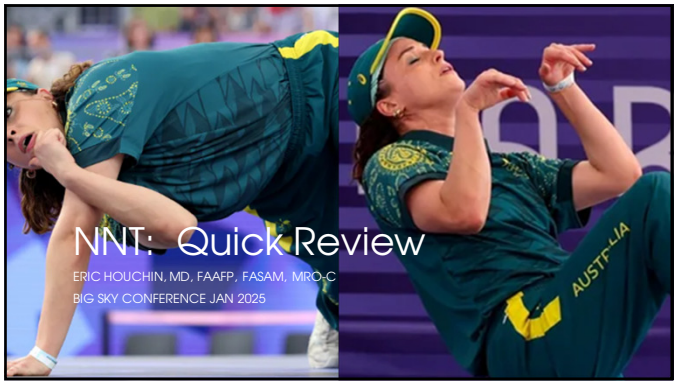


1

Disclosures

- I am paid presenter for Alkermes: Vivitrol

2

"Most middle- and high-income countries globally have become largely inured to the endemic premature mortalities related to more commonly used substances such as alcohol and tobacco. While these account for a much larger number of deaths and economic and social harms than opioids each year, the devastation wreaked by these substances, their casualties, and the associated blood and tears are all relatively willingly absorbed into the social fabric."

John F. Kelly and Sarah E. Wakeman, 2019

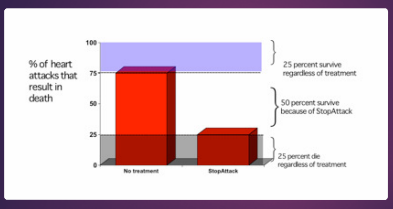
Perspective

3

NNT: Explained: NNT= 100/ARR

- Basic idea:
  - There is a way of understanding how much modern medicine has to offer individual patients. It is a simple statistical concept called the "Number-Needed-to-Treat", or for short the 'NNT'. The NNT offers a measurement of the **impact** of a medicine or therapy by estimating the number of patients that need to be treated in order to have an impact on **one** person. The concept is statistical, but intuitive, for we know that not everyone is helped by a medicine or intervention — some benefit, some are harmed, and some are unaffected. The NNT tells us how many of each.

4



Fictional treatment

5

Possibilities: Helped, Harmed or Unaffected

- The tricky part is that for most treatments we don't know which group a person undergoing treatment will end up in, the group that was **helped**, the group that was **harmed**, or the group that was **unaffected**.
- Here's how that estimation works: If we calculate how many people we need to treat with StopAttack in order for one person to be positively affected, the number is 2. This is because StopAttack positively affected (saved the lives of) 50 percent, but did not help the 25 percent who would have died, nor the 25 percent who would have survived either way. This means that "1 in 2 heart attack victims are affected by StopAttack", or that "there's a 50 percent chance that treatment with StopAttack will save a heart attack victim's life." Therefore the number of people we need to treat with StopAttack in order for us to know it affected one person is, on average, two people. In other words the NNT = 2.

6

NNT: How calculate: 100/ARR

- In controlled trials of medical interventions (drugs, surgeries, etc.) there is always an **'outcome measure',** which is a researcher's way of saying that there is always something that they are measuring to determine whether or not the intervention helped. In the above case of StopAttack, the outcome measure was **mortality** (i.e. death rate). StopAttack was aimed at reducing deaths from heart attacks, and in our fictional example it worked, reducing deaths by 50%, a tremendous effect. This translated into an NNT of 2, and the formal calculation for this is: 100/50 = 2. This comes from the following formula for calculating the NNT: 100/ARR = NNT. So what's the 'ARR'? It's the 'absolute risk reduction', which means the reduction in the risk of the outcome (mortality in this case). The reduction in the risk of mortality using StopAttack was 50%.

7

StopAttack2

- If we now imagine a scenario in which 10% of people who have untreated heart attacks die and 90% survive (this is pretty close to reality), then we'll find a very different effect for a treatment we'll call StopAttack2. In fact, StopAttack2 can't be nearly as effective as StopAttack, since above StopAttack reduced death from 75% to 25% (a total of a 50% reduction) and in this scenario only 10%, or 1 out of 10 people, die without the treatment. This means that the maximum amount that StopAttack2 could possibly reduce deaths is only 10%. In other words when only 1 out of 10 people die of a disease the best you could possibly do is to save the 1 out of 10 people who were going to die. And if we were able to find a miracle treatment that could do that (take the 10% mortality rate down to 0%) this would translate into an NNT of 10. Why? Because 100/ARR = NNT, and in this case the reduction in risk is 10% (we went from 10% mortality to 0%, an absolute risk reduction, or ARR, of 10%).

8

StopAttack3

- But let's say that we had a third treatment, StopAttack3, which reduced death by 2%, from 10% to 8%. While this is a small number, it also represents a potentially important reduction in deaths when it is used on many people. This is an ARR of 2%, which means 2 out of every 100 people are saved by using StopAttack3, for an NNT of 50. We would, on average, have to treat 50 patients for 1 patient to have been saved from death. But it does mean that, like above, there is a significant group of patients that will be treated with StopAttack3 that will be unaffected in either direction — they will either die or survive regardless of the drug. In this case 90% will survive regardless of whether they receive StopAttack3 and 8% will die regardless of their treatment. This means 98% of the patients, in total, who are subjected to it will be unaffected by StopAttack3.
- But there's another way to describe what's happening here. We could say that a reduction of 2% from an expected death rate of 10% is a "20% reduction in death", and we would be correct, at least semantically. Here's why: if we only concentrate on the 10% of people who die of their heart attacks we can see in the graph below that a 2% reduction is actually a 20% relative reduction in risk, RRR. In other words relative to the 10% who would normally die, if only 8% die then this is a 20% proportional reduction in death rate.

9

Bisphosphonates

- **Source**
- Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Welch V, Coyle D, Tugwell P. Etidronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD003376.

  Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Welch V, Coyle D, Tugwell P. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD001155.

  Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Welch V, Coyle D, Tugwell P. Risedronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD004523.
- **Efficacy Endpoints**
- Fracture prevention
- **Harm Endpoints**
- Atypical fractures, jaw osteonecrosis, GI and musculoskeletal side effects (harms are uncommon but do clearly occur and are not well-studied)

10

Bisphosphonates: High Risk Group

- The bisphophonates (etidronate, alendronate, risedronate) are anti-resorptive medicines that block the resorptive action in bone, increasing the density of the bone in some areas
- The medicines reduced fractures. Their greatest impact was on the rate of vertebral fractures, but they also demonstrated statistically demonstrable benefits in the reduction of dreaded hip fractures, and also wrist fractures. Typically for every 100 women taking the medicines six avoided a fracture of some sort over three years of therapy. Particularly based on the one hip fracture that is avoided per 100 women this benefit may be highly important in terms of reducing morbidity or disability.
- it is not clear that it would be important to prevent subclinical vertebral fractures, nor is it clear that reducing this outcome represents an aggregate benefit when one considers the adverse effects of the medicines. However a reduction in hip fractures, even at 1 per 100, may represent a potentially important public health measure.

11

100 for hip fracture

Benefits in NNT	
20	1 in 20 were helped (vertebral fracture prevented)
100	1 in 100 were helped (hip fracture prevented)
Harms in NNT	
	A small number were harmed

Bisphosphonates for Fracture Prevention in Post-Menopausal Women With Prior Fractures or With Very Low Bone Density

12

Anti-Hypertensive Treatment for the Primary Prevention of Cardiovascular Events In Mild Hypertension

- **Source**
- Diao D, Wright JM, Cundiff DK, Gueyffier F. Pharmacotherapy for mild hypertension. Cochrane Database of Systematic Reviews 2012, Issue 8. Art. No.: CD006742
- **Efficacy Endpoints**
- Mortality, stroke, coronary artery disease, cardiovascular events
- **Harm Endpoints**
- Stopping medication due to adverse events
- **Narrative**
- Hypertension affects almost 29% of adults in the United States, most of whom are taking medication to lower their blood pressure[1]. Blood pressure control has been shown to reduce the chances of developing cardiovascular problems and stroke however these reductions are derived from studies of patients with moderate or severe hypertension, and those with a history of prior cardiovascular events such as heart attack or stroke. However, evidence has been unclear on whether pharmacological treatment for previously healthy patients with 'mild' hypertension is beneficial.

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Anti-Hypertensive Treatment for the Primary Prevention of Cardiovascular Events In Mild Hypertension

- This review included four randomized-controlled trials enrolling 8,912 subjects with mild elevations in blood pressure (systolic blood pressure 140-159 or diastolic blood pressure 90-99) without preexisting cardiovascular disease. Patient data for individuals satisfying the inclusion criteria were obtained from three studies; pooled data was used from the fourth study since it met the a priori inclusion criteria of having less than 20% of its total subjects with moderately elevated blood pressure.

  At a period of four to five years follow up, no differences were seen in mortality, cardiovascular events, CAD, or stroke. Approximately 9% more patients in the treatment arms withdrew due to medication side effects.

14

12 for medication side effects

☺ Benefits in NNT	
	None were helped (preventing death, stroke, heart disease, or cardiovascular events)

☹ Harms in NNT	
12	1 in 12 were harmed (medication side effects and stopped the drug)

15

Aspirin to Prevent Cardiovascular Disease in Patients with Known Heart Disease or Strokes

- **Source**
- Antithrombotic Trialists Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009; 373(9678): 1849-60

  Antithrombotic Trialists Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002 Jan 12;324(7329):71-86.
- **Efficacy Endpoints**
- Heart attack, stroke, death
- **Harm Endpoints**
- Bleeding, death
- **Narrative**
- Aspirin blocks the action of platelets, reducing clots and ostensibly lowering the risk of heart attacks, strokes, and deaths. This review examined and summarized the magnitude of benefits from daily aspirin when compared to placebo for 'secondary prevention', i.e. among patients who have had a recent heart attack or stroke.

  Aspirin works: those taking aspirin in these studies suffered fewer heart attacks, strokes, and deaths than those taking a placebo, at the cost of a small number of bleeding events. In addition, the benefits outlined here were seen after just over two years of daily aspirin therapy, in contrast to the 4 and 5 year periods seen with many other cardiovascular preventive interventions.

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Aspirin to Prevent Cardiovascular Disease in Patients with Known Heart Disease or Strokes

50 for cardiac benefit

☺ Benefits in NNT	
50	1 in 50 were helped (cardiovascular problem prevented)
333	1 in 333 were helped (prevented death)
77	1 in 77 were helped (prevented non-fatal heart attack)
200	1 in 200 were helped (prevented non-fatal stroke)

☹ Harms in NNT	
400	1 in 400 were harmed (major bleeding event: required hospital admission and transfusion)

17

Aspirin to Prevent a First Heart Attack or Stroke

- **Source**
- Antithrombotic Trialists Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009; 373(9678): 1849-60
- **Efficacy Endpoints**
- Heart attack, stroke, death
- **Harm Endpoints**
- Bleeding, death
- **Narrative**
- Aspirin blocks the action of platelets, reducing clots and ostensibly lowering the risk of heart attacks, strokes, and deaths. This review examined and summarized the magnitude of benefits from daily aspirin when compared to placebo for 'primary prevention', i.e. among patients who have never had a heart attack or stroke.

  Aspirin did reduce certain clotting events (all of them nonfatal) but it also increased bleeding events. In the end the miniscule potential benefit does not seem worth it in comparison to the harms and in light of the aggregate impact.

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Aspirin to Prevent a First Heart Attack or Stroke

1667 for cardiac benefit

Benefits in NNT	
1667	1 in 1667 were helped (cardiovascular problem prevented)
	None were helped (prevented death)
2000	1 in 2000 were helped (prevented non-fatal heart attack)
3000	1 in 3000 were helped (prevented non-fatal stroke)

Harms in NNT	
3333	1 in 3333 were harmed (major bleeding event: required hospital admission and transfusion)

19

Buprenorphine Maintenance vs. Placebo for Opioid Dependence

- **Source**
- Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2014;(2):CD002207.

Study Population: Adults with opioid dependence

- **Efficacy Endpoints**
- Treatment retention and illicit drug use suppression
- **Harm Endpoints**
- Mortality and adverse effects

20

Buprenorphine Maintenance vs. Placebo for Opioid Dependence

2 for retention in treatment (using high-dose buprenorphine, ≥ 16 mg)

Benefits in NNT	
4	1 in 4 using low-dose buprenorphine (2 to 6 mg) had retention in treatment
3	1 in 3 using medium-dose buprenorphine (7 to 16 mg) had retention in treatment
2	1 in 2 using high-dose buprenorphine (≥ 16 mg) had retention in treatment

Harms in NNT	
	No study-related medication mortality was reported
	Uncertain adverse effects

21

Abx for COPD

Source

Ram, FS, Rodriguez-Roisin, R, Granados-Navarrete, A, et al Antibiotics for exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2006.

Efficacy Endpoints

Mortality, Treatment Failure (Lack of resolution, worsening, or death)

Harm Endpoints

Diarrhea

22

Antibiotics for COPD exacerbation

- **Narrative**
- Chronic obstructive pulmonary disease (COPD), a term that encompasses both patients diagnosed with chronic bronchitis and emphysema, is an obstructive lung disease, in many cases caused by tobacco smoking. It is thought that patients with COPD 'exacerbation' (increased shortness of breath or change in their chronic cough and sputum) may benefit from antibiotics, though the reasons for this are not well elucidated.

Benefits: Benefits were robust. 11 randomized trials are included from this review, totaling 817 subjects. The data suggest that overall COPD exacerbations benefit from antibiotics – both by reducing subjects' short term (1-2 week) mortality and by reducing the chance of treatment failure (not getting better or getting worse). Mortality was reduced by 11.6%, a NNT of 8—a number that held consistently across subgroups. Treatment failure was reduced by 30.7% (NNT of 3) but this seemed most applicable to hospitalized subjects. The best effects on primary outcomes likely apply to the sickest patients: those admitted to the hospital and to the intensive care unit.

Harms: Only two studies collected data on diarrhea (a common side effect of antibiotics): antibiotics increased the risk of developing diarrhea by 5.0%, for a NNH of 20.

23

Abx for COPD

8 for mortality

Benefits in NNT	
8	1 in 8 were helped (life saved)
3	1 in 3 were helped (preventing failed treatment)

Harms in NNT	
20	1 in 20 were harmed (diarrhea)

24

Statins in Persons at Low Risk of Cardiovascular Disease

Source

Chou R, Dana T, Blazina I, Daeges M, Jeanne TL. Statins for Prevention of Cardiovascular Disease in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2016;316(19):2008-2024.

Efficacy Endpoints

Death, heart attack (myocardial infarction), stroke

Harm Endpoints

New-onset diabetes mellitus, muscle symptoms

25

Statins in Persons at Low Risk of Cardiovascular Disease

- In summary, studies have found no significant overall mortality benefit with statin therapy in low-risk patients, as well as no reduction in the risk of serious illness overall and very small benefits for nonfatal heart attack and stroke. Statins also appear to cause diabetes. Although this is uncommon, diabetes may occur more often than the prevention of a heart attack or stroke in patients taking statins. It appears that the existing evidence is in disagreement that statins should be used for patients with a 10-year cardiovascular risk below 20%.4,11,12 With no mortality benefit, no reduction in serious illness, an approximately 1% chance of avoiding a nonfatal heart attack or stroke, a similar or greater chance of developing diabetes, and a one in 21 chance of muscle damage, it seems wiser to focus on lifestyle changes (such as adopting a Mediterranean diet, exercising, and not smoking) instead of cholesterol drugs in low-risk patients. These individuals should be informed of the known risks and benefits of statins, and the decision to start statin therapy should be shared by the patient and physician, rather than imposed by guidelines.

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Statins in Persons at Low Risk of Cardiovascular Disease

No statistically significant mortality benefit

Benefits in NNT	
	No statistically significant mortality benefit
217	1 in 217 avoided a nonfatal heart attack (myocardial infarction)
313	1 in 313 avoided a nonfatal stroke

Harms in NNT	
21	1 in 21 experienced pain from muscle damage
204	1 in 204 developed diabetes mellitus

27

Adding SGLT-2 inhibitors and GLP-1 agonists to standard treatment reduces death, nonfatal heart attack, and severe kidney disease

- **Source**
- Davila E, McCormack J. sglt -2 inhibitors and glp -1 receptor agonists for type 2 diabetes. Academic Emergency Medicine. 2024;31(4):408-411.

  Study Population: 421,346 patients with Type 2 diabetes, already on standard treatments, followed for 24 weeks or longer
- **Efficacy Endpoints**
- Death, nonfatal heart attack, nonfatal stroke, end-stage kidney disease, body weight change
- **Harm Endpoints**
- Severe hypoglycemia, severe gastrointestinal events, genital infection, amputation, ketoacidosis

28

SGLT / GLP

- **Narrative**
- Type 2 diabetes is a condition that can affect many organs and can lead to serious complications. Recently, new classes of medications have been introduced for the treatment of Type 2 diabetes, including glucagon-like peptide 1 (GLP-1) receptor agonists and sodium-glucose transport protein 2 (SGLT-2) inhibitors. SGLT-2 medications increase the elimination of glucose and sodium in the urine by blocking the reuptake of filtered glucose in the kidney. GLP-1 receptor medications mimic the intestinal hormone incretin, increasing glucose-dependent endogenous insulin excretion. Both medications slow gastric emptying, decrease appetite, and regulate insulin and glucagon.[1] Several trials have shown benefits prompting some guidelines to recommend these class of medications for patients with Type 2 diabetes (T2DM).[2,3,4]

  The systematic review and network meta-analysis summarized here[2] included 764 randomized trials testing SGLT-2 inhibitors or GLP-1 receptor agonists typically added to other antidiabetes medications. Trial groups received SGLT-2 or GLP-1 medications while control groups received placebos. However, both trial arms were on—and stayed on—standard background treatments that could include a variety of other medications (metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitors, thiazolidinediones, alpha-glucosidase inhibitors, glitinides, or insulin).[2] A total of 421,346 patients were involved in the 764 studies.

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SGLT / GLP

- Outcomes of interest included death, nonfatal stroke, end-stage kidney disease, nonfatal heart attack, body weight change, severe hypoglycemia, severe gastrointestinal events, genital infection, ketoacidosis, amputation, and hyperkalemia. End-stage kidney disease is defined in studies as a glomerular filtration rate <15 mL/min (per 1.73 m^2) or initiation of dialysis. Tables 1 and 2 show the results found in the review. Of note, the review reports medication effects according to a patient's baseline cardiovascular risk. This is because the magnitude of the effect of diabetes medications varies according to a person's chance of developing the problem the medication is aiming to prevent. For instance, among those already at little to no risk of having a stroke, a medication's ability to demonstrate a reduction in strokes is obviously small. For those who are at higher risk of future strokes, there is a greater possibility for improvement, and effective medications can have a greater impact. Effective medications therefore tend to have different impacts in people with different risks—the higher the risk, likely the greater the impact. The authors therefore analyzed and reported medication effects separately for people in each of the following risk categories: very low (fewer than three cardiovascular risk factors), low (three or more risk factors), moderate (patients who already had known cardiovascular disease), high (those with chronic kidney disease), and very high (known cardiovascular and kidney disease).[2]

  Major harms included severe hypoglycemic episodes, severe gastrointestinal adverse events, genital infections, amputation, and ketoacidosis. SGLT-2 inhibitors increased genital infections (odds ratio [OR] 3.5, 95% confidence interval [CI] 3.0–4.0, absolute risk difference [ARD] 14%; NNH 7; high certainty). GLP-1 receptor agonists increased the risk of severe gastrointestinal symptoms (OR 2.5, 95% CI 1.2–5.0; ARD 6%; NNH 17; low certainty). There were no other differences in risks of harm between SGLT-2 inhibitors and GLP-1 receptor agonists.

30

SGLT / GLP

- Importantly, when any of these medication classes were compared directly to metformin, no additional benefit was seen other than greater weight loss of varying degrees (0.2–7.7 kg).[3,5,8] However, patients on metformin had fewer genital infections and gastrointestinal adverse events.[3,5,8] While head-to-head trials are comparatively few, a large population-based study of the new medications from 2022 appears to confirm their lack of benefit over metformin, showing almost 9000 on SGLT-2 medications, when matched to over 17,000 on metformin, had identical rates of heart attack, stroke, and death but higher rates of genital infection.

31

SGLT / GLP

- n summary, while SGLT-2 and GLP-1 medications appear to reduce mortality, heart attack, and end-stage kidney disease compared to many other classes, available evidence does not show them to be better than metformin, though some (particularly tirzapetide) may lead to greater weight loss. The newer medications also cause genital infections, particularly SGLT-2s, at a NNH of 7. The cost and harms of SGLT-2 and GLP-1 medications therefore should be balanced against weight loss and other effects compared to metformin.

32

SGLT 2 inhibiots and GLP-1 agonist

Benefits in NNT	
	SGLT-2 inhibitors:
38	1 in 38 high-risk people was helped (death prevented)
100	1 in 100 low-risk people was helped (death prevented)
71	1 in 71 high-risk people was helped (heart attack prevented)
143	1 in 143 low-risk people was helped (heart attack prevented)
	No one was helped (no stroke prevented)
40	1 in 40 high-risk people was helped (end-stage kidney disease prevented)
333	1 in 333 low-risk people was helped (end-stage kidney disease prevented)
	Average weight loss: 2 kg
	GLP-1 receptor agonists:
59	1 in 59 was helped (death prevented, high risk)
125	1 in 125 was helped (death prevented, low risk)
111	1 in 111 was helped (heart attack prevented, high risk)
250	1 in 250 was helped (heart attack prevented, low risk)

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GLP

	GLP-1 receptor agonists:
59	1 in 59 was helped (death prevented, high risk)
125	1 in 125 was helped (death prevented, low risk)
111	1 in 111 was helped (heart attack prevented, high risk)
250	1 in 250 was helped (heart attack prevented, low risk)
59	1 in 59 was helped (stroke prevented, high risk)
111	1 in 111 was helped (stroke prevented, low risk)
40	1 in 40 was helped (end stage kidney disease prevented, high risk)
500	1 in 500 was helped (end stage kidney disease prevented, low risk)

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HARMS

Harms in NNT	
	SGLT-2 inhibitors:
7	1 in 7 was harmed (experienced a genital infection)
	GLP-1 receptor agonists:
17	1 in 17 was harmed (experienced a severe gastrointestinal event)

35

Paxlovid

Source

Johari F, Verma R. Paxlovid for nonhospitalized patients with COVID -19. Academic Emergency Medicine. Published online March 22, 2024:acem.14896.

Study Population: Two randomized controlled trials with 3286 nonhospitalized symptomatic adults with acute mild to moderate COVID-19

Efficacy Endpoints

All-cause mortality and hospitalization

Harm Endpoints

Adverse events (e.g., rebound, dysgeusia, diarrhea)

36

Paxlovid

- The first trial, called EPIC-HR,[3] enrolled 2246 outpatients with <5 days of symptomatic COVID infection and at least one high-risk criterion for worsening. The most common criteria were obesity (80%), smoking, and hypertension. Any patients vaccinated against COVID or previously exposed to COVID were excluded from the trial. In this group, the drug reduced a composite endpoint of hospitalization for COVID or death: 6.3% with placebo versus 0.8% with Paxlovid (absolute risk difference [ARD] 5.5%, p < 0.001, number needed to treat [NNT] 18). This includes 12 deaths during the study period, all in the placebo group. Of note, a Cochrane systematic review in 2023 included the EPIC-HR trial and did not note or mention the results of the unpublished EPIC-SR trial.

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Paxlovid

- The second trial, EPIC-SR, remains unpublished but data have been uploaded to a trial registry site.[4] The results report on 1288 symptomatic outpatients with acute COVID-19 given Paxlovid or placebo. No high-risk criteria were necessary for enrollment and COVID-vaccinated and previously exposed people were eligible. The trial found no difference between groups in hospitalization for COVID or death (0.8% vs. 1.6%, p = 0.2) and was stopped early for futility.

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Paxlovid

The effectiveness of nirmatrelvir/ritonavir (Paxlovid) in reducing mortality or hospitalization in mild to moderate COVID-19 is uncertain

	Benefits in NNT
	Uncertain, likely none
	Harms in NNT
5	1 in 5 were harmed (virologic rebound)
25	1 in 25 were harmed (experienced adverse events including dysgeusia)

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Summary

- Reviewed: Bisphosphonates, HTN treatment for primary prevention, aspirin to prevent cardiovascular disease in patients with it, Aspirin to prevent first heart attack, Buprenorphine maintenance, Abx for COPD, Statin for low risk CVD, SGLT-2 / GLP vs metformin, Paxlovid for mild to mod covid.

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