellasi et al. 2016; de-Brito Ashurst et al. 2009) were evaluated as low risk of bias, which was attributable to a robust protocol and clear presentation of information within the research publication i.e. there was an element of transparency. The Goraya et al. (2012) study was evaluated as having some concerns with respect to bias. This was secondary to concerns highlighted in the 'deviations from intended interventions' domain. The concerns related to the inability to blind one of the study arms, a reduced confidence in the balance of co-interventions between the two study groups and no evaluation of concordance with sodium bicarbonate supplementation. The impact of this upon the overall bias judgement was limited due to low risk of bias judgements in the remaining domains evaluated. In comparison, the Mathur et al. (2006) bias assessment returned

judgements of ‘some concerns’ for all domains, except the ‘selection of the reported result’. There are several reasons which caused this publication to underperform: no pre-published protocol, lack of information available within the publication, a lack of evaluation of data presented and a lack of justification for missing data. Whilst ‘serious concerns’ were not identified in any domain of bias, a result of ‘some concerns’ for 4 of 5 domains, accounts for the overall result of serious concerns. However, except for one study, the studies included in this analysis were of low or moderate risk of bias and consequently support the credibility of the review findings.

The NRSi evaluated for this review returned ‘high risk of bias’ judgements which limits the ability to interpret the data extracted (see fig. 3). The ROBINS preintervention domain evaluates bias due to confounding and bias in selection of participants into the study as an alternative to the randomisation. It may be difficult for the NRSi included in this review to perform well in the ROBINS pre-intervention domain due to the dependence upon ‘other’ outcome data. A primary outcome is a variable which is most relevant to answer the research question, whereas secondary or other outcomes are additional variables which provide supportive evidence to the primary outcome (Ferreira and Patino 2017). Randomisation aims to ensure that the study groups are comparable and reduces the risk of an outcome being the result of extraneous factors instead of the factor being investigated. Randomisation reduces the risk of confounding for primary and secondary outcomes and non-randomised trials tend to result in larger estimates of effect when compared to randomised trials (Odgaard-Jensen et al. 2011). The use of ‘other’ outcome data in the NRSi included in this review increases the possibility of introducing confounders and increases the risk of a high risk of bias decision using the ROBINS tool.

The predominant reasons for concerns relating to high risk of bias in three studies included in this review (Mathur et al. 2006; Jeong, Kwon and Kim 2014; Phisitkul et al. 2010), related to a lack of detail within the publications or a lack of accessible, pre-published protocols. A research protocol is an integral part of scientific research since it ensures transparency and provides a basis for quality control. A protocol is a documented plan of action, providing information regarding study rationale, methodology and analysis, which supports the generation of evidence-based medicine (Sucksmith 2015). Thus, any study publication which does not have a published research protocol, is at risk of bias which may reduce confidence in the results produced. However, it should also be recognised that some of the included studies predate the published recommendations to pre-register a protocol (Simera et al. 2009). This raises an interesting dilemma regarding evaluation of publications using post publication guidance. Thus, whilst the importance of rigorous evaluation of bias cannot be under estimated, it is important to be mindful that the included studies may reflect the era of publication and were all published in peer reviewed journals.

5.2.2 Change in systolic blood pressure

The RCT and NRSi meta-analysis identified the presence of considerable heterogeneity which precluded combining study data to produce a reliable result and necessitated sensitivity and subgroup analysis. The RCT sensitivity and subgroup analysis by dose of sodium bicarbonate (see fig. 5) excluded one study (Mathur et al. 2006). This reduced heterogeneity to statistically acceptable levels, suggesting that the meta-analysis result was due to a true effect. It is not possible to elucidate if the resulting reduction in heterogeneity was due to exclusion of high risk of bias or high dose sodium bicarbonate, since the study excluded expressed both variables. However, this review demonstrates that: in CKD stages I-V non-RRT, where 0.2 – 0.5 mEq/kg bw of sodium bicarbonate is prescribed, SBP expressed as an estimate of the average

effect of low to moderate risk of bias studies included in the analysis, reduces by 0.51 mmHg (CI 95% 0.18, 0.84). Whilst this is not a clinically important reduction in SBP i.e. a reduction in SBP that will modulate clinical outcomes, this result is clinically significant since it suggests that SBP is not adversely affected by sodium bicarbonate supplementation in CKD. This finding is comparable to existing knowledge of small population (n = <20), limited quality, before and after or intervention studies without a control arm, where participants with CKD stage III-V non-RRT did not demonstrate a significant change in SBP following sodium bicarbonate supplementation (Abramowitz et al. 2013; Chen et al. 2016; Ori et al. 2015; Verove et al. 2002). Furthermore, the larger participant numbers (n=412) in this meta-analysis increases confidence in the detection of a true effect, when compared to existing publications.

Excess dietary sodium consumption has been linked to the development of hypertension (Kotchen, Cowley and Frohlich 2013; Farquhar et al. 2015; WHO 2013; Elliott et al. 1996) and recommendations exist for the reduction in sodium intake to support the management of hypertension in CKD and non-CKD populations (McMahon et al. 2015; WHO 2013). Studies demonstrating a causal link between sodium intake and hypertension, usually evaluate sodium consumption in the form of sodium chloride (salt). This systematic review suggests that sodium in the form of sodium bicarbonate does not have a detrimental effect upon blood pressure. This raises the following questions: do differing sodium-based salts have divergent effects upon blood pressure in CKD? Does CKD acidosis induce hypertension? Does treatment of acidosis reduce blood pressure? Is chloride implicated in the development of CKD hypertension? The answer to these questions is beyond the scope of this review and further research is required to increase understanding in this area.

5.2.3 Change in antihypertensive and diuretic medications

One of the unique features of this systematic review is that it attempted to evaluate change in antihypertensive/diuretic therapy as a marker of SBP change following supplementation with sodium bicarbonate/citrate in CKD. The narrative data summary (table 8), suggested that no changes to antihypertensive or diuretic medications were made during the conduct of the studies or no differences in the distribution of antihypertensive and/or diuretics were identified between the control and intervention (sodium bicarbonate/citrate) groups. Whilst a lack of available quantitative data and consequent ability to statistically evaluate changes to antihypertensive and/or diuretic medication may limit confidence in the results, there appears to be a common theme emerging: every study evaluated documented that anti-hypertensive and/or diuretic medications did not change significantly following sodium bicarbonate or citrate supplementation, in CKD stage I-V non-RRT. Furthermore, excluding studies with a high risk of bias or using high doses of sodium bicarbonate would maintain this finding. Looking beyond the literature included in this systematic review, there does not appear to be any literature which diminishes this finding, since the studies previously cited do not contain relevant information regarding antihypertensive or diuretic medication changes in response to sodium bicarbonate therapy.

This outcome result which suggests that antihypertensive and/or diuretic medications do not change in response to sodium bicarbonate therapy, serves to strengthen the finding that sodium bicarbonate does not adversely affect blood pressure in CKD. Comparing this combined result to existing literature not included in this review, is challenging for two principal reasons: firstly, as previously discussed, this is the first study identified which primarily evaluates SBP change to include antihypertensive and/or diuretic medication adjustments, following introduction of sodium bicarbonate/citrate. Secondly, comparing this

result to available publications is difficult since, there is a tendency for trials to include participants with later stage CKD, i.e. stage III-V, participants with clinical acidosis at baseline and/or specific CKD diagnoses e.g. diabetic CKD, hypertensive nephropathy. This meta-analysis included all stages of CKD (excluding RRT), populations of differing ethnicity, participants who are acidotic and non-acidotic at baseline and participants with varying CKD diagnosis. This is important since, this systematic review may consequently contain a clinically more heterogeneous sample than other studies published, which may result in a more representative sample of the clinical population.

5.2.4 Use of Sodium Bicarbonate

Sodium bicarbonate was the most frequently used alkali salt in the studies evaluated with only one study using sodium citrate (Phisitkul et al. 2010). The dose and duration of intervention varied considerably for the studies included in this review (see table 9). This is partially expected due to limited published guidance relating to dosage requirements for sodium bicarbonate/citrate in CKD and the differing primary outcomes of the included studies. International guidance (KDIGO 2013) recommends the use of alkali therapy in the absence of any contraindications such as hypertension and oedema in CKD but does not provide formulation or dose guidance. In the UK, guidance is more specific, the British National Formulary (Joint Formulary Committee 2018) recommends a dose of 4.8g sodium bicarbonate/d in CKD acidosis, no recommendations are made for the use of sodium citrate. Interestingly, only one study included in this review was conducted in the UK and used lower than BNF recommended dosage (de-Brito Ashurst et al. 2009). Anecdotally, this is reflective of current clinical practice and perhaps highlights the cautious use of sodium bicarbonate in clinical practice, due to concerns relating to sodium load.

5.2.5 Change in mean serum bicarbonate levels.

The results of the meta-analysis for the outcome of change in serum bicarbonate levels secondary to sodium bicarbonate or citrate supplementation identified that the studies included were too heterogeneous to produce a valid result. This high level of heterogeneity was not significantly reduced by a sensitivity analysis or subgroup analysis except for analysis conducted by presence of acidosis at baseline (see fig. 7). This analysis suggests that acidotic subjects treated with sodium bicarbonate therapy have a mean increase in serum bicarbonate of 4.47 units, 95% CI 3.93-5.00. Whilst, this is physiologically intuitive, this result may also have been due to the relative contributions of data made by the constituent studies. In this analysis, heterogeneity as measured using I^2 dropped to 0% and evaluation of the forest plot data revealed that 98.45% of the data for the analysis was provided by one study (de-Brito Ashurst et al. 2009). Whilst this study was of low risk of bias and methodologically very strong, such a large dependence upon one study in a meta-analysis opens debate regarding the number of studies required to conduct a meta-analysis and their data contribution to the overall result. Information regarding proportional representation for data in a meta-analysis appears to be limited. Valentine, Pigott and Rothstein (2010) suggest that the minimum number of studies required to conduct a meta-analysis is two, yet do not reference the minimum size of data contribution each study should make. This publication also suggests that power calculations may be used to determine the numbers of studies required for both random effects and fixed effect model meta-analysis. These calculations were not conducted for this meta- analysis and may be a consideration for future work.

5.3 Strengths and limitations

Clinical research is not a perfect science and clinical researchers continue to strive to improve the quality of research output to produce more robust and trustworthy findings. It is therefore

necessary to identify and evaluate the strengths and limitations of this systematic review to further understand the outcomes produced and guide future research. The use of a pre-published protocol endeavoured to provide methodological quality and scientific transparency to produce credible outcomes, this is a strength of this review. However, this is the first systematic review identified, which evaluates the impact of sodium bicarbonate therapy upon SBP in CKD non-RRT and the evidence base is a limited. Consequently, there is a dependency upon 'other' outcome data and this is a limitation of this review. These strengths and limitations will be discussed in detail below.

5.3.1 Research protocol, research question and search strategy

This systematic review was developed using PRISMA guidance and a pre-registered protocol, the benefit of this approach is discussed at length in chapter 3 and includes: efficient integration of existing information; efficient use of research resources; limitation of bias using explicit methodology and where applicable, a meta-analysis, which can increase power and precision of estimates of treatment effect. The pre-registered protocol was developed using a scoping search which highlighted two main issues to address: firstly, there appeared to be a limited number of randomised controlled trials which evaluated the use of sodium bicarbonate salts in CKD. Secondly, there were no RCT which evaluated the impact of sodium bicarbonate salts upon blood pressure in CKD as a primary outcome. The protocol addressed the potentially limited number of RCTs available for the review, by reducing search limits applied and using a methodology which included NRSi with a control arm. Ultimately, the broad nature of this search strategy may be considered a strength of this review since it supported the identification of all possible studies where sodium bicarbonate or citrate salts were used in CKD. The lack of limits applied to the search strategy also increased the clinical heterogeneity

of studies included in the review. This may be a limitation for a meta-analysis yet is clinically relevant since it reflects the population seen in clinical practice.

Single data extraction has been shown to generate significantly more errors than double data extraction, and systematic reviews (Buscemi et al. 2005). The data for this review was extracted by two reviewers, this reduces the potential for error and increases confidence in the results produced. In addition, the use of EPPI reviewer software enabled the use of specific functions to identify and resolve data extraction inconsistencies between the two reviewers. This approach to data extraction may be considered a strength of this review.

5.3.2 Statistical analysis

To address the potential for increased clinical heterogeneity introduced by the broad search strategy and the limited numbers of studies available, sub-group analyses were conducted. All analysis used a random effects model with a Hartung-Knapp adjustment. A random effects model calculates a summary result which is the estimate of the average effect, not the common treatment effect as seen in fixed effect analysis. The effect of a Hartung-Knapp adjustment is to widen confidence intervals, which provides greater margin for any errors which may result from small study numbers. Thus, the use of the statistical measures which recognises the inherent heterogeneity associated with this research question and adjusts for the limited volume of information available, is a considerable strength of this review. Furthermore, whilst real study differences i.e. heterogeneity, exist and are accounted for by the choice of methodology, it is likely that the studies included in the meta-analysis combine to reflect clinical practice and may be considered acceptable.

5.3.3 Inclusion of RCT and NRSi data

Whilst a strength of the search strategy was to ensure the identification of appropriate data, the inclusion of RCT and NRSi publications also required careful evaluation of bias using two appraisal tools and separate meta-analyses for RCT and NRSi publication data. Whilst at the protocol stage of this review this was a justifiable decision due to the high risk of bias and statistical heterogeneity, the NRSi analysis did not provide any usable results. Despite the lack of usable data, it is important that this NRSi analysis was included in the results for two reasons: firstly, to reduce reporting bias and secondly, it has helped to deepen understanding of techniques to evaluate multiple study designs in systematic reviews and meta-analyses. The ability to utilise multiple types of data may support ethical use of research resources to inform future research.

5.3.4 Outcome data

A systematic review is designed to evaluate a specific aspect of an intervention. When studies evaluating different outcomes of the same intervention are combined, it is possible to introduce a level of bias or confounding. This is particularly evident when there is variation in the use of primary, secondary or other outcome data for a meta-analysis (Arabi and Preiser 2017). Power calculations for sample size in an RCT are determined for primary outcomes not secondary outcomes, unless otherwise stated or alternative multiple outcome power calculations e.g. Bonferroni are used (Freemantle 2001). Secondary and 'other' outcome data is considered descriptive and where statistically significant generates additional research questions to evaluate. In this systematic review SBP and antihypertensive/diuretic medications were not a primary or secondary outcome for any of the studies included. The use of 'other' outcome data may potentially compromise the external validity of the generated evidence, due to a lack of statistical power. Some methodologists argue that potentially under powered

secondary or other outcome data should be published, to facilitate its use in a systematic review or meta-analysis, since the combined data may achieve enough power for statistical significance (Schulz et al. 2010). The absence of primary outcome data is not strictly a limitation of this review, since systematic review is only as good as the data on which it is based (Charrois 2015). It does, highlight the need for further research in this area, to include power calculations for the meta-analysis and partially justifies the findings of the GRADE evaluation discussed below.

Whereas SBP data facilitated a meta-analysis for the primary outcome measure of SBP change, there was a lack of statistical data to support a meta-analysis for the primary outcome measures of antihypertensive and/or diuretic medication change. This necessitated a narrative approach to summarising the extracted data. It is possible that a lack of statistical analysis reduces confidence in an outcome, however, the narrative summary demonstrated that all studies included suggest that antihypertensive and all diuretic medication change does not occur following administration of sodium bicarbonate/citrate. Again, this is not a limitation of this study's conduct or methodology, it reflects information available to answer the research question.

5.3.5 Reporting bias

Reporting bias is a collective term which encompasses bias due to publication, language, citation and time lag from study completion to publication, it can influence the nature and direction of trial results (Sedgwick and Marston 2015). Reporting bias is a significant issue, since if not adjusted for can result in the publication of misleading results. This review protocol was written to include peer-reviewed and grey literature sources to identify all suitable publications for inclusion and reduce the potential for reporting bias, which is a

strength of the review. Due to changes beyond the control of the research team the searches did deviate from protocol. This was due to the merging of the OpenGrey and OpenSIGLE databases and the enclosure of the GreyLit database. It is unlikely that the merger of the OpenGrey and OpenSIGLE databases impacted the searches since the same sources of information remained available. It is not possible to assess the impact the closure of the GreyLit database had upon the searches and wider review. In addition, due to a limited number of publications identified it was not possible to evaluate publication bias using the funnel plot produced by the systematic review software. A funnel plot is expected to be symmetrical with all points scattered centrally, in a funnel shape around the point estimate, where there is no publication bias i.e. when all relevant trials are included in a meta-analysis. In the funnel plot produced for the SBP RCT analysis, there is an asymmetric scatter of points around the total point estimate (appendix 8). This is expected for two reasons: firstly, as per protocol the use of a funnel plot is an unreliable method for detecting bias if there are less than 10 included studies (Sedgwick and Marston 2015). Secondly, the lack of grey literature identified in the searches increases the potential for publication bias. These findings are in keeping with existing literature: in a review of published meta-analysis, researchers found that only 29% of publications searched for and successfully included data from 'grey' literature and the potential for publication bias was only discussed in 32% of studies, with only one study evaluating the potential for publication bias statistically (Ahmed, Sutton and Riley 2012). A considerable strength of this review is the attempt to reduce reporting bias through the broad search strategy, inclusion of grey literature searches and the effort to evaluate reporting bias using a funnel plot.

5.3.6 Risk of bias evaluation and EPPI reviewer formatting

Unfortunately, the ROBINS tool was not compatible with the formatting used by the EPPI reviewer 4 software purchased for this review and required modification. This was achieved by combining the serious and critical risk of bias outcomes to form a high risk of bias group, for the software to produce a risk of bias table. Ultimately modifying any validated tool has the capacity to invalidate the results produced, since the tool was validated in its original format. The impact of this change upon the review was minimal since both studies evaluated using ROBINS were of serious or critical risk of bias and when combined in a meta-analysis, the studies were too heterogenous to produce a valid result. However, if a larger number of NRSi had been identified and included in this review, the inability to differentiate between serious and high risk of bias may have had a deleterious effect on a sensitivity analysis. This maybe a consideration for evaluating bias and using software to generate risk of bias tables in future reviews, where NRSi studies are included.

5.4 Confidence in results produced

In recognising the limitations of this review e.g. small analysis numbers and the potential for reporting bias, the pre-protocol decision to use GRADE to rate the certainty of the outcomes is a significant strength of this review. The use of GRADE did categorise certainty of the outcomes for this review as 'low' or 'very low', which reflects a lack of confidence in the estimate of the effect being true. Heterogeneity, use of 'other' outcome data, variation in the point estimates across meta-analysis for the outcomes assessed or a lack of statistical data to facilitate a meta-analysis were the primary reasons for downgrade. In a review of oral health systematic reviews, researchers found the use of GRADE was predominately associated with the downgrading of certainty of results to 'low' or 'very low', with no differences observed in Cochrane and non-Cochrane reviews (Pandis et al. 2015). This is of interest for two reasons:

firstly, it suggests that the outcome of GRADE assessment for this review is consistent with existing literature. Secondly, it highlights the need for higher quality RCT studies to inform clinical practice and future research, blood pressure and sodium bicarbonate or citrate use in CKD.

5.5 Conclusions

The aim of this study was to systematically review the evidence regarding the impact of sodium bicarbonate and/or citrate upon blood pressure in CKD stages I-V and if sufficient data allowed, to undertake a meta-analysis. This review achieved its aim and the result suggests for individuals with CKD stage I-V non-RRT prescribed sodium bicarbonate at a dose of 0.2-0.5mEq/kg bw/d SBP may reduce by 0.51 mmHg CI 95% (-0.84, -0.18). In addition, a narrative data summary suggests that antihypertensive and/or diuretic medications prescriptions are not significantly changed through use of sodium bicarbonate/citrate therapy. This review was limited by the small evidence based available upon which to formulate results and further research is needed to confirm the findings.

5.6 Implications of this research

5.6.1 Implications for future research

Systematic reviews of this nature, endeavor to inform future research and the clinical management of CKD, to preserve renal function and delay disease progression. The dependence on 'other' outcome data and the GRADE conclusion highlight uncertainty associated with the results of this review. This uncertainty identifies a gap in research knowledge. There are currently three ongoing, large, multicentre trials evaluating the impact of sodium bicarbonate therapy on progression of CKD (Witham et al. 2015; Gaggl et al. 2013;

Di Iorio et al. 2012). Two of these trials (Witham et al. 2015; Di Iorio et al. 2012) are measuring blood pressure change, to include medication changes as a secondary outcome, whereas one trial (Gaggl et al. 2013) is measuring blood pressure change as an additional 'other' outcome. These trials may well provide conclusive information with respect to blood pressure change, in response to correction of acidosis with sodium bicarbonate in CKD. However, it is also possible that as these trials measure blood pressure change as secondary or 'other' outcomes, the issue of sample size and power identified in this review could apply i.e. since blood pressure is not a primary outcome, the trials may not be sufficiently powered to evaluate blood pressure results produced.

If due to a lack primary outcome data, the current multi-centre RCT do not provide conclusive data to support the findings of this review then a definitive RCT is required. An RCT will provide evidence to support the use of sodium bicarbonate, particularly as an adjunct to blood pressure therapy in CKD. However, due to the difficulties associated with conducting a high quality RCT and to ensure ethical use of research resources, alternate approaches to RCT evidence maybe required help to answer the research question. Whilst these options do not have the benefit of a control arm and sit lower in the hierarchy of evidence, they could provide essential information regarding safety, feasibility, utility, cost-effectiveness and stratification, which will support the design of a future high-quality RCT. These options could include:

I. A retrospective, observational study, using large-scale healthcare informatics databases to evaluate change in blood pressure and antihypertensive/diuretic medication following use of sodium bicarbonate in CKD.
II. A prospective, national, observational study e.g. using renal registry data collection. A significant proportion of the data required is currently collected by renal units

throughout the UK and submitted to the UK renal registry. Evaluation of such large-scale data may help to identify significant changes in blood pressure response to sodium bicarbonate supplementation and potentially, population subgroups who respond more favourably to sodium bicarbonate supplementation.

5.6.2 Implications for clinical practice

The result of this review may improve clinical confidence in the use of sodium bicarbonate therapy in CKD where concerns exist regarding sodium loading and hypertension

6 References

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7 Appendix

7.1 Appendix 1: Ethical approval documentation

REGISTRY RESEARCH UNIT

ETHICS REVIEW FEEDBACK FORM

(Review feedback should be completed within 10 working days)

Name of applicant: Beverley Beynon-Cobb.....

Faculty/School/Department: [Faculty of Health and Life Sciences] FRC Technology Enabled Health Research (CTEHR).....

Research project title: The effect of Sodium Bicarbonate on Blood Pressure in Chronic Kidney Disease: a systematic review

Comments by the reviewer

1. Evaluation of the ethics of the proposal: No concerns. Low risk	
2. Evaluation of the participant information sheet and consent form: N/A	
3. Recommendation: (Please indicate as appropriate and advise on any conditions. If there any conditions, the applicant will be required to resubmit his/her application and this will be sent to the same reviewer).	
X	Approved - no conditions attached
	Approved with minor conditions (no need to re-submit)
	Conditional upon the following – please use additional sheets if necessary (please re-submit application)
	Rejected for the following reason(s) – please use other side if necessary
	Not required

Name of reviewer: Anonymous.....

Date: 26/05/2017.....

External Ethical Review

Question		Yes	No
1	Will this study be submitted for ethical review to an external organisation? (e.g. Another University, Social Care, National Health Service, Ministry of Defence, Police Service and Probation Office)		X
	If YES, name of external organisation		
2	Will this study be reviewed using the IRAS system?		X
3	Has this study previously been reviewed by an external organisation?		X

Low Risk Research Ethics Approval Checklist

Project Information

Project Ref	P48545
Full name	Beverley Beynon-Cobb
Faculty	Faculty of Health and Life Sciences
Department	FRC Technology Enabled Health Research (CTEHR)
Supervisor	Bernice Tighe
Module Code	MRES-CTEHR
EFAAF Number	
Project title	The effect of Sodium Bicarbonate on Blood Pressure in Chronic Kidney Disease: a systematic review
Date(s)	26/09/2016 - 28/09/2018
Created	23/11/2016 09:39

Project Summary

A systematic review of the evidence to evaluate the impact of bicarbonate supplementation on blood pressure in CKD, to inform the course of future research to improve clinical practice.

Names of Co-Investigators and their organisational affiliation (place of study/employer)	
Is the project self-funded?	YES
Who is funding the project?	NIHR/HEE
Has the funding been confirmed?	YES
Are you required to use a Professional Code of Ethical Practice appropriate to your discipline?	NO
Have you read the Code?	NO

Project Details

What is the purpose of the project?	To evaluate the impact of sodium bicarbonate supplementation on blood pressure in chronic kidney disease stages I-V (non renal replacement therapy), to inform future research.	
What are the planned or desired outcomes?	• To systematically review the evidence regarding the impact of sodium bicarbonate supplementation on blood pressure in CKD I-V (non-renal replacement therapy. to inform the course of future research and improve clinical practice. • If sufficient homogeneity, to undertake a meta-analysis of study data evaluating the impact of sodium bicarbonate supplementation on blood pressure in CKD stages I-IV non-RRT.	
Explain your research design	Quantitative systematic review using PRISMA guidance.	
Outline the principal methods you will use	Formation of a review team Production of a systematic review protocol in accordance with PRISMA-P guidance Registration of the systematic review on PROSPERO, subject to CU ethical approval Complete the systematic review in accordance with the stated protocol, ensuring to document and register any protocol changes as required. Disseminate the findings of the systematic review through journal publication, conference presentations and discussions with relevant renal patient groups.	
Are you proposing to use an external research instrument, validated scale or follow a published research method?		YES
If yes, please give details of what you are using	PRISMA guidance. RoB 2.0 & ROBINS-1 risk of bias tools EPPI REVIEWER 4 systematic review software GRADE evidence review software	
Will your research involve consulting individuals who support, or literature, websites or similar material which advocates, any of the following: terrorism, armed		NO

struggles, or political, religious or other forms of activism considered illegal under UK law?	
Are you dealing with Secondary Data? (e.g. sourcing info from websites, historical documents)	YES
Are you dealing with Primary Data involving people? (e.g. interviews, questionnaires, observations)	NO
Are you dealing with personal or sensitive data?	NO
Is the project solely desk based? (e.g. involving no laboratory, workshop or off-campus work or other activities which pose significant risks to researchers or participants)	YES
Are there any other ethical issues or risks of harm raised by the study that have not been covered by previous questions?	NO
If yes, please give further details	

External Ethical Review

Question		Yes	No
1	Will this study be submitted for ethical review to an external organisation? (e.g. Another University, Social Care, National Health Service, Ministry of Defence, Police Service and Probation Office)		X
	If YES, name of external organisation		
2	Will this study be reviewed using the IRAS system?		X
3	Has this study previously been reviewed by an external organisation?		X

Risk of harm, potential harm and disclosure of harm

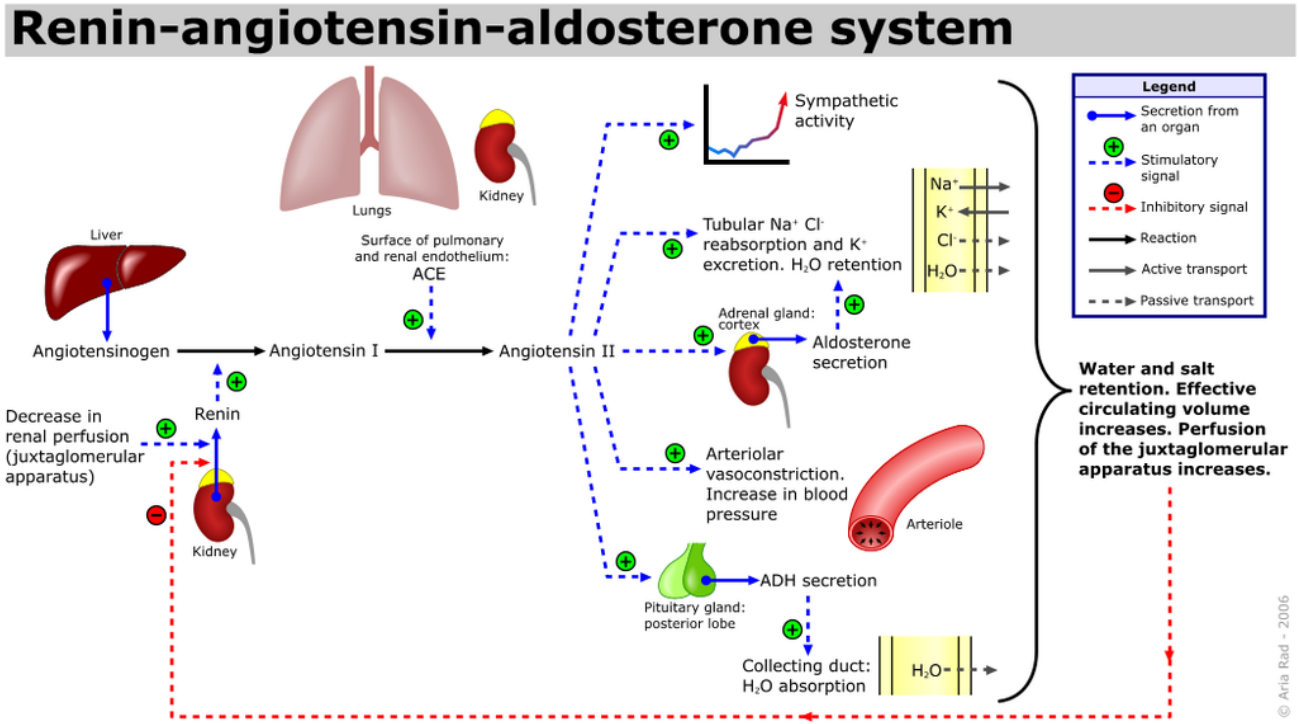
Question		Yes	No
1	Is there any significant risk that the study may lead to physical harm to participants or researchers?		X
	If YES, please explain how you will take steps to reduce or address those risks		
2	Is there any significant risk that the study may lead to psychological or emotional distress to participants?		X
	If YES, please explain how you will take steps to reduce or address those risks		
3	Is there any risk that the study may lead to psychological or emotional distress to researchers?		X
	If YES, please explain how you will take steps to reduce or address those risks		
4	Is there any risk that your study may lead or result in harm to the reputation of participants, researchers, or their employees, or any associated persons or organisations?		X
	If YES, please explain how you will take steps to reduce or address those risks		
5	Is there a risk that the study will lead to participants to disclose evidence of previous criminal offences, or their intention to commit criminal offences?		X
	If YES, please explain how you will take steps to reduce or address those risks		
6	Is there a risk that the study will lead participants to disclose evidence that children or vulnerable adults are being harmed, or at risk or harm?		X
	If YES, please explain how you will take steps to reduce or address those risks		
7	Is there a risk that the study will lead participants to disclose evidence of serious risk of other types of harm?		X
	If YES, please explain how you will take steps to reduce or address those risks		
8	Are you aware of the CU Disclosure protocol?	X	

Online and Internet Research

Question				Yes	No
1	Will any part of your study involve collecting data by means of electronic media (e.g. the Internet, e-mail, Facebook, Twitter, online forums, etc)?				X
	If YES, please explain how you will obtain permission to collect data by this means				
2	Is there a possibility that the study will encourage children under 18 to access inappropriate websites, or correspond with people who pose risk of harm?				X
	If YES, please explain further				
3	Will the study incur any other risks that arise specifically from the use of electronic media?				X
	If YES, please explain further				
4	Will you be using survey collection software (e.g. BoS, Filemaker)?				X
	If YES, please explain which software				
5	Have you taken necessary precautions for secure data management, in accordance with data protection and CU Policy?				X
	If NO	please explain why not	The data being used is already in the public domain since this is a systematic review. The EEPI software which will be used is a secure data repository for systematic reviews.		
	If YES	Specify location where data will be stored			
		Planned disposal date			
		If the research is funded by an external organisation, are there any requirements for storage and disposal?			
		If YES, please specify details			

7.2 Appendix 2: The Renin-Angiotensin-Aldosterone-System (RAAS)

As per the diagram on the page below RAAS serves to regulate blood pressure, primarily through the manipulation of plasma sodium concertation. A reduction in blood flow is detected by the kidney's juxtaglomerular complex. This results in the conversion of pro-renin (which is present in the circulation) to renin. Renin is a hormone which converts inactive angiotensinogen (secreted by the liver) in to angiotensin I. Angiotensin I, in turn travels to the lungs, where is converted into angiotensin II. Angiotensin II, a hormone acts to increase blood pressure via: vasoconstriction, activation of the sympathetic nervous system and increasing blood volume. The latter is achieved through an increase in renal resorption of sodium and chloride and secretion of potassium, which increases water retention and consequently blood volume. This mechanism may be a direct result of angiotensin II on the renal tubules or mediated via the action of aldosterone. Angiotensin II stimulates the adrenal cortex to secrete aldosterone. Angiotensin II also stimulates the secretion of anti-diuretic hormone from the pituitary glands, the result of which is an increased tubular resorption of water and increased blood volume. This system runs via a negative feedback loop: once normal blood pressure is restored this is detected by the juxtaglomerular complex and the conversion of prorenin to renin stops.



Page URL: https://commons.wikimedia.org/wiki/File:Renin-angiotensin-aldosterone_system.png
File URL: https://upload.wikimedia.org/wikipedia/commons/a/a2/Renin-angiotensin-aldosterone_system.png
Attributions: A. Rad [CC BY-SA 3.0 (http://creativecommons.org/licenses/by-sa/3.0/)]. By Soupvector - Own work, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=66583851

7.3 Appendix 3: PRISMA CHECKLIST

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Evidence
ADMINISTRATIVE INFORMATION			
Title			
Identification	1a	Identify the report as a protocol of a systematic review	Title
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	**N/A**
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	PROSPERO CRD42017058933
Authors			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	See PROSPERO
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	See PROSPERO
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes;	N/A

		otherwise, state plan for documenting important protocol amendments	
Support			
Sources	5a	Indicate sources of financial or other support for the review	See PROSPERO
Sponsor	5b	Provide name for the review funder and/or sponsor	See PROSPERO
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	See PROSPERO
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	CU ethics application
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	See PROSPERO
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	See PROSPERO
Information sources	9	Describe all intended information sources (such as electronic	See PROSPERO

		databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	
Study records			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	See PROSPERO
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	See PROSPERO
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	See PROSPERO & CU ethics application
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	CU ethics application & Research methods module submission
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including	See PROSPERO & CU ethics application

		prioritization of main and additional outcomes, with rationale	
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	See PROSPERO & CU ethics application
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	See PROSPERO & CU ethics application
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	See PROSPERO & CU ethics application
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	See PROSPERO & CU ethics application
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	See PROSPERO & CU ethics application
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	See PROSPERO & CU ethics application

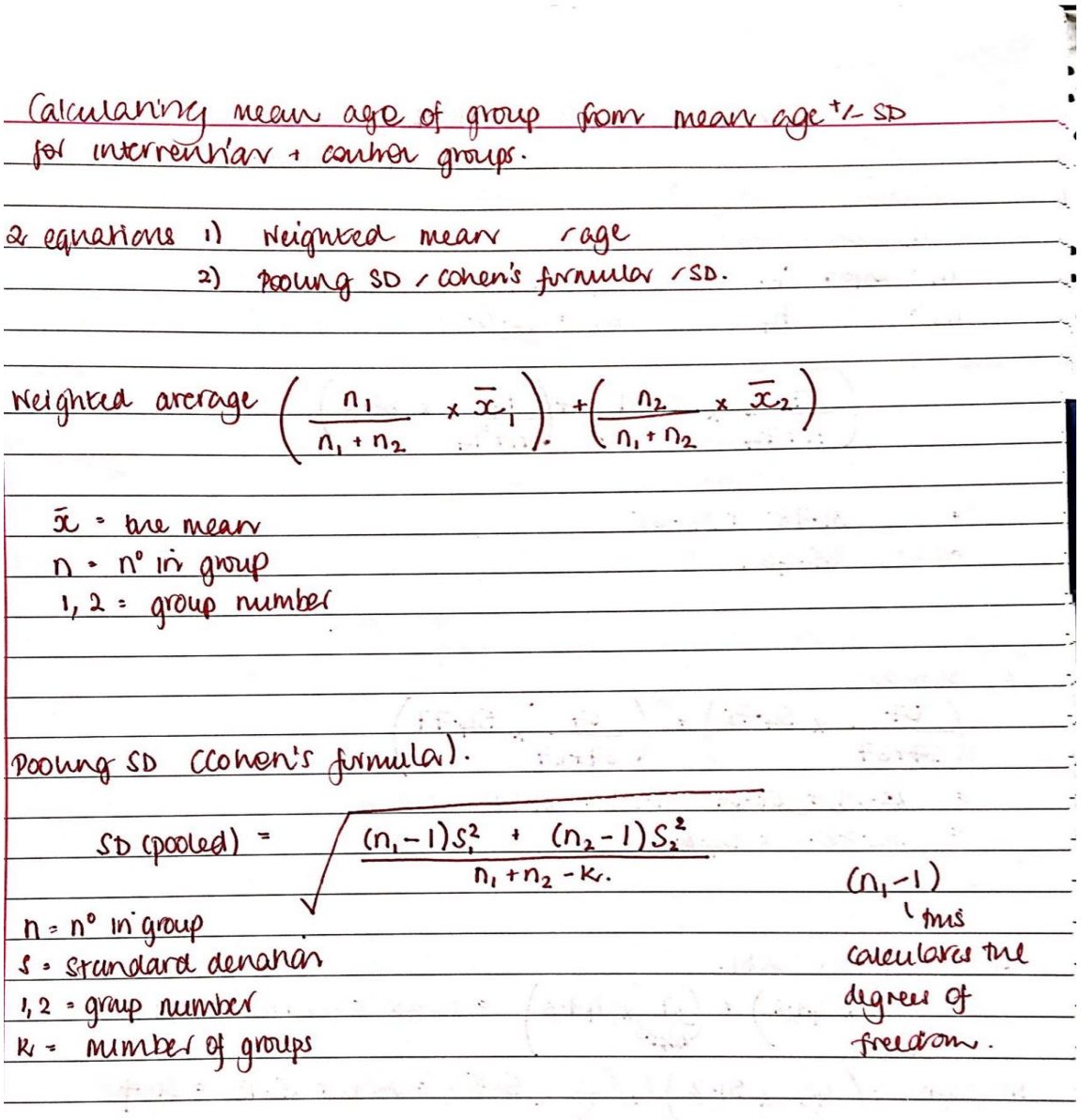
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	See PROSPERO & CU ethics application

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

7.4 Appendix 4: URL for Cochrane Community Data Extraction Template

https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&cad=rja&uact=8&ved=2ahUKEwjEgubR_LfdAhUSdcAKHUIsBvgQFjABegQIARAC&url=https%3A%2F%2Fcommunity.cochrane.org%2Fsites%2Fdefault%2Ffiles%2Fuploads%2Finline-files%2FERC%2520data%2520collection%2520form%2520for%2520intervention%2520reviews%2520for%2520RCTs%2520and%2520non-RCTs.doc&usg=AOvVaw2f0Wx5fM1jBDFLsLBbNpI-

7.5 Appendix 5: Calculations of mean age and serum bicarbonate for included studies using Cohens formula and standard mean difference. Calculations of dose sodium bicarbonate using the Taylor expansion equation



Calculating mean age of group from mean age +/- SD for intervention + control groups.

2 equations 1) Weighted mean age
2) Pooling SD / cohen's formula / SD.

Weighted average $\left(\frac{n_1}{n_1+n_2} \times \bar{x}_1\right) + \left(\frac{n_2}{n_1+n_2} \times \bar{x}_2\right)$

$\bar{x}$ = the mean
n = n° in group
1, 2 = group number

Pooling SD (cohen's formula).

$$SD\ (pooled) = \sqrt{\frac{(n_1-1)s_1^2 + (n_2-1)s_2^2}{n_1+n_2-k.}}$$

n = n° in group
s = standard deviation
1, 2 = group number
k = number of groups

(n_1-1) this calculates the degrees of freedom.

mean age corrections made to 2dp. calculations 1dp answer.

1. Belassi

a. mean age.

n_1 = 71 x_1 = 64.9

n_2 = 74 x_2 = 66.0.

$$\left(\frac{71}{71+74} \times 64.9\right) + \left(\frac{74}{71+74} \times 66.0\right)$$

= 31.78 + 33.68

= 65.46.

2. DCBNO.

$$\left(\frac{67}{67+67} \times 54.78\right) + \left(\frac{67}{67+67} \times 54.77\right)$$

= 27.39 + 27.39

= 54.78. = 54.8.

3a. Goraya 2012 CKD1.

$$\left(\frac{26}{53} \times 49.9\right) + \left(\frac{27}{53} \times 49.3\right) = 24.48 + 25.12 = 49.6$$

3b. CKD2. $\left(\frac{40}{80} \times 51.2\right) + \left(\frac{40}{80} \times 51.5\right) = 25.6 + 25.75 = 51.4$

CD2 + CKD1 $= \left(\frac{53}{133} \times 49.6\right) + \left(\frac{80}{133} \times 51.4\right) = 19.77 +$ [illegible] 30

= 50.7

Manner $\sqrt{\frac{(19 \times 17^2) + (19 \times 10.5^2)}{38}}$

$= \sqrt{\frac{289 + 110.25}{38}}$

$= \sqrt{10.5065} \quad = 3.241 \quad = 3.2$

Phisikal $\sqrt{\frac{(30-1 \times 6.4^2) + (29-1 \times 5.0^2)}{59-2}}$

$\sqrt{\frac{1187.84 + 700}{57}} \quad = \sqrt{33.12} \quad = 5.8.$

03105/18.

Mean serum bicarbonate.

Pritikal ~~Mean/SD~~ control $n=29$ 20.6 ± 0.8 intervention $n=30$ 20.8 ± 1.2.

Weighted average $= \left(\frac{29}{59} \times 20.6\right) + \left(\frac{30}{59} \times 20.8\right) = 9.98 + 10.58$

$= 20.56 = 20.6.$

Pooled SDs. $\sqrt{\frac{(28 \times 0.8^2) + (29 \times 1.2^2)}{57}} = \sqrt{\frac{17.92 + 41.76}{57}} = \sqrt{1.05}$

$= 1.02$

$= 1.0$

Jeong n=40 cont + int.

cont 18.5 +/- 3.9 18.9 +/- 4.1.

$(0.5 \times 18.5) + (0.5 \times 18.9) = 9.25 + 9.45 = 18.7$.

$$\sqrt{\frac{39 \times 3.9^2 + 39 \times 4.1^2}{78}}$$

$$= \sqrt{\frac{593.19 + 655.59}{78}} \quad \sqrt{16.01} = 4.0$$

If the data is too poor should it be included at all?

Calculation of mean dose of sodium bicarbonate between-Arms.

dose
1.82 +/- 0.8
~~Mt 76.6 +/-~~
21.

mean dose /kg = $\frac{1.82}{76.6\ kg} = 0.0238\ g/kg$.

0.4g/kg

1g = 11.9 mmol

84mg $NaHCO_3$ = 1mEq Na^+ + 1mEq HCO_3^-

4.76 mEq/kg.

Bellasi, Granja 2012, between ~0.5 mEq/kg

0.24

mean dose = 0.0238g +/- 0.24g

1g = 1000mg. 0.1 = 100mg

0.01 = 10mg

84mg HCO_3 = 1meq HCO_3 + 1meq Na.

24mg

24mg 0.3

0.0238 +/- 0.012g

= 0.024 +/- 0.01

0.02 +/- 0.01 g

= 20mg +/- 10mg

= 0.2 mEq/kg +/- 0.1 mEq.

7.6 Appendix 6: Search strings

EMBASE SR FINAL SEARCH STRINGS 24/08/17

1. exp chronic kidney failure/
2. (Chronic adj kidney adj disease).ab.
3. (Chronic adj kidney adj disease).ti.
4. (renal adj insufficiency).ab.
5. renal insufficiency.ti.
6. (renal adj failure).ti.
7. (renal adj failure).ab.
8. (Kidney adj failure).ab.
9. (Kidney adj failure).ti.
10. (Renal adj disease).ti.
11. (Renal adj disease).ab.
12. (Kidney adj disease).ab.
13. (Kidney adj disease).ti.
14. exp kidney function/
15. (Kidney adj function).ti.
16. (Kidney adj function).ab.
17. (Renal adj function).ab.
18. (Renal adj function).ti.
19. exp glomerulus filtration rate/
20. (Glomerular adj filtration adj rate).ti.
21. (Glomerular adj filtration adj rate).ab.
22. GFR.ab. or GFR.ti.
23. exp creatinine clearance/
24. (Creatinine adj clearance).ab.
25. (Creatinine adj clearance).ti.
26. Pre-dialysis.ti. or Pre-dialysis.ab.
27. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28. exp bicarbonate/
29. (Sodium adj bicarbonate).ti.
30. (Sodium adj bicarbonate).ab.
31. Bicarbonate.ab. or Bicarbonate.ti.
32. NaHCO3.ab. or NaHCO3.ti.
33. exp citrate sodium/
34. (Sodium adj Citrate).ab.
35. (Sodium adj Citrate).ti.
36. (Baking adj soda).ti.
37. (Baking adj soda).ab.
38. (Acidosis adj treatment).ab.
39. (Acidosis adj treatment).ti.
40. (Acidosis adj2 treatment).ti.
41. (Acidosis adj2 treatment).ab.
42. (Acidosis adj2 correction).ab.
43. (Acidosis adj2 correction).ti.
44. (Alkali adj therapy).ti.
45. (Alkali adj therapy).ab.

46. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
47. 27 and 46
48. exp acute kidney failure/
49. (Acute adj kidney).ab.
50. (Acute adj kidney).ti.
51. (Acute adj renal).ti.
52. (Acute adj renal).ab.
53. exp pregnancy/
54. pregnan*.ab. or pregnan*.ti.
55. newborn/
56. Neonat*.ab. or Neonat*.ti.
57. exp intensive care unit/
58. (Intensive adj therapy adj unit).ab.
59. (Intensive adj therapy adj unit).ti.
60. (Intensive adj care adj unit).ti.
61. (Intensive adj care adj unit).ab.
62. (Critical adj care).ab.
63. (Critical adj care).ti.
64. exp dialysis fluid/
65. (Dialysis adj solutions).ti.
66. (Dialysis adj solutions).ab.
67. (dialysis adj fluid).ab.
68. (dialysis adj fluid).ti.
69. Dialysate.ti. or Dialysate.ab.
70. exp renal replacement therapy/
71. (Renal adj replacement).ti.
72. (Renal adj replacement).ab.
73. Dialysis.ab. or Dialysis.ti.
74. Haemodialysis.ab. or Haemodialysis.ti.
75. hemodialysis.ab. or hemodialysis.ti.
76. (Peritoneal adj dialysis).ab.
77. (Peritoneal adj dialysis).ti.
78. exp hemofiltration/
79. exp continuous hemofiltration/
80. Hemofiltration.ti. or Hemofiltration.ab.
81. haemofiltration.ti. or haemofiltration.ab.
82. exp contrast sensitivity/ or exp contrast induced nephropathy/ or exp contrast/
83. Contrast.ti. or Contrast.ab.
84. exp nephrolithiasis/
85. stones.ti. or stones.ab.
86. exp hyperoxaluria/
87. hyperoxaluria.ti. or hyperoxaluria.ab.
88. exp cystinuria/
89. exp cystinosis/
90. Cystin*.ti. or Cystin*.ab.
91. calcul*.ti. or calcul*.ab.
92. exp renal osteodystrophy/
93. (Renal adj bone adj disease).ti.

94. (Renal adj bone adj disease).ab.
95. 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94
96. (((chronic kidney failure or (Chronic adj kidney adj disease) or (Chronic adj kidney adj disease) or (renal adj insufficiency) or renal insufficiency or (renal adj failure) or (renal adj failure) or (Kidney adj failure) or (Kidney adj failure) or (Renal adj disease) or (Renal adj disease) or (Kidney adj disease) or (Kidney adj disease) or kidney function or (Kidney adj function) or (Kidney adj function) or (Renal adj function) or (Renal adj function) or glomerulus filtration rate or (Glomerular adj filtration adj rate) or (Glomerular adj filtration adj rate) or (GFR or GFR) or creatinine clearance or (Creatinine adj clearance) or (Creatinine adj clearance) or (Pre-dialysis or Pre-dialysis)) and (bicarbonate or (Sodium adj bicarbonate) or (Sodium adj bicarbonate) or (Bicarbonate or Bicarbonate) or (NaHCO3 or NaHCO3) or citrate sodium or (Sodium adj Citrate) or (Sodium adj Citrate) or (Baking adj soda) or (Baking adj soda) or (Acidosis adj treatment) or (Acidosis adj treatment) or (Acidosis adj2 treatment) or (Acidosis adj2 treatment) or (Acidosis adj2 correction) or (Acidosis adj2 correction) or (Alkali adj therapy) or (Alkali adj therapy))) not (acute kidney failure or (Acute adj kidney) or (Acute adj kidney) or (Acute adj renal) or (Acute adj renal) or pregnancy or (pregnan* or pregnan*) or newborn or (Neonat* or Neonat*) or intensive care unit or (Intensive adj therapy adj unit) or (Intensive adj therapy adj unit) or (Intensive adj care adj unit) or (Intensive adj care adj unit) or (Critical adj care) or (Critical adj care) or dialysis fluid or (Dialysis adj solutions) or (Dialysis adj solutions) or (dialysis adj fluid) or (dialysis adj fluid) or (Dialysate or Dialysate) or renal replacement therapy or (Renal adj replacement) or (Renal adj replacement) or (Dialysis or Dialysis) or (Haemodialysis or Haemodialysis) or (hemodialysis or hemodialysis) or (Peritoneal adj dialysis) or (Peritoneal adj dialysis) or hemofiltration or continuous hemofiltration or (Hemofiltration or Hemofiltration) or (haemofiltration or haemofiltration) or (contrast sensitivity or contrast induced nephropathy or contrast) or (Contrast or Contrast) or nephrolithiasis or (stones or stones) or hyperoxaluria or (hyperoxaluria or hyperoxaluria) or cystinuria or cystinosis or (Cystin* or Cystin*) or (calcul* or calcul*) or renal osteodystrophy or (Renal adj bone adj disease) or (Renal adj bone adj disease))).ti.

AMED FINAL SEARCH 04/09/2017

1. exp Kidney disease/ or exp Kidney failure chronic/
2. (Chronic adj kidney adj disease).ti.
3. (Chronic adj kidney adj disease).ab.
4. (renal adj insufficiency).ti.
5. (renal adj insufficiency).ab.
6. (renal adj failure).ab.
7. (renal adj failure).ti.
8. (Kidney adj failure).ti.
9. (Kidney adj failure).ab.
10. (Renal adj disease).ab.
11. (Renal adj disease).ti.
12. (Kidney adj disease).ab.
13. (Kidney adj function).ab.
14. (Kidney adj function).ti.
15. (Renal adj function).ti.
16. (Renal adj function).ab.
17. (Glomerular adj filtration adj rate).ti.
18. (Glomerular adj filtration adj rate).ab.
19. GFR.ab.
20. GFR.ti.
21. (Creatinine adj clearance).ti.
22. (Creatinine adj clearance).ab.
23. Pre-dialysis.ab.
24. Pre-dialysis.ti.
25. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. (Sodium adj bicarbonate).ti.
27. (Sodium adj bicarbonate).ab.
28. Bicarbonate.ab.
29. Bicarbonate.ti.
30. NaHCO3.ti.
31. NaHCO3.ab.
32. (Sodium adj Citrate).ab.
33. (Sodium adj Citrate).ti.
34. (Baking adj soda).ti.
35. (Baking adj soda).ab.
36. (Acidosis adj2 treatment).ab.
37. (Acidosis adj2 treatment).ti.
38. (Acidosis adj2 correction).ti.
39. (Acidosis adj2 correction).ab.
40. (Alkali adj therapy).ab.
41. (Alkali adj therapy).ti.
42. 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41

MEDLINE SEARCH STRINGS

S72 s34 NOT s71
S71 S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70
S70 TI Renal bone disease OR AB Renal bone disease
S69 TI nephrocalcinosis OR AB nephrocalcinosis
S68 (MH "Nephrocalcinosis")
S67 TI Cystin* OR AB Cystin*
S66 TI Cystinosis OR AB Cystinosis
S65 (MH "Cystinuria")
S64 TI hyperoxaluria OR AB hyperoxaluria
S63 TI calcul* OR AB calcul*
S62 (MH "Kidney Calculi+")
S61 TI Contrast OR AB Contrast
S60 (MH "Contrast Media+")
S59 TI haemofiltration OR AB haemofiltration
S58 TI Hemofiltration OR AB Hemofiltration
S57 (MH "Hemofiltration+")
S56 TI Peritoneal dialysis OR AB Peritoneal dialysis
S55 TI haemodialysis OR AB haemodialysis
S54 TI Hemodialysis OR AB Hemodialysis
S53 TI Dialysis OR AB Dialysis
S52 TI Renal dialysis OR AB Renal dialysis
S51 TI Renal replacement therapy OR AB Renal replacement therapy
S50 (MH "Renal Replacement Therapy+")
S49 TI Dialysate OR AB Dialysate
S48 (MH "Dialysis Solutions")
S47 TI Dialysis solutions OR AB Dialysis solutions
S46 TI Critical care OR AB Critical care
S45 (MH "Critical Care+")
S44 TI Intensive care unit OR AB Intensive care unit
S43 TI Intensive therapy unit OR AB Intensive therapy unit
S42 (MH "Intensive Care Units+")
S41 TI neonat* OR AB neonat*
S40 (MH "Infant, Newborn+")
S39 TI Pregnan* OR AB Pregnan*
S38 TI Pregnancy OR AB Pregnancy
S37 TI acute renal OR AB acute renal
S36 TI Acute kidney OR AB Acute kidney
S35 (MH "Kidney Failure, Acute+")
S34 S20 AND S32
S33 S20 AND S32
S32 S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31
S31 TI Alkali therapy OR AB Alkali therapy
S30 TI Acidosis correction OR AB Acidosis correction
S29 TI Acidosis treatment OR AB Acidosis treatment
S28 TI Baking soda OR AB Baking soda

S27 TI Na citrate OR AB Na citrate
S26 TI NaHCO3 OR AB NaHCO3
S25 TI Bicarbonate OR AB bicarbonate
S24 TI Sodium citrate OR AB Sodium citrate
S23 (MH "Sodium Citrate")
S22 TI Sodium bicarbonate OR AB Sodium bicarbonate
S21 (MH "Sodium Bicarbonate+")
S20 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19
S19 TI Pre-dialysis OR AB Pre-dialysis
S18 TI Kidney disease progression OR AB Kidney disease progression
S17 TI Renal disease progression OR AB Renal disease progression
S16 TI Creatinine clearance OR AB Creatinine clearance
S15 TI GFR OR AB GFR
S14 TI Glomerular filtration rate OR AB Glomerular filtration rate
S13 (MH "Glomerular Filtration Rate")
S12 TI Renal function OR AB Renal function
S11 (MH "Kidney Function Tests+")
S10 TI Renal Disease OR AB Renal Disease
S9 TI Chronic Renal disease OR AB Chronic Renal disease
S8 TI Kidney failure OR AB Kidney failure
S7 TI Renal failure OR AB Renal failure
S6 TI Chronic renal failure OR AB Chronic renal failure
S5 TI Renal insufficiency OR AB Renal insufficiency
S4 TI Chronic renal insufficiency OR AB Chronic renal insufficiency
S3 TI Kidney disease OR AB Kidney disease
S2 TI Chronic kidney disease OR AB Chronic kidney disease
S1 (MH "Kidney Failure, Chronic+")

CINHAL SEARCH STRINGS

S34 NOT S71
S71 S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70
S70 TI Renal bone disease OR AB Renal bone disease
S69 TI nephrocalcinosis OR AB nephrocalcinosis
S68 (MH "Nephrocalcinosis")
S67 TI Cystin* OR AB Cystin*
S66 TI Cystinosis OR AB Cystinosis
S65 (MH "Cystinuria")
S64 TI hyperoxaluria OR AB hyperoxaluria
S63 TI calcul* OR AB calcul*
S62 (MH "Kidney Calculi+")
S61 TI Contrast OR AB Contrast
S60 (MH "Contrast Media+")
S59 TI haemofiltration OR AB haemofiltration
S58 TI Hemofiltration OR AB Hemofiltration
S57 (MH "Hemofiltration+")
S56 TI Peritoneal dialysis OR AB Peritoneal dialysis
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S54 TI Hemodialysis OR AB Hemodialysis
S53 TI Dialysis OR AB Dialysis
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S40 (MH "Infant, Newborn+")
S39 TI Pregnan* OR AB Pregnan*
S38 TI Pregnancy OR AB Pregnancy
S37 TI acute renal OR AB acute renal
S36 TI Acute kidney OR AB Acute kidney
S35 (MH "Kidney Failure, Acute+")
S34 S20 AND S32
S33 S20 AND S32
S32 S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31
S31 TI Alkali therapy OR AB Alkali therapy
S30 TI Acidosis correction OR AB Acidosis correction
S29 TI Acidosis treatment OR AB Acidosis treatment
S28 TI Baking soda OR AB Baking soda

S27 TI Na citrate OR AB Na citrate
S26 TI NaHCO3 OR AB NaHCO3
S25 TI Bicarbonate OR AB bicarbonate
S24 TI Sodium citrate OR AB Sodium citrate
S23 (MH "Sodium Citrate")
S22 TI Sodium bicarbonate OR AB Sodium bicarbonate
S21 (MH "Sodium Bicarbonate+")
S20 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19
S19 TI Pre-dialysis OR AB Pre-dialysis
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S17 TI Renal disease progression OR AB Renal disease progression
S16 TI Creatinine clearance OR AB Creatinine clearance
S15 TI GFR OR AB GFR
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S13 (MH "Glomerular Filtration Rate")
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S10 TI Renal Disease OR AB Renal Disease
S9 TI Chronic Renal disease OR AB Chronic Renal disease
S8 TI Kidney failure OR AB Kidney failure
S7 TI Renal failure OR AB Renal failure
S6 TI Chronic renal failure OR AB Chronic renal failure
S5 TI Renal insufficiency OR AB Renal insufficiency
S4 TI Chronic renal insufficiency OR AB Chronic renal insufficiency
S3 TI Kidney disease OR AB Kidney disease
S2 TI Chronic kidney disease OR AB Chronic kidney disease
S1 (MH "Kidney Failure, Chronic+")

COCHRANE SEARCH
To include Cochrane reviews, protocols and trials

(Chronic kidney disease or Kidney disease or Chronic renal insufficiency or Renal insufficiency or Chronic renal failure or Renal failure or Kidney failure or Chronic Renal disease or Renal Disease Renal function Glomerular filtration rate GFR Creatinine clearance Renal disease progression or Kidney disease progression or Pre-dialysis Acidosis or Metabolic acidosis or Renal tubular acidosis or Acid-base imbalance or Chronic metabolic acidosis or Acid-base equilibrium):ti,ab,kw

AND (Bicarbonate or Bicarbonate supplementation or Oral bicarbonate Bicarbonate therap* or Bicarbonate buffer or Sodium bicarbonate or NaHCO3 or Sodium citrate or Na citrate or Baking soda or Acidosis treatment or Acidosis correction or Alkali therapy):ti,ab,kw

NOT (Acute kidney injury or Acute kidney disease or Acute kidney failure or Acute renal failure or Pregnancy or pregnan* or Neonat* or neonate or Intensive therapy unit or Intensive care unit or Critical care or Dialysis solutions or Dialysate or Renal dialysis or Renal replacement therapy or Dialysis or Hemodialysis or haemodialysis or Peritoneal dialysis or Hemofiltration or haemofiltration or Contrast or Renal stones or kidney stones or Oxalate or oxalosis or oxal* or hyperoxaluria or Cystinuria or Cystinosis or Cystin* or nephrocalcinosis or Calculus or calculi or calcul*):ti,ab,kw

WHO TRIALS PORTAL SEARCH

Terms entered:

Title	kidney or renal
Condition	kidney or renal
Intervention	bicarbonate or citrate or alkali

Synonyms searched by portal software

Title/condition
BENIGN RENAL NEOPLASM, BENIGN RENAL NEOPLASM NOS, BENIGN RENAL TUMOUR, NEPHR(O)-, REN(O)-, RENAL, RENAL NEOPLASM OF UNCERTAIN BEHAVIOUR, RENAL NEOPLASMS BENIGN, RENAL PROBLEM, RENAL TISSUE, RENO-, kidney - 71 KIDNEYS, DISEASE (OR DISORDER); URINARY TRACT, DISEASE OF URINARY TRACT, NOS, DISEASE OR SYNDROME OF URINARY TRACT, DISEASE, URINARY TRACT, DISEASE, UROLOGIC, DISEASE, UROLOGICAL, DISEASE;UROLOGICAL, DISEASES AND SYNDROMES OF THE URINARY TRACT, DISEASES AND SYNDROMES OF URINARY TRACT, DISEASES OF THE URINARY SYSTEM, DISEASES, URINARY TRACT, DISEASES, UROLOGIC, DISEASES, UROLOGICAL, DISORDER OF THE URINARY SYSTEM, DISORDER OF THE URINARY SYSTEM (DISORDER), DISORDER OF URINARY SYSTEM, UNSPECIFIED, DISORDER OF URINARY TRACT, DISORDER OF URINARY TRACT PROPER (DISORDER), DISORDER URINARY TRACT, DISORDERS OF URINARY TRACT, DISORDERS OF URINARY TRACT (DIAGNOSIS), KIDNEY, KIDNEY STRUCTURE, KIDNEY STRUCTURE (BODY STRUCTURE), KIDNEY, NOS, KIDNEY/URINARY DISEASE (NON-SPECIFIC), KIDNEYS, NEPHR(O)-, OBSTRUCTIVE UROPATHY, REN(O)-, RENO-, SECTION 7-1 DISEASES AND SYNDROMES OF THE URINARY TRACT, UNSPECIFIED DISORDER OF URETHRA AND URINARY TRACT, URINARY SYSTEM DISORDER, URINARY SYSTEM DISORDERS, URINARY TRACT DIS, URINARY TRACT DIS NOS, URINARY TRACT DISEASE, URINARY TRACT DISEASES, URINARY TRACT DISORDER, URINARY TRACT DISORDER NOS, URINARY TRACT DISORDER OF, URINARY TRACT DISORDERS, UROL DIS, UROLOGIC DISEASE, UROLOGIC DISEASES, UROLOGIC DISEASES [DISEASE/FINDING], UROLOGIC DISORDERS, UROLOGIC DISORDERS (DIAGNOSIS), renal –

Intervention
BICARB, CARBONATE, HYDROGEN, CARBONATES, HYDROGEN, HC0 3- MEASUREMENT, HC03- MEASUREMENT, HC0>3<- MEASUREMENT, HCO3, HYDROGEN CARBONATE, HYDROGEN CARBONATES, KETOACIDOSIS DIABETIC, bicarbonate - citrate - BASE, alkali

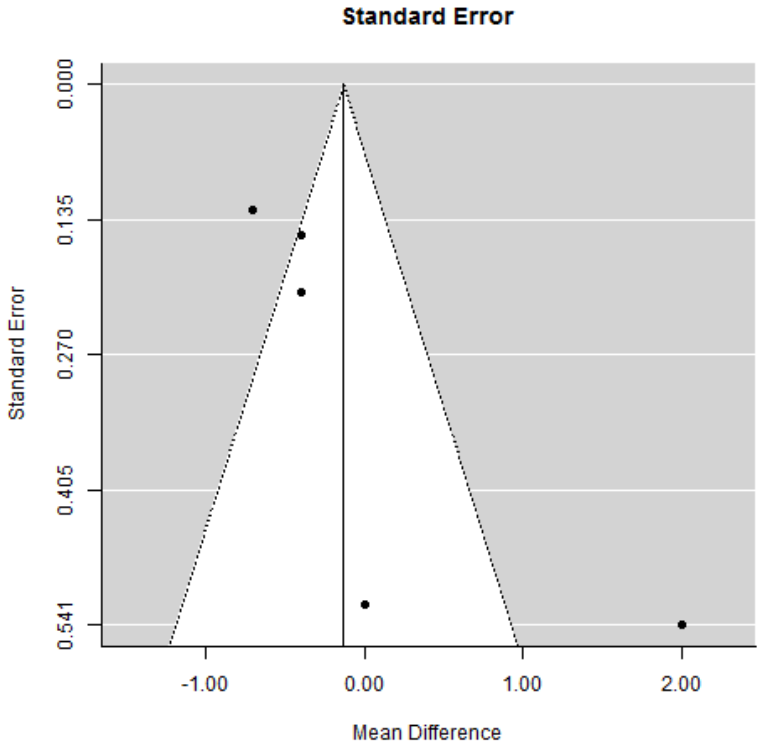
This software is not as sophisticated as many medical search engines, the list produced then had to be reviewed applying the 'nots' as per generic search strategy to identify appropriate trials.

The list then had to be filtered by those with published search results.

7.7 Appendix 7: Blood pressure change data with SE calculations

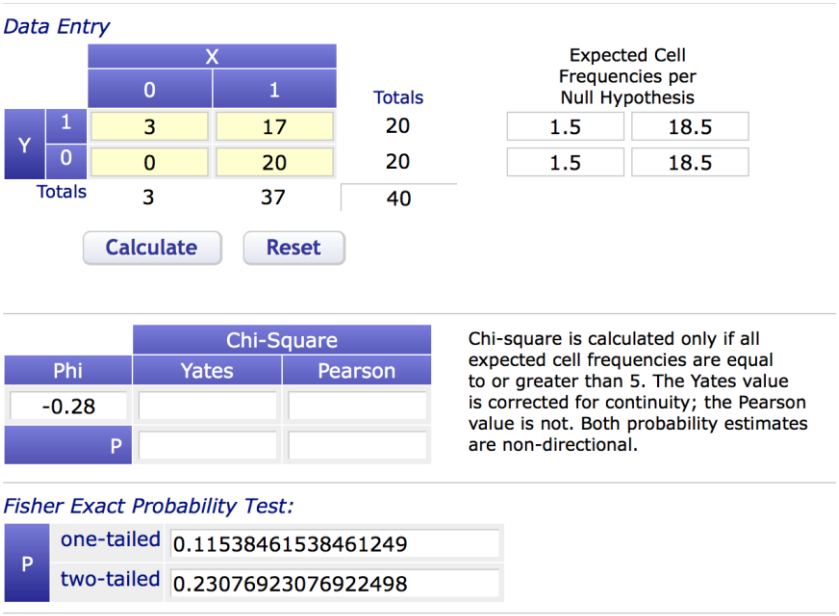
Study	Intervention group		Control group		Standard Mean Difference	Standard Error
	Mean BP change (mmHg)	SE	Mean BP change (mmHg)	SE		
Bellassi et al. (2016)	1	3.026	1	3.162	0	0.168
De Brito-Ashurst et al. (2009)	2.5	1.225	2.9	1.13	-0.043	0.176
Goraya et al. (2012) CKD 1	0.3	0.588	0.1	0.5004	-0.142	0.275
Goraya et al. (2012) CKD 2	-0.2	0.459	0.5	0.648	-0.195	0.224
Mathur et al. (2006)	4	1.803	2	1.61	0.256	0.318
Jeong, Kwon and Kim (2014)	1.28	0.641	-2.42	0.637	0.907	0.236
Phisitkul et al. (2010)	0.3	1.538	-0.2	1.366	0.062	0.260

7.8 Appendix 8: Assessment of Publication bias for RCT analysis of SBP change



7.9 Appendix 9: Example of using Fishers exact test online tool.

This was used to calculate change in antihypertensive and diuretic medication therapy



Data Entry

		X = 0	X = 1	Totals
Y	1	3	17	20
Y	0	0	20	20
Totals		3	37	40

Expected Cell Frequencies per Null Hypothesis

1	1.5	18.5
0	1.5	18.5

Calculate Reset

Chi-Square		
Phi	Yates	Pearson
-0.28		
P		

Chi-square is calculated only if all expected cell frequencies are equal to or greater than 5. The Yates value is corrected for continuity; the Pearson value is not. Both probability estimates are non-directional.

Fisher Exact Probability Test:

P	one-tailed	0.11538461538461249
	two-tailed	0.23076923076922498

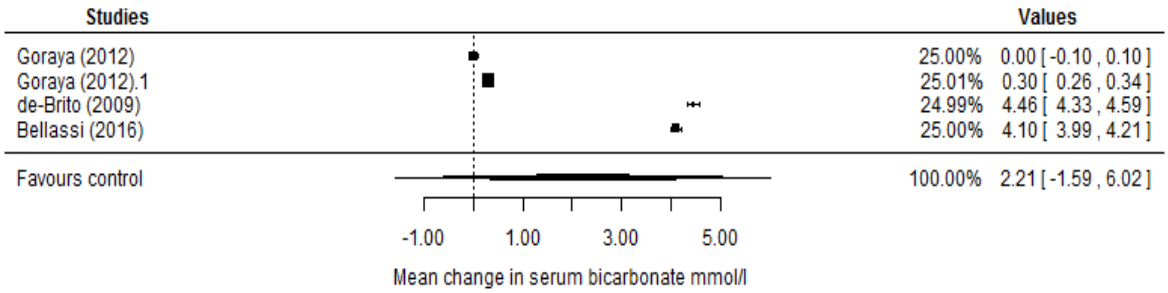
7.10 Appendix 10: Serum bicarbonate change data with SE calculations

Study	Intervention group		Control group		Standard Mean Difference	Standard Error
	Mean serum bicarbonate change (mmol/l)	SE	Mean serum bicarbonate change (mmol/l)	SE		
Bellassi et al. (2016)	0.48	0.327	0.7	0.321	1.494	0.188
De Brito-Ashurst et al. (2009)	5.29	0.386	0.83	0.383	1.465	0.199
Goraya et al. (2012) CKD 1	0	0.137	0	0.231	0	0.273
Goraya et al. (2012) CKD 2	0.1	0.095	-0.2	0.079	0.538	0.228
Mathur et al. (2006)	3.34	2.013	-1.46	1.338	0.616	0.324
Jeong, Kwon and Kim (2014) CKD 4	2.4	1.191	-1.4	1.12	0.720	0.327
Jeong, Kwon and Kim (2014) CKD 5	2.7	0.662	-3.1	1.056	1.442	0.359

Phisitkul et al. (2010)	3.34	2.013	-0.9	0.268	2.807	0.373

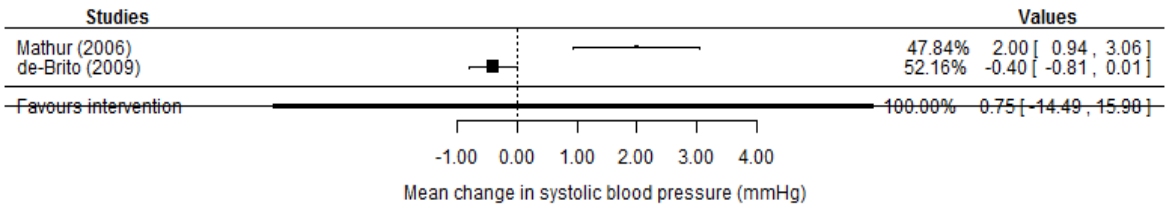
7.11 Appendix 11: A sensitivity analysis for the outcome change in mean SBP from beginning to end of sodium bicarbonate therapy for low and moderate risk of bias studies

n = 412. Heterogenicity: *Tau*^{2} = 4.90; *Chi*^{2} = 7535 *df* = 3 (*p* <0.0001); I^2 = 100%



7.12 Appendix 12: Subgroup analysis mean change in SBP in stages IV-V CKD (non-RRT) and by presence of clinical acidosis

n = 174. Heterogenicity: *Tau*^{2} = 2.71; *Chi*^{2} = 17.17, *df* = 1 (*p* <0.0001); I^2 = 94%


Studies
Values
Mathur (2006)
de-Brito (2009)
47.84% 2.00 [0.94 , 3.06]
52.16% -0.40 [-0.81 , 0.01]
Favours intervention
100.00% 0.75 [-14.49 , 15.98]
-1.00 0.00 1.00 2.00 3.00 4.00
Mean change in systolic blood pressure (mmHg)

7.13 Appendix 13: Explanation of GRADE decisions

a. Using the RoB 2.0 tool: 2 studies were low RoB, 1 moderate RoB and 1 high RoB. The high RoB study has many elements of bias, consequently, this led to the classification of serious RoB overall.

b. There is a widely differing estimate of effect due to the heterogeneous nature of the sample (I^2 = 84%, $p<0.0001$). Sources of heterogenicity include varying stages of CKD, presence or absence of acidosis at baseline, the dose of sodium bicarbonate intervention, duration of intervention and level of bias of studies included. Whilst the evidence has been downgraded to account for these causes of inconsistency, the sub-population analysis should be used to inform decisions.

c. The differences in study populations i.e. heterogeneity e.g. stage CKD, the cause of CKD (one study included diabetic patients only, one study included HTN nephropathy only and the final study was a mixed group of CKD diagnosis). This downgraded the level of evidence by one stage. In addition, the outcome measured was a secondary outcome which caused further downgrade by one level.

d. Statistically, there is no evidence of effect.

e. Using the RoB 2.0 tool 2 studies were low ROB and one moderate. The moderate risk study was due to not being able to extract certain data and due to a lack of published protocol. The inclusion criteria were very strict in an attempt to control confounders.

f. The results presented are a sensitivity analysis and sub-group analysis by the dose of sodium bicarbonate. The following heterogenicity is not considered: the stage of CKD and duration of the intervention. These sources of heterogenicity are recognized by downgrading the quality of the evidence. I^2 was 25%, CI overlapped and there was not a great variation in effect which meant that impression was only downgraded by one level.

g. The outcome of this systematic review is classified as an 'other' outcome for the trials being evaluated, consequently, power calculations do not apply to these outcomes and not all confounders will have been accounted for. In addition, there are population differences which include the stage of CKD, the presence of acidosis at baseline and different doses of sodium bicarbonate. The recommendation is to downgrade for both issues, however, the wider CKD population is the outcome of interest and high dose sodium bicarbonate has been excluded, so the doses used reflects clinical practice, thus this outcome has only been downgraded by one level to reflect the use of secondary outcomes which influences confounders.

h. It is recommended that where participant numbers are <400 that outcomes should be considered for down rating for imprecision by 2 levels. However, the study numbers were slightly above 400 and the statistics suggestive of an effect, therefore the grading of evidence was reduced by one level.

i. A meta-analysis was not possible for this outcome due to a lack of numerical data in the studies evaluated. There were significant sources of clinical and methodological heterogenicity in the studies included: the stage of CKD, the cause of CKD, dose/duration of intervention and presence or absence of acidosis at baseline, these support a downgrade in level of evidence.