Prompt: Help me understand the benefits or lack of benefits of salt restriction in hypertensive individuals from the point of view of all cause mortality and other hard end points.

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The evidence on salt restriction in hypertensive individuals is multifaceted. While almost every study agrees that reducing dietary sodium lowers blood pressure—a key surrogate for cardiovascular risk—the translation of this blood-pressure lowering into hard outcomes (like all-cause mortality and cardiovascular events) is less robust and sometimes mixed.

Below is a synthesis of the key evidence:

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1. Evidence from the Trials of Hypertension Prevention (TOHP)

Randomized Evidence:
In two landmark phases of the TOHP studies (TOHP I and II), hypertensive or pre-hypertensive adults were randomized to either a sodium-reduction intervention or a usual care (control) group. In a combined analysis of these trials, the active sodium reduction group experienced a 15% lower risk of all-cause mortality compared with controls (hazard ratio [HR] 0.85 with a 95% confidence interval [CI] of 0.66 to 1.09; p=0.19) [jacc.org].

> **Interpretation:** Although the direction of effect favored sodium reduction, the difference did not reach statistical significance. This could be due to sample size limitations, long follow-up with potential attenuation of the intervention effect, or other unmeasured factors.

Observational Evidence within TOHP:
When sodium intake was assessed using multiple 24-hour urine collections (a “gold standard” method), an observational analysis found a direct linear relationship between sodium intake and mortality. Specifically, for every additional 1,000 mg/day of sodium excreted, the risk of death increased by about 12% (HR 1.12; 95% CI 1.00–1.26; p=0.05) [jacc.org].

> **Interpretation:** This analysis did not reveal any J- or U-shaped pattern—suggesting that, within the range studied, lower sodium intake is associated with lower mortality risk.

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2. Meta-Analytic Findings

A meta-analysis by Graudal and colleagues (2014) pooled data from multiple cohort studies and two follow-up studies of randomized controlled trials. Their results showed that:

- **Low Sodium Intake:** Compared with “usual” sodium intake, very low sodium intakes were associated with an increased risk of mortality (with an HR of approximately 0.91 when “usual” intake was compared to low intake; 95% CI 0.82–0.99).
- **High Sodium Intake:** Conversely, high sodium intake (above the “usual” range) was associated with an increased risk (HR ~1.16; 95% CI 1.03–1.30) [pubmed.ncbi.nlm.nih.gov].

However, when analyses were restricted to population-representative samples and adjusted for multiple confounders, the risk difference became less pronounced (e.g. HR 0.86 for usual vs. low sodium and HR 1.04 for high vs. usual sodium, with confidence intervals that included 1).

> **Interpretation:** These mixed findings have led some researchers to propose a U-shaped curve. Yet, the studies that use more accurate sodium measurements (like repeated 24-hour urine collections) tend to support a more linear relationship—i.e. “lower is better” within the studied range.

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3. Salt Substitution Trials

Recent large-scale trials using potassium-enriched salt substitutes (which reduce the overall sodium content) have also contributed important insights. For example, a 2021 randomized controlled trial in China of approximately 21,000 older individuals showed that replacing regular salt (100% sodium chloride) with a substitute composed of 75% sodium chloride and 25% potassium chloride reduced:

- Stroke risk by 14%,
- Major cardiovascular events by 13%, and
- All-cause mortality by 12%
  (with similar error margins reported in the study’s confidence intervals) [en.wikipedia.org].

> **Interpretation:** Although this study was conducted in a high-salt-intake population (and not exclusively among individuals already defined as hypertensive), it provides additional support that reducing sodium—and in parallel increasing potassium—can improve hard cardiovascular outcomes.

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4. Synthesis and Final Recommendation

Benefits:

- **Blood Pressure Reduction:** The most consistent and robust finding is that salt restriction lowers blood pressure, a key risk factor for cardiovascular events. This effect

has been demonstrated in numerous trials (including the DASH-Sodium trial) and is especially pronounced in hypertensive individuals.
- **Possible Mortality Benefit:** Observational data (e.g., from TOHP) and some meta-analyses suggest that, over the long term, a reduction in sodium intake is associated with modest reductions in all-cause mortality (e.g., a roughly 12% increase in risk per additional 1,000 mg/day of sodium).
- **Additional Cardiovascular Protection:** Salt substitution studies add to the evidence by demonstrating reductions in stroke and cardiovascular events when sodium is reduced and potassium is increased.

Lack of Clear Benefit (or Uncertainty):

- **Randomized Trial Limitations:** In the TOHP randomized comparisons, the 15% lower mortality risk (HR 0.85; 95% CI 0.66–1.09) did not reach statistical significance.
- **Conflicting Meta-Analytic Data:** Some meta-analyses have reported a U-shaped association, suggesting that both very low and very high sodium intakes might be harmful. However, this may be influenced by measurement error or confounding in studies that do not use objective sodium assessment methods.

Recommendation:
For hypertensive patients, the preponderance of evidence supports moderate salt restriction—aiming for an intake of around 2,300 mg per day (and even 1,500 mg/day in higher-risk groups such as older adults or those with additional cardiovascular risk factors). This strategy is justified by the clear blood pressure–lowering benefits and the likelihood that, over the long term, modest reductions in sodium intake contribute to lower cardiovascular risk. In clinical practice, it remains reasonable to advise hypertensive individuals to reduce their consumption of processed foods (the main source of dietary sodium) and to consider using salt substitutes when appropriate.

In Summary

- **RCT data (e.g., TOHP):** Sodium reduction associated with a non-significant 15% lower mortality (HR 0.85; 95% CI: 0.66–1.09).
- **Observational data (TOHP):** A linear increase in mortality risk—about 12% increased risk per extra 1,000 mg/day sodium (HR 1.12; 95% CI: 1.00–1.26).
- **Meta-analysis (Graudal et al.):** Mixed findings with some evidence of a U-shaped curve, though better-quality studies tend to support a linear benefit.
- **Salt substitution trials:** Show benefits in reducing stroke and cardiovascular events, with reductions in all-cause mortality (~12% lower risk).

Given these findings, even though the mortality benefit seen in randomized trials is modest and sometimes not statistically significant, the consistent blood pressure reduction—and by

extension, the likely reduction in cardiovascular events—provides a strong rationale for recommending moderate salt restriction in hypertensive individuals.

Final Clinical Recommendation:
Hypertensive individuals should be counseled to limit their sodium intake (ideally to 2,300 mg/day or even 1,500 mg/day in high-risk cases) as part of an overall strategy to lower blood pressure and reduce cardiovascular risk. While the direct evidence for mortality reduction is modest, the cumulative data—especially those using rigorous measurement techniques—support the notion that lower sodium intake is beneficial over the long term.

References:

- TOHP RCT and observational data: jacc.org
- Meta-analysis by Graudal et al.: pubmed.ncbi.nlm.nih.gov
- Salt substitution trial results: en.wikipedia.org

This balanced approach aligns with current guidelines and reflects the best available evidence linking salt restriction to improved outcomes in hypertensive populations.
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Based on the search results, there is ongoing debate and some conflicting evidence regarding the benefits of salt restriction, particularly concerning all-cause mortality in hypertensive individuals. Here's a breakdown of the findings from the search results:

Studies Suggesting Potential Benefits of Salt Restriction:

- **Trials of Hypertension Prevention (TOHP) Study (2017):** This study examined the relationship between sodium intake and all-cause mortality over 20 years in participants of the Trials of Hypertension Prevention. It used carefully measured sodium intake from urinary sodium excretion.
    - **Key Result:** A direct linear association was found between average sodium intake and mortality. For every 1000 mg/24hr increase in sodium intake, there was a 12% increased risk of mortality (Hazard Ratio (HR)=1.12, 95% CI = 1.00-1.26, p=0.05). There was no evidence of a J-shaped curve.
    - **Conclusion:** This study suggests a direct relationship between higher sodium intake and increased total mortality, even at lower levels of sodium intake, supporting the benefit of reduced sodium intake for long-term mortality.
- **Cochrane Systematic Review and Meta-analysis (2013):** This meta-analysis reviewed randomized controlled trials (RCTs) of longer-term modest salt reduction on blood

pressure, hormones, and lipids.

    - **Key Result:** Modest salt reduction led to significant falls in blood pressure in both hypertensive and normotensive individuals.
    - **Conclusion:** The study supports the recommendation for modest salt reduction to lower blood pressure, which is a major risk factor for cardiovascular disease. It also notes a dose-response relationship, suggesting greater blood pressure reduction with further salt reduction.

Studies Suggesting a U-shaped or No Clear Benefit for Mortality:

- **Meta-analysis by Graudal et al. (2014):** This meta-analysis of cohort studies and RCTs investigated the association between different levels of sodium intake and all-cause mortality (ACM) and cardiovascular disease events (CVDEs).

    - **Key Result:** The analysis suggested a U-shaped association between sodium intake and health outcomes. Both low sodium intake (<115 mmol) and high sodium intake (>215 mmol) were associated with increased mortality compared to usual sodium intake. Usual sodium intake was categorized into "low usual" (115-165 mmol) and "high usual" (166-215 mmol). Compared to low sodium intake, usual sodium intake was associated with decreased risk of ACM (HR = 0.91, 95% CI = 0.82-0.99) and CVDEs (HR = 0.90, 95% CI = 0.82-0.99). High sodium intake, compared to usual sodium intake, was associated with increased risk of ACM (HR = 1.16, 95% CI = 1.03-1.30) and CVDEs (HR = 1.12, 95% CI = 1.02-1.24).
    - **Conclusion:** This meta-analysis suggests that both very low and very high sodium intakes may be detrimental, and that there might be a "sweet spot" of usual sodium intake that is associated with the lowest mortality. However, this study has been criticized for methodological flaws (as mentioned in another search result [1.2]).
- **Meta-analysis of RCTs (Cochrane Review, 2011, updated in 2014):** This meta-analysis of RCTs examined the effect of reduced dietary salt on cardiovascular disease (CVD) events.

    - **Key Result:** While salt reduction was associated with small reductions in blood pressure, there was insufficient evidence to demonstrate clinically important effects of reduced dietary salt on mortality or CVD morbidity in hypertensive individuals (Longest follow-up RR for all-cause mortality in hypertensives 0.96, 95% CI: 0.83–1.11, 565 deaths). Salt restriction even increased the risk of all-cause mortality in those with heart failure (end of trial RR 2.59, 1.04–6.44, 21 deaths).
    - **Conclusion:** This meta-analysis indicates that despite blood pressure reduction, the evidence for salt restriction improving mortality or CVD events in hypertensive individuals is not strong. It also raises concerns about potential harm in specific populations like heart failure patients.

Criticism of U-shaped Curve Meta-analysis:

- A letter to the editor (2014) critiqued the meta-analysis by Graudal et al. [1.4] for methodological flaws.
    - **Key Points of Criticism:** The critique argues that the U-shaped association conclusion is invalid due to methodological flaws in the included studies. It points out that the meta-analysis included studies with abrupt and severe salt restriction over short periods, which is not relevant to public health recommendations for modest, longer-term salt reduction. The critique also highlights that other meta-analyses of randomized trials show only a small increase in renin activity and no significant changes in sympathetic nervous activity or lipids with modest salt reduction.
    - **Counter-argument:** The letter emphasizes that the totality of evidence, including epidemiological studies, animal studies, randomized trials, and outcome studies, supports the substantial benefits of salt reduction for population health.

Synthesis and Recommendation:

The evidence regarding salt restriction and mortality in hypertensive individuals is complex and not entirely conclusive.

- **Blood Pressure Reduction:** There is consistent evidence that modest salt reduction lowers blood pressure in hypertensive individuals. This is a well-established benefit and is likely to translate to reduced cardiovascular risk in the long term.
- **All-Cause Mortality:** The relationship between salt restriction and all-cause mortality is less clear. Some studies suggest a direct benefit of lower sodium intake on mortality, while others suggest a U-shaped curve or no significant benefit. The meta-analysis suggesting a U-shaped curve has been criticized for methodological issues. The most recent study from the TOHP data suggests a linear relationship with increased mortality at higher sodium intakes.
- **Hard Endpoints:** Evidence for the impact of salt restriction on hard endpoints like cardiovascular events and mortality from RCTs is still limited, with some meta-analyses showing insufficient power to detect clinically important effects.

Recommendation:

For hypertensive individuals, **modest salt restriction is generally recommended** as part of a healthy lifestyle approach to manage blood pressure and reduce cardiovascular risk. This recommendation is primarily based on the consistent evidence that salt reduction lowers blood pressure.

However, **very low salt intake should be approached with caution.** Some evidence suggests a potential U-shaped curve where very low sodium intake might not be beneficial or could even be harmful, although this is debated. It's important to note that the definition of "very low" salt

intake varies across studies, and the methodological quality of some studies suggesting harm at very low levels has been questioned.

Practical Advice:

- **Focus on Modest Reduction:** Aim for a modest reduction in salt intake, aligning with public health recommendations (e.g., reducing intake from 9-12g/day to 5-6g/day of salt, or aiming for less than 2300mg of sodium per day).
- **Dietary Changes:** Emphasize dietary changes such as reducing processed foods, limiting added salt during cooking and at the table, and increasing intake of fruits, vegetables, and whole grains (like the DASH diet).
- **Individualized Approach:** The optimal level of salt intake might vary for individuals. People with specific conditions like heart failure or kidney disease should consult their doctor for personalized recommendations.
- **Further Research:** More high-quality, long-term randomized controlled trials are needed to definitively clarify the relationship between salt restriction and hard endpoints like all-cause mortality and cardiovascular events, especially at different levels of sodium intake and in specific populations.

It's important to have an informed discussion with a healthcare provider to determine the most appropriate dietary sodium intake level based on individual health status and risk factors.

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Impact of Salt Restriction on All-Cause Mortality in Hypertensive Individuals

Introduction

Hypertension, or high blood pressure, is a major risk factor for cardiovascular disease (CVD) and all-cause mortality. Dietary salt intake is a modifiable risk factor for hypertension [1], and reducing salt intake is a common recommendation for managing blood pressure. However, the impact of salt restriction on all-cause mortality and other hard endpoints in hypertensive individuals remains a subject of debate. This report aims to review the evidence from meta-analyses, systematic reviews, and randomized controlled trials (RCTs) to provide a comprehensive understanding of the benefits or lack of benefits of salt restriction in this population. It is worth noting that salt reduction is considered a cost-effective measure to reduce population morbidity and mortality [1].

Meta-Analyses and Systematic Reviews

Several meta-analyses and systematic reviews have investigated the relationship between salt restriction and all-cause mortality in hypertensive individuals.

- **Aburto et al.**
  A meta-analysis by Aburto et al[1]. examined the effect of decreased sodium intake on blood pressure, related cardiovascular diseases, and potential adverse effects. The study included

14 cohort studies and 5 RCTs reporting all-cause mortality, cardiovascular disease, stroke, or coronary heart disease, as well as 37 RCTs measuring blood pressure, renal function, blood lipids, and catecholamine levels in adults. The meta-analysis found that a reduction in sodium intake significantly reduced resting systolic blood pressure by 3.39 mm Hg (95% confidence interval 2.46 to 4.31) and resting diastolic blood pressure by 1.54 mm Hg (0.98 to 2.11) in adults. However, there were insufficient RCTs to assess the effects of reduced sodium intake on mortality and morbidity.

- **He et al.**
  Another meta-analysis by He et al[2]. examined the relationship of well-characterized measures of sodium intake, estimated from urinary sodium excretion, with long-term mortality. The study included two trials from the Trials of Hypertension Prevention (TOHP) that implemented sodium reduction interventions. These interventions included lifestyle interventions and nutritional supplement interventions. Post-trial deaths were ascertained over a median of 24 years. Among 744 Phase I and 2382 Phase II participants randomized to sodium reduction or control, 251 deaths occurred, with a...source (95% CI = 1.01-1.27, p=0.04).
- **Graudal et al.**
  A meta-analysis by Graudal et al[3]. investigated the incidence of all-cause mortality (ACM) and cardiovascular disease events (CVDEs) in populations exposed to dietary intakes of low sodium (<115 mmol), usual sodium (low usual sodium: 115-165 mmol; high usual sodium: 166-215 mmol), and high sodium (>215 mmol). Data from 23 cohort studies and 2 follow-up studies of RCTs (n = 274,683) showed that the risks of ACM and CVDEs were...source This meta-analysis suggests a U-shaped association between sodium intake and health outcomes, with both low and high sodium intakes being associated with increased mortality.
- **Taylor et al.**
  Another meta-analysis by Taylor et al[4]. investigated RCTs with follow-up of at least 6 months that compared dietary salt reduction (restricted salt dietary intervention or advice to reduce salt intake) to control/no intervention in adults and reported mortality or CVD morbidity data. Seven studies were identified: three in normotensives, two in hypertensives, one in a mixed population of normo- and hypertensives, and one in heart failure. Salt reduction was associated with reductions in urinary salt excretion of between 27 and 39 mmol/24 h and reductions in systolic BP between 1 and 4 mm Hg. Relative risks (RRs) for all-cause mortality in normotensives (longest follow-up—RR: 0.90, 95% confidence interval (CI): 0.58–1.40, 79 deaths) and hypertensives (longest follow-up RR 0.96, 0.83–1.11, 565 deaths) showed no strong evidence of any effect of salt reduction on CVD morbidity in people with normal BP. Salt restriction increased the risk of all-cause mortality in those with heart failure (end of trial RR 2.59, 1.04–6.44, 21 deaths).

Randomized Controlled Trials

Several RCTs have investigated the impact of salt restriction on all-cause mortality in hypertensive individuals.

- **TOHP Trials**
  The TOHP trials [2] included 2,182 men and women aged 30-54 years with pre-hypertensive blood pressure. Phase I lasted 18 months, and Phase II lasted 36 months. Among 744 Phase I and 2382 Phase II participants randomized to sodium reduction or control, 251 deaths occurred, with a nonsignificant 15% lower risk in the active intervention (hazard ratio (HR)=0.85, 95% CI=0.66-1.09, p=0.19).
- **Wu et al.**
  One such trial by Wu et al[5]. reported an exploratory follow-up of mortality outcomes from a previous randomized controlled trial to assess the long-term effect of low-sodium salt on total

and cardiovascular disease (CVD) mortality. Four hundred and forty participants completed the intervention trial, of which 428 participants had death outcome data recorded after 10 years of follow-up: 209 in a salt substitute group and 219 in a normal salt group. Fifty participants died during...source After adjusting for age and alcohol drinking status, there were significant reductions for stroke mortality among all participants (HR = 0.26, 95% CI: 0.08–0.84) and for CVD mortality (HR = 0.38, 95% CI: 0.16–0.92) and stroke mortality (HR = 0.25, 95% CI: 0.08–0.82) among hypertensive participants.

Comparison of Findings

The findings of different studies on the relationship between salt restriction and all-cause mortality in hypertensive individuals are not entirely consistent. Some studies, such as the TOHP trials [2], suggest a direct linear association between sodium intake and mortality, while others, such as Graudal et al[3]., report a U-shaped or J-shaped association. These discrepancies may be due to differences in study design, population characteristics, and methods for assessing sodium intake. For example, the TOHP trials focused on pre-hypertensive individuals, while Graudal et al. included a broader range of sodium intakes in their meta-analysis.

Strengths and Limitations of Studies

Meta-analyses and systematic reviews have the advantage of pooling data from multiple studies, increasing statistical power and providing a more comprehensive overview of the evidence. However, they are subject to limitations such as publication bias and heterogeneity between studies. For example, the meta-analysis by Taylor et al[4]. included studies with varying durations of follow-up and different types of interventions, which could have influenced the results.

RCTs are considered the gold standard for evaluating the efficacy of interventions, but they can be expensive and time-consuming to conduct. Additionally, RCTs may not always be generalizable to the broader population due to strict inclusion and exclusion criteria. For instance, the RCT by Wu et al[5]. focused on a specific type of salt substitute and may not be applicable to all forms of salt restriction.

Recommendation

Based on the totality of the evidence, it appears that salt restriction may have a modest beneficial effect on all-cause mortality in hypertensive individuals. However, the evidence is not conclusive, and further research is needed to confirm these findings. In the meantime, it is reasonable to recommend that hypertensive individuals follow current guidelines for sodium intake, which typically recommend limiting sodium to less than 2,300 mg per day.

It is important to note that excessive salt restriction may have potential adverse effects [6]. Additionally, the relationship between sodium and potassium intake may play a role in mortality [2]. Further research is needed to fully understand these complex interactions.

Salt substitutes might be a viable alternative for reducing CVD mortality, especially stroke, in hypertensive patients [5]. Individuals who struggle with reducing salt intake may consider using salt substitutes as a potential strategy.

Importantly, reducing sodium intake has no significant adverse effect on blood lipids,

catecholamine levels, or renal function [1]. This finding could alleviate concerns about potential negative consequences of salt restriction.

Synthesis of Findings

The evidence regarding the impact of salt restriction on all-cause mortality in hypertensive individuals is mixed. While some studies suggest a benefit, others show no significant effect or even a U-shaped association. This highlights the complexity of the relationship between sodium intake and health outcomes.

Works cited

1. Effect of lower sodium intake on health: systematic review and meta-analyses - PMC, accessed February 9, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC4816261/
2. Sodium Intake and All-Cause Mortality over 20 Years in the Trials of ..., accessed February 9, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC5098805/
3. Compared with usual sodium intake, low- and excessive-sodium ..., accessed February 9, 2025, https://pubmed.ncbi.nlm.nih.gov/24651634/
4. Reduced Dietary Salt for the Prevention of Cardiovascular Disease: A Meta-Analysis of Randomized Controlled Trials (Cochrane Review) | American Journal of Hypertension | Oxford Academic, accessed February 9, 2025, https://academic.oup.com/ajh/article/24/8/843/226001
5. Long-Term Effect of Salt Substitute on All-Cause and Cardiovascular ..., accessed February 9, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC8165103/
6. Salt and hypertension: current views - European Society of Cardiology, accessed February 9, 2025, https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-22/salt-and-hypertension-current-views

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Here's a breakdown of the benefits and lack of benefits of salt restriction in hypertensive individuals, focusing on all-cause mortality (ACM) and other hard endpoints (like cardiovascular events), drawing from the provided information and incorporating specific study citations:

Key Concepts Upfront

- **Blood Pressure (BP) as a Surrogate:** Lowering BP is *generally* accepted as beneficial because high BP is a major risk factor for cardiovascular disease. Salt restriction reliably lowers BP. However, the core of the debate is whether this BP reduction *reliably* translates into improved *hard outcomes*.
- **Hard Endpoints vs. Surrogate Markers:** Blood pressure is a *surrogate marker* for cardiovascular risk. Hard endpoints are clinically meaningful outcomes like death, stroke, heart attack, or heart failure events. The ideal study demonstrates benefits on hard endpoints.
- **Sodium Measurement Matters:** Accurate sodium measurement is *crucial*. Many older studies used dietary questionnaires (unreliable). The "gold standard" is multiple 24-hour urine collections, which are more objective and reflect actual intake.

- **Modest vs. Severe Restriction:** Public health recommendations typically advocate for *modest* salt reduction (e.g., from ~9-12g/day to ~5-6g/day of salt, or around 2300mg sodium/day). Some studies showing potential harm involved *severe* restriction, which is not generally recommended.
- **Usual Sodium Intake:** It is the range of dietary sodium found in most populations, and it is difficult to define. Gradual separates usual intake into "low usual" (115-165 mmol, or 2645-3795 mg) and "high usual" (166-215 mmol, or 3818-4945 mg)

1. Benefits of Salt Restriction

- **Consistent Blood Pressure Reduction:** This is the strongest and most consistent finding across numerous studies.
    - **Aburto et al. (Systematic Review and Meta-analysis):** Showed that reduced sodium intake significantly lowered systolic BP by 3.39 mmHg (95% CI: 2.46-4.31) and diastolic BP by 1.54 mmHg (95% CI: 0.98-2.11) in adults. This supports the use of salt reduction to lower BP.
    - **DASH-Sodium Trial (Not explicitly cited in your text, but a landmark study):** Demonstrated that the combination of a Dietary Approaches to Stop Hypertension (DASH) diet *and* sodium restriction had a powerful BP-lowering effect, especially in hypertensive individuals.
    - **He et al. (2013, meta-analysis)**. Modest salt reduction led to significant falls in blood pressure in both hypertensive and normotensive individuals
- **Potential Mortality Benefit (Observational Evidence & Some RCT Data):**
    - **TOHP (Trials of Hypertension Prevention) - Observational Analysis:** This is a key study using *multiple 24-hour urine collections*. It found a *linear* relationship: For every 1000mg/day increase in sodium excretion, the risk of death increased by about 12% (HR 1.12; 95% CI: 1.00-1.26; p=0.05). *Crucially, this analysis did NOT find a J- or U-shaped curve.*
    - **TOHP (Trials of Hypertension Prevention) - RCT Component:** While the *randomized* comparison showed a 15% lower risk of all-cause mortality with sodium reduction (HR 0.85; 95% CI: 0.66-1.09), this did *not* reach statistical significance (p=0.19). This is often cited as a limitation, but the trend is in favor of benefit.
- **Benefits of Salt Substitution (Important Evidence):**
    - **Salt Substitute and Stroke Prevention Study (SSaSS) in China (2021) (referenced via Wikipedia link):** This large RCT (n=21,000) showed that replacing regular salt with a salt substitute (75% sodium chloride, 25% potassium chloride) significantly reduced:
        - Stroke risk by 14%
        - Major cardiovascular events by 13%
        - All-cause mortality by 12%
          This study, while not *exclusively* in hypertensives, provides strong evidence for the benefit of reducing sodium (and increasing potassium).
- **Wu et al. (2021)** Long term salt substitute use showed:
    - All participants reduction for stroke mortality HR = 0.26, 95% CI: 0.08–0.84

    - Hypertensive participants reduction for CVD mortality HR= 0.38, 95% CI: 0.16–0.92
    - Hypertensive participants reduction for stroke mortality (HR = 0.25, 95% CI: 0.08–0.82)

2. Lack of Clear Benefit / Uncertainty / Potential Harm

- **Conflicting Meta-Analytic Data (The U-Shaped Curve Debate):**
    - **Graudal et al. (2014) Meta-analysis:** This is the *primary* study suggesting a U-shaped curve. They found that *both* very low and very high sodium intakes were associated with increased mortality compared to "usual" intake.
        - Low Sodium (<115 mmol or <2645mg) vs. Usual: Increased mortality (HR ~0.91; 95% CI: 0.82-0.99).
        - High Sodium (>215 mmol or >4945mg) vs. Usual: Increased mortality (HR ~1.16; 95% CI: 1.03-1.30).
    - **Criticism of Graudal et al.:** This study has been heavily criticized for methodological flaws, including:
        - Including studies with *abrupt and severe* salt restriction (not relevant to public health recommendations).
        - Using less reliable methods of sodium assessment in many included studies.
        - Potential for confounding factors.
- **Lack of Significant Mortality Benefit in Some RCTs:**
    - **TOHP - RCT Component (as mentioned above):** The 15% reduction in mortality, while suggestive, was not statistically significant.
    - **Taylor et al. (2011, updated 2014) Cochrane Review:** This meta-analysis of RCTs found *insufficient evidence* to demonstrate clinically important effects of reduced dietary salt on mortality or CVD morbidity in hypertensive individuals, despite small reductions in BP. They even found an *increased* risk of all-cause mortality in heart failure patients (RR 2.59; 95% CI: 1.04-6.44). *This highlights the need for caution in specific subgroups.*

3. Synthesis and Recommendations

- **Strong Evidence for BP Lowering:** Salt restriction consistently lowers blood pressure, especially in hypertensive individuals. This is a well-established benefit.
- **Mortality Benefit - Less Clear, but Likely Beneficial with Moderate Restriction:** The evidence for a direct mortality benefit from salt restriction in hypertensives is less robust than the BP-lowering effect. However, the *totality* of the evidence, particularly from studies using accurate sodium measurements (like the TOHP observational data) and the salt substitution trials, suggests that *moderate* salt restriction is likely beneficial for reducing cardiovascular risk and potentially all-cause mortality.
- **Avoid Very Low Sodium Intake:** The U-shaped curve controversy highlights the potential for harm with *very low* sodium intake. While the evidence for this is debated, it's prudent to avoid overly restrictive diets without medical supervision.

- **Current Guidelines:** Most guidelines recommend limiting sodium intake to around 2300 mg/day (or even 1500 mg/day for higher-risk individuals, like older adults or those with other cardiovascular risk factors). This aligns with the evidence for BP reduction and the likely long-term benefits on cardiovascular risk.
- **Practical Advice:**
    - Focus on reducing processed foods (the major source of sodium).
    - Limit added salt during cooking and at the table.
    - Consider salt substitutes (containing potassium) when appropriate, especially in populations with high salt intake.
    - Individualize recommendations: People with heart failure, kidney disease, or other conditions should consult their doctor.
- **Need for Further Research:** More high-quality, long-term RCTs are needed to definitively clarify the relationship between different levels of sodium intake and hard endpoints, particularly in diverse populations and subgroups.

In conclusion, while the direct evidence for a mortality benefit from salt restriction in hypertensive individuals is not as strong as the evidence for blood pressure reduction, the overall body of evidence supports moderate salt restriction as part of a comprehensive strategy to manage hypertension and reduce cardiovascular risk. The strongest evidence against severe salt restriction comes from studies with flawed methodology, and more recent studies utilizing salt substitutes demonstrate a clear mortality benefit.