

Angiotensin receptor-neprilysin inhibitors

A fixed combination of neprilysin inhibition and AT1 receptor blockade used in chronic heart failure, whose defining safety point is that it can never be given alongside an ACE inhibitor and needs a 36-hour washout when switching.

Online guide: <https://www.medguideglobal.com/pharmacology/cardiovascular/angiotensin-receptor-neprilysin-inhibitors>

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Quick revision

One Liner: An ARNI blocks the AT1 receptor and inhibits neprilysin at the same time, so the harmful renin-angiotensin arm is suppressed while the protective natriuretic peptide arm is preserved - and because neprilysin also degrades bradykinin, it must never overlap with an ACE inhibitor.

1. Sacubitril-valsartan is the first approved agent in the angiotensin receptor-neprilysin inhibitor class. [1]
2. Neprilysin degrades natriuretic peptides, so inhibiting it prolongs their vasodilating, natriuretic and diuretic effects. [1]
3. Neprilysin is not selective for the natriuretic peptides, and angiotensin II is described among its other substrates, so inhibiting neprilysin alone would not suppress the renin-angiotensin arm. The angiotensin receptor blocker supplies that suppression: approved labelling attributes the benefit of the combination to raised levels of peptides degraded by neprilysin, such as the natriuretic peptides, together with simultaneous blockade of angiotensin II at the AT1 receptor. [1]
4. Neprilysin degrades bradykinin as well, so combining it with an ACE inhibitor stacks two routes of bradykinin accumulation and raises angio-oedema risk. [1]
5. A 36-hour washout is required when switching between an ACE inhibitor and sacubitril-valsartan in either direction. [1][2]
6. It is used in place of an ACE inhibitor or an ARB, not in addition to either, alongside the rest of standard heart failure therapy. [1]
7. Hypotension is the adverse effect most consistently increased compared with an ACE inhibitor. [1]
8. Fetal toxicity carries a boxed warning, as it does for every drug acting directly on the renin-angiotensin system. [2]
9. A prior history of angio-oedema on an ACE inhibitor or an ARB is an absolute bar to this class. [2]

Overview

1. Sacubitril-valsartan is the first approved agent in the class of drugs called angiotensin receptor-neprilysin inhibitors. It is used in place of an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker, alongside other standard heart failure treatments such as a beta blocker or an aldosterone antagonist. [1]
2. The reasoning behind the class starts from two systems pulling in opposite directions. Heart failure activates the renin-angiotensin-aldosterone system, producing vasoconstriction, hypertension, raised aldosterone, increased sympathetic tone and eventually cardiac remodelling. At the same time the natriuretic peptide system is activated, which is why B-type natriuretic peptide and its N-terminal fragment rise; that compensatory arm causes vasodilation, natriuresis and diuresis, and lowers blood pressure, sympathetic tone and aldosterone. [1]
3. Neprilysin is the enzyme that degrades natriuretic peptides, so blocking it prolongs the favourable arm rather than merely suppressing the harmful one. That is the conceptual novelty: existing renin-angiotensin blockers only remove a bad signal, whereas an ARNI also preserves a good one. [1]
4. The complication is that neprilysin is not selective for natriuretic peptides. It also degrades angiotensin II, which is why the neprilysin inhibitor must be paired with an angiotensin receptor blocker, and it degrades bradykinin, which is why the combination cannot be used with an ACE inhibitor and why a 36-hour separation is required when switching. Almost every safety rule attached to this class descends from those two facts. [1]

Classification and drug examples

Intro: This is a single-agent class in current practice, so the useful division is between the two components of the fixed combination rather than between rival members.

1. Name: The neprilysin inhibitor component

1. Note: A prodrug that must be converted before it acts, and which cannot be used on its own.

Name: Sacubitril

LBQ657 (active metabolite)

Route: Oral

Note: A prodrug converted by esterases to LBQ657, which inhibits neprilysin and so prevents the breakdown of natriuretic peptides. Absolute oral bioavailability is estimated at 60% or greater. [1] [1]

2. Name: The angiotensin receptor blocker component

2. Note: Present to neutralise the angiotensin II that accumulates when neprilysin is inhibited, and to provide the renin-angiotensin blockade the patient would otherwise get from a separate ACE inhibitor or ARB.

Name: Valsartan

Route: Oral

Note: An angiotensin receptor blocker that blocks the renin-angiotensin system at the AT1 receptor. It is minimally metabolised, with a hydroxyl metabolite present in plasma at low concentrations. [1][3] [1]

3. Name: The fixed combination as prescribed

3. Note: Dispensed as one product because the two components are not interchangeable or separable in practice.

Name: Sacubitril-valsartan

Entresto

Route: Oral

Note: Supplied as film-coated tablets in three fixed strengths, plus an oral-pellet sprinkle formulation in two strengths for patients unable to swallow tablets, and taken twice daily regardless of meals. [1] [1]

Mechanism of action

Summary: An ARNI inhibits neprilysin and blocks the AT1 receptor at the same time. Neprilysin inhibition prevents degradation of natriuretic peptides and prolongs their vasodilating, natriuretic and diuretic effects; AT1 blockade suppresses the renin-angiotensin arm and neutralises the angiotensin II that neprilysin inhibition would otherwise allow to accumulate.

Target: Neprilysin (via the active metabolite of sacubitril) together with the angiotensin II type 1 receptor (via valsartan)

1. Step: 1

1. Title: Heart failure activates two opposing systems

1. Detail: The renin-angiotensin-aldosterone system produces vasoconstriction, hypertension, raised aldosterone and increased sympathetic tone, ending in cardiac remodelling. Simultaneously the natriuretic peptide system is activated, producing vasodilation, natriuresis and diuresis and reducing blood pressure, sympathetic tone and aldosterone. [1]

2. Step: 2

2. Title: Sacubitril is converted to its active form

2. Detail: Sacubitril is a prodrug converted by esterases to LBQ657. That metabolite is the neprilysin inhibitor; sacubitril itself is not. [1]

3. Step: 3

3. Title: Neprilysin inhibition preserves natriuretic peptides

3. Detail: Neprilysin is the enzyme that degrades natriuretic peptides. Blocking it prevents that breakdown and prolongs their favourable haemodynamic effects instead of allowing them to be cleared. [1]

4. Step: 4

4. Title: The ARB component supplies the renin-angiotensin blockade

4. Detail: Neprilysin is described as breaking down angiotensin II as well as the natriuretic peptides, so inhibiting it alone would leave the renin-angiotensin arm unopposed. Valsartan blocks angiotensin II at the AT1 receptor, and the approved labelling attributes the combination's benefit to that blockade alongside the preserved natriuretic peptides. [1]
5. Step: 5
5. Title: Bradykinin also builds up - and that sets the safety rules
5. Detail: Bradykinin is another substrate of neprilysin, so its concentration rises too. Adding an ACE inhibitor would remove a second route of bradykinin clearance, which is why the combination is contraindicated and why a 36-hour washout separates the two drugs when therapy is switched. [1]

Major clinical uses

1. Drug: Sacubitril-valsartan
 1. Indication: Chronic heart failure in adults, to reduce the risk of cardiovascular death and hospitalisation for heart failure
 1. Line: guideline-directed
 1. Note: Benefits are described as most clearly evident where left ventricular ejection fraction is below normal, and the labelling notes that ejection fraction is a variable measure so clinical judgement decides whom to treat. [2]
2. Drug: Sacubitril-valsartan
 2. Indication: Chronic symptomatic heart failure with reduced ejection fraction, NYHA class II to IV
 2. Line: guideline-directed
 2. Note: Used instead of an ACE inhibitor or ARB and alongside other standard therapy; patients should be able to tolerate an ACE inhibitor or ARB before it is initiated. [1]
3. Drug: Sacubitril-valsartan
 3. Indication: Heart failure with preserved ejection fraction
 3. Line: add-on
 3. Note: Recommended in the 2022 ACC/AHA/HFSA guidelines for this group, with a 2023 ACC expert consensus placing it after an SGLT2 inhibitor in sequence. [1]
4. Drug: Sacubitril-valsartan
 4. Indication: Symptomatic heart failure with systemic left ventricular systolic dysfunction in children aged one year and older
 4. Line: guideline-directed
 4. Note: A sprinkle formulation exists to make administration easier in this group. [2][1]
5. Drug: Sacubitril-valsartan
 5. Indication: Patients recently stabilised after an episode of worsening heart failure
 5. Line: alternative
 5. Note: Reported to reduce N-terminal pro-B-type natriuretic peptide and lower the risk of cardiovascular death or heart failure hospitalisation compared with control therapy, at the cost of more symptomatic hypotension. [1]

Pharmacokinetics

1. Drug: Sacubitril
 1. Route: Oral
 1. Absorption: Absolute oral bioavailability estimated at 60% or greater; peak concentration at about 0.5 hours
 1. Metabolism: Converted by esterases to the active metabolite LBQ657
 1. Elimination: About 52% to 68% excreted in urine as LBQ657, and 37% to 48% in faeces
 1. Half Life: Approximately 1.4 hours for sacubitril
 1. Dose Adjust: Lower starting dose where eGFR is below 30 mL/min/1.73 m squared or in moderate hepatic impairment [1]
2. Drug: LBQ657 (active neprilysin inhibitor)

- 2. Route: Formed in vivo
- 2. Absorption: Peak concentration at about 2 hours; accumulates roughly 1.6-fold at steady state
- 2. Csf Penetration: Crosses the blood-brain barrier only to a small extent, about 0.28%
- 2. Metabolism: The active moiety itself
- 2. Elimination: Predominantly urinary, with a substantial faecal component
- 2. Half Life: Approximately 11.5 hours
- 2. Dose Adjust: See the combination product entry [1]
- 3. Drug: Valsartan
- 3. Route: Oral
- 3. Absorption: Peak concentration at about 1.5 hours; mean apparent volume of distribution 75 L
- 3. Metabolism: Minimally metabolised, around 20%, with a low-concentration hydroxyl metabolite
- 3. Elimination: About 13% urinary and about 86% faecal
- 3. Half Life: Approximately 9.9 hours
- 3. Dose Adjust: Not recommended in severe hepatic impairment [1]
- 1. Plasma protein binding is high for all three moieties, in the range of 94% to 97%, and steady state is reached in about three days. Food has no clinically significant effect on absorption, so the product is taken with or without food. [1]
- 2. The 36-hour separation from an ACE inhibitor is a pharmacological requirement rather than a scheduling convenience, and it applies whichever direction the switch is made in. [2]
- 3. Serum creatinine is monitored closely because inhibiting the renin-angiotensin-aldosterone system can reduce renal function in susceptible patients, and serum potassium is monitored periodically for the same mechanistic reason. [2]
- 4. Renal and hepatic function guide dosing in older patients, and the product is not recommended in severe hepatic impairment. [1]
- 5. This page gives no dose regimens by design. Doses depend on prior therapy, renal and hepatic function, blood pressure and tolerance, and belong in a prescribing reference used by the treating clinician.

Adverse effects

- 1. Effect: Hypotension
 - 1. Detail: The most consistently increased adverse effect relative to an ACE inhibitor. Patients with an activated renin-angiotensin system, including those volume- or salt-depleted by high-dose diuretics, are at greater risk. [1][2]
- 2. Effect: Hyperkalaemia
 - 2. Detail: Occurs through the drug's actions on the renin-angiotensin-aldosterone system, with higher risk in severe renal impairment, diabetes, hypoaldosteronism or a high-potassium diet. [2]
- 3. Effect: Reduced renal function
 - 3. Detail: Anticipated in susceptible individuals. In patients whose renal function depends on renin-angiotensin activity, agents of this kind have been associated with oliguria, progressive azotaemia and, rarely, acute renal failure. [2]
- 4. Effect: Cough
 - 4. Detail: Reported with the class, but at a lower rate than with enalapril in the comparative trial. [1]
- 1. Effect: Angio-oedema
 - 1. Detail: Incidence is rare but more frequent than with an angiotensin receptor blocker alone. Swelling confined to face and lips has generally resolved without treatment, but angio-oedema with laryngeal oedema may be fatal, and a higher rate has been recorded in Black than in non-Black patients.
 - 1. Action: The drug is discontinued immediately, appropriate therapy given and the airway monitored; it must not be re-administered. [2]
- 2. Effect: Fetal toxicity
 - 2. Detail: Carried as a boxed warning. Drugs acting directly on the renin-angiotensin system can cause injury and death to the developing fetus, and use in the second and third trimesters reduces fetal renal function and increases fetal and neonatal morbidity and death.

2. Action: Treatment is discontinued as soon as pregnancy is detected and an alternative considered. [2]
3. Effect: Symptomatic hypotension requiring intervention
3. Detail: Distinct from asymptomatic blood pressure lowering, and the reason volume status is corrected before the first dose or a lower starting dose used.
3. Action: Diuretic and antihypertensive doses are reviewed first; if hypotension persists the dose is reduced or the drug temporarily interrupted, and permanent discontinuation is usually not required. [2]
4. Effect: Renal impairment in renal artery stenosis
4. Detail: As with all drugs affecting the renin-angiotensin-aldosterone system, blood urea and serum creatinine may rise in patients with bilateral or unilateral renal artery stenosis.
4. Action: Renal function is monitored in that group specifically. [2]
1. Drug: Sacubitril-valsartan compared with enalapril
1. Effect: In PARADIGM-HF it showed a higher incidence of hypotension and symptomatic hypotension, but a lower risk of elevated serum potassium or serum creatinine and a lower risk of cough. More patients experienced angio-oedema in the sacubitril-valsartan arm, though that difference was not statistically significant. [1]
2. Drug: Sacubitril-valsartan in breastfeeding
2. Effect: Milk levels are low and valsartan was undetectable at the highest dosage studied, but there is potential for severe adverse reactions in a breastfed infant, so breastfeeding is not recommended during treatment. [1]

Contraindications, precautions and interactions

1. Hypersensitivity to any component of the product. [2]
2. A history of angio-oedema related to previous ACE inhibitor or angiotensin receptor blocker therapy, and hereditary angio-oedema. [2]
3. Concomitant use of an ACE inhibitor, including administration within 36 hours of switching from or to one. [2]
4. Concomitant use of aliskiren in patients with diabetes. [2]
5. Pregnancy, under a boxed warning for fetal toxicity, with discontinuation as soon as pregnancy is detected. [2]
1. Volume or salt depletion, including treatment with high doses of diuretics, which is corrected before the first dose or handled by starting lower. [2]
2. Severe congestive heart failure and other states where renal function depends on renin-angiotensin activity, with close monitoring of serum creatinine. [2]
3. Bilateral or unilateral renal artery stenosis, where blood urea and creatinine may rise. [2]
4. Moderate hepatic impairment, which calls for a lower starting dose; the product is not recommended in severe hepatic impairment. [1]
5. Reduced kidney function, where an estimated glomerular filtration rate below 30 mL/min/1.73 m squared calls for the lowest starting strength. [1]
6. Breastfeeding, where the potential for severe adverse reactions in the infant means it is not recommended during treatment. [1]
1. With: ACE inhibitors
1. Effect: Contraindicated, because both reduce bradykinin breakdown and the combination increases the risk of angio-oedema; a 36-hour interval separates them when switching. [1][2]
2. With: Separate angiotensin receptor blockers
2. Effect: Avoided, because the product already contains valsartan and adding another would duplicate the same blockade. [1]
3. With: Aliskiren
3. Effect: Contraindicated in patients with diabetes, and avoided where estimated glomerular filtration rate is below 60. [2]
4. With: Potassium-sparing diuretics such as spironolactone, triamterene or amiloride, and potassium supplements or potassium-containing salt substitutes

4. Effect: May increase serum potassium; periodic monitoring is recommended. [1]
5. With: Non-steroidal anti-inflammatory drugs
5. Effect: In older, volume-depleted or renally compromised patients, concomitant use may worsen renal function or precipitate acute kidney injury; these effects are usually reversible and renal function is monitored periodically. [1]
6. With: Lithium
6. Effect: May increase serum lithium concentrations and the risk of lithium toxicity, so levels are monitored during coadministration. [1]

Comparison tables

Title: How an ARNI differs from an ACE inhibitor or an ARB alone

Caption: All three act on the renin-angiotensin system; only the ARNI also protects the opposing natriuretic peptide arm. Therapy is governed by a prescribing reference and the treating clinician.

1. Key: feature
1. Label: Feature
1. Is Row Header: true
2. Key: acei
2. Label: ACE inhibitor
3. Key: arb
3. Label: ARB
4. Key: arni
4. Label: ARNI
1. Feature: Renin-angiotensin blockade
1. Acei: Blocks formation of angiotensin II
1. Arb: Blocks angiotensin II at the AT1 receptor
1. Arni: Blocks angiotensin II at the AT1 receptor, via its valsartan component [4][3][1]
2. Feature: Effect on natriuretic peptides
2. Acei: None
2. Arb: None
2. Arni: Neprilysin inhibition prevents their breakdown and prolongs their effect [1]
3. Feature: Effect on bradykinin
3. Acei: Breakdown inhibited via ACE
3. Arb: Unaffected
3. Arni: Breakdown inhibited via neprilysin [4][3][1]
4. Feature: Can be combined with an ACE inhibitor
4. Acei: Not applicable
4. Arb: Not recommended
4. Arni: Contraindicated, with a 36-hour washout when switching [3][2]
5. Feature: Pregnancy
5. Acei: Contraindicated
5. Arb: Contraindicated under a boxed warning
5. Arni: Contraindicated under a boxed warning [4][3][2]
6. Feature: Position in heart failure therapy
6. Acei: Long-established, and the comparator in the pivotal ARNI trial
6. Arb: Used where an ACE inhibitor is not tolerated
6. Arni: Used instead of either, in patients who already tolerate one of them [1]

High-yield exam pearls

1. Pearl: The neprilysin inhibitor is never given alone.
1. Why: Neprilysin degrades angiotensin II as well as natriuretic peptides, so inhibiting it in isolation causes angiotensin II to accumulate. Pairing it with an angiotensin receptor blocker is what neutralises that excess, which is why the drug exists as a fixed combination rather than as two options. [1]
2. Pearl: 36 hours is the number to remember.
2. Why: When switching between an ACE inhibitor and sacubitril-valsartan, a 36-hour washout is required to minimise the risk of angio-oedema, and the label states it applies switching from or to an ACE inhibitor. [1][2]
3. Pearl: The natriuretic peptide system is the RAAS's natural opponent.
3. Why: It causes vasodilation, natriuresis and diuresis, lowers blood pressure and sympathetic tone and reduces aldosterone - the mirror image of what the renin-angiotensin-aldosterone system does. An ARNI suppresses one arm while protecting the other. [1]
4. Pearl: Patients are expected to have tolerated an ACE inhibitor or ARB first.
4. Why: The guideline position is that patients should be able to tolerate an ACE inhibitor or ARB before sacubitril-valsartan is initiated, which makes this a substitution step rather than a first move. [1]
5. Pearl: It is a prodrug pairing, not a single molecule.
5. Why: Sacubitril is a prodrug converted by esterases to LBQ657, which is the active neprilysin inhibitor; valsartan is the angiotensin receptor blocker component and is only minimally metabolised. [1]
6. Pearl: Angio-oedema risk is not evenly distributed.
6. Why: The label records a higher rate of angio-oedema in Black than in non-Black patients, and states the drug must not be re-administered after an episode. [2]
7. Pearl: Compared with enalapril, the trade is hypotension for potassium and creatinine.
7. Why: In PARADIGM-HF, sacubitril-valsartan was associated with a higher incidence of hypotension and symptomatic hypotension, but a lower risk of elevated serum potassium or creatinine and a lower risk of cough than enalapril. [1]

Common exam traps

1. Trap: "An ARNI is added on top of an ACE inhibitor for extra benefit."
1. Correction: It replaces the ACE inhibitor or ARB. Concomitant use with an ACE inhibitor is contraindicated because of the angio-oedema risk, and use with a separate ARB is avoided because the product already contains valsartan. [1][2]
2. Trap: "The washout only matters when starting the ARNI."
2. Correction: The label states the drug must not be administered within 36 hours of switching from or to an ACE inhibitor. The interval applies in both directions. [2]
3. Trap: "Neprilysin inhibition alone would work just as well."
3. Correction: It would not. Neprilysin breaks down angiotensin II, so inhibiting the enzyme without receptor blockade allows angiotensin II to accumulate, and the angiotensin receptor blocker is needed to block the effect of that excess. [1]
4. Trap: "Angio-oedema on this drug can be managed and the drug restarted."
4. Correction: If angio-oedema occurs the drug is discontinued immediately and must not be re-administered. Laryngeal oedema may be fatal, and prior angio-oedema on an ACE inhibitor or ARB is itself a contraindication. [2]
5. Trap: "It only applies to heart failure with reduced ejection fraction."
5. Correction: The labelled indication is to reduce cardiovascular death and heart failure hospitalisation in adults with chronic heart failure, with benefits most clearly evident where ejection fraction is below normal, and guideline recommendations also extend to heart failure with preserved ejection fraction. A paediatric indication from one year of age also exists. [2][1]
6. Trap: "Persistent hypotension means the drug has to be abandoned."

6. Correction: The labelled sequence is to correct volume or salt depletion first, then consider adjusting diuretics and other antihypertensives, and only then reduce the dose or temporarily interrupt. Permanent discontinuation is usually not required. [2]

Self-test questions

1. Question: Why is a neprilysin inhibitor combined with an angiotensin receptor blocker rather than given alone?

1. Because neprilysin inhibitors are too short-acting to be used as monotherapy
2. Because neprilysin also degrades angiotensin II, so inhibiting it causes angiotensin II to accumulate
3. Because the angiotensin receptor blocker is needed to make the neprilysin inhibitor absorbable
4. Because neprilysin inhibition alone causes severe hypokalaemia

1. Explanation: Neprilysin breaks down angiotensin II as well as natriuretic peptides. Inhibiting the enzyme therefore causes an accumulation of angiotensin II, so a neprilysin inhibitor cannot be used alone and is combined with an angiotensin receptor blocker to block the effect of that excess. [1]

2. Question: What washout period is required when switching between an ACE inhibitor and sacubitril-valsartan?

1. 6 hours
2. 12 hours
3. 36 hours
4. 7 days

2. Explanation: A 36-hour washout is required when switching between an ACE inhibitor and sacubitril-valsartan, and the labelling states the drug must not be administered within 36 hours of switching from or to an ACE inhibitor. The reason is bradykinin: both drugs reduce its breakdown, and overlapping them raises the risk of angio-oedema. [1][2]

3. Question: What does inhibiting neprilysin do to the natriuretic peptide system?

1. It blocks natriuretic peptide receptors, reducing natriuresis
2. It prevents breakdown of natriuretic peptides, prolonging vasodilation, natriuresis and diuresis
3. It increases synthesis of natriuretic peptides in the atria
4. It converts natriuretic peptides into angiotensin II

3. Explanation: The enzyme neprilysin degrades natriuretic peptides. Blocking it prevents that breakdown and prolongs their favourable effects - vasodilation, natriuresis and diuresis, with lower blood pressure, lower sympathetic tone and reduced aldosterone. That system functions antagonistically to the renin-angiotensin-aldosterone system. [1]

4. Question: Which of the following is an absolute contraindication to sacubitril-valsartan?

1. A history of angio-oedema related to previous ACE inhibitor or ARB therapy
2. A resting heart rate below 60 beats per minute
3. Concurrent treatment with a beta blocker
4. New York Heart Association class II symptoms

4. Explanation: The drug is contraindicated in patients with hypersensitivity to any component, in patients with a history of angio-oedema related to previous ACE inhibitor or ARB therapy, with concomitant use of an ACE inhibitor, and with concomitant aliskiren in patients with diabetes. Beta blockers are in fact part of the standard therapy it is used alongside. [2][1]

5. Question: In PARADIGM-HF, how did sacubitril-valsartan compare with enalapril on adverse effects?

1. More hyperkalaemia and more cough, but less hypotension
2. More hypotension, but lower risk of raised potassium or creatinine and less cough
3. Identical rates of every adverse effect measured
4. Less hypotension and less angio-oedema, with no other differences

5. Explanation: Compared with enalapril, sacubitril-valsartan was associated with a higher incidence of hypotension and symptomatic hypotension, and a lower risk of elevated serum potassium or serum creatinine as well as a lower risk of cough. More patients experienced angio-oedema in the sacubitril-valsartan arm, although that difference was not statistically significant. [1]

6. Question: Which statement about starting sacubitril-valsartan is correct?

1. It is started first-line before any renin-angiotensin blockade is attempted
2. Patients should be able to tolerate an ACE inhibitor or an ARB before it is initiated
3. It is only started once an ACE inhibitor has caused angio-oedema
4. It requires prior treatment with a mineralocorticoid receptor antagonist

6. Explanation: The guideline position is that patients should be able to tolerate an ACE inhibitor or an ARB before sacubitril-valsartan is initiated, and the drug is then used instead of that agent alongside other standard heart failure treatments such as a beta blocker or an aldosterone antagonist. Previous angio-oedema on an ACE inhibitor or ARB is a contraindication, not an indication. [1][2]

7. Question: Why does combining an ARNI with an ACE inhibitor raise the risk of angio-oedema?

1. Both drugs directly activate mast cells
2. Both reduce bradykinin breakdown, so kinin accumulation is compounded
3. The combination causes an immune complex reaction in the airway
4. The ACE inhibitor prevents conversion of sacubitril to its active form

7. Explanation: Bradykinin is another substance broken down by neprilysin, so inhibiting neprilysin causes bradykinin to build up. An ACE inhibitor blocks a second route of bradykinin degradation. Using them together, or too close in time, therefore compounds kinin accumulation and increases the risk of angio-oedema. [1][4]

Frequently asked questions

1. Question: What does neprilysin actually do?

1. Answer: It degrades natriuretic peptides, which is why blocking it prolongs their vasodilating, natriuretic and diuretic effects. It also degrades angiotensin II and bradykinin, and those two additional substrates are the reason the drug is a combination and the reason it cannot overlap with an ACE inhibitor. [1]

2. Question: Why is a 36-hour gap needed when switching from an ACE inhibitor?

2. Answer: Both drugs slow the breakdown of bradykinin - the ACE inhibitor through angiotensin-converting enzyme, the ARNI through neprilysin. Overlapping them compounds kinin accumulation and raises the risk of angio-oedema, so a 36-hour washout separates them, in either direction of switch. [1][2]

3. Question: Is an ARNI added to existing renin-angiotensin blockade?

3. Answer: No - it replaces it. The drug is used instead of an ACE inhibitor or an ARB, alongside the rest of standard heart failure treatment such as a beta blocker or an aldosterone antagonist. Adding a separate ARB is avoided because the product already contains valsartan. [1]

4. Question: Who cannot be given this class at all?

4. Answer: Anyone with hypersensitivity to a component, anyone with a history of angio-oedema on a previous ACE inhibitor or ARB, anyone with hereditary angio-oedema, anyone currently on an ACE inhibitor or within 36 hours of one, anyone with diabetes taking aliskiren, and anyone who is pregnant. [2]

5. Question: What is monitored during treatment?

5. Answer: Blood pressure, because symptomatic hypotension is the most consistently increased adverse effect; serum creatinine, because renal function can fall in patients who depend on renin-angiotensin activity; and serum potassium, because hyperkalaemia follows from the same mechanism. [2][1]

6. Question: Does an ARNI cause less cough than an ACE inhibitor?

6. Answer: Yes. In the comparative trial against enalapril, sacubitril-valsartan carried a lower risk of cough, along with a lower risk of raised serum potassium or creatinine - the trade-off being a higher incidence of hypotension. [1]

References

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