



# THE BURDEN OF RECURRENT PERICARDITIS

Current challenges in disease management

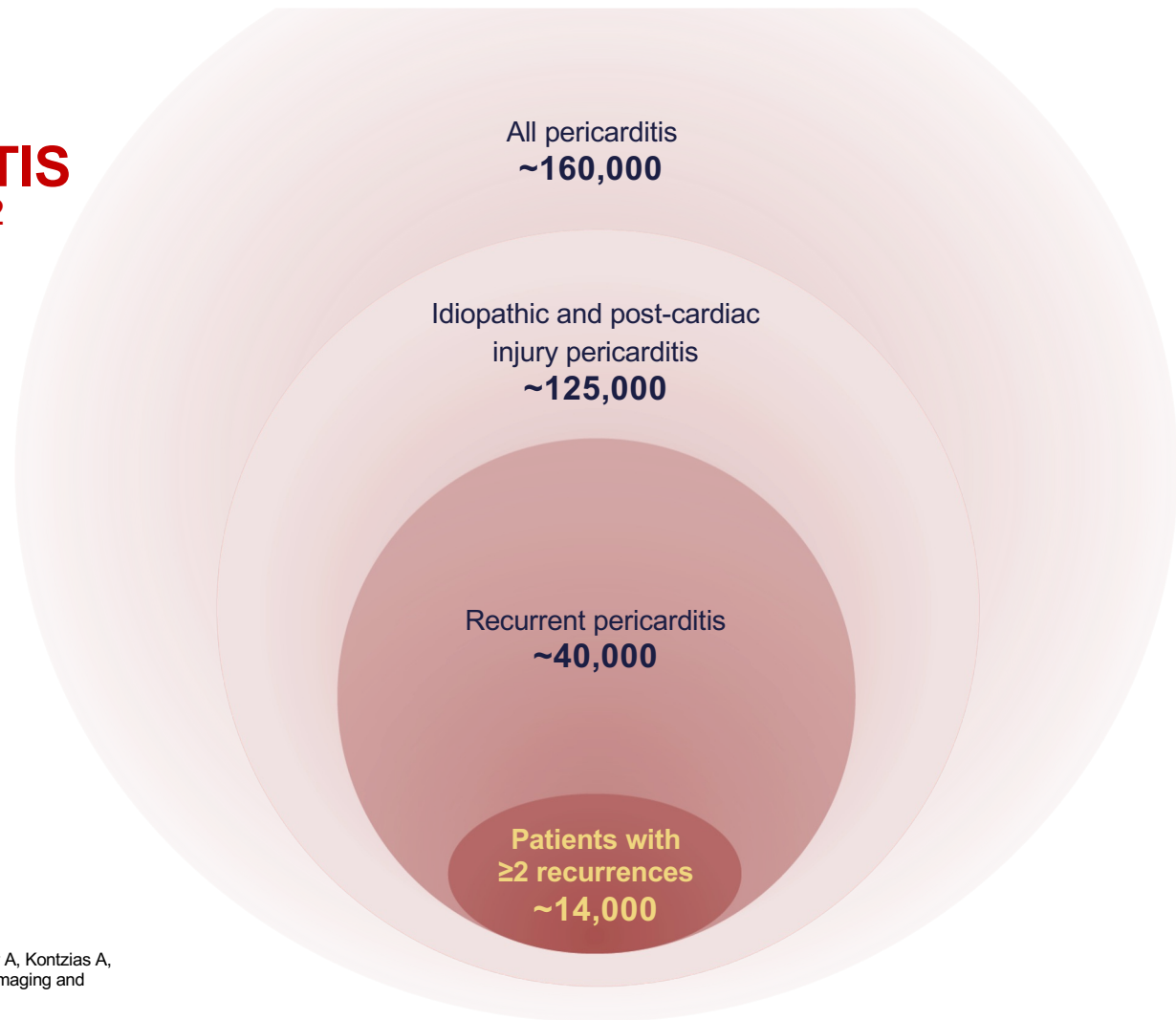
# TODAY'S PROGRAM

- OVERVIEW OF RECURRENT PERICARDITIS
- CHALLENGES WITH DIAGNOSIS
- FIRST-EPIISODE PERICARDITIS VS RECURRENT PERICARDITIS
- THE CHANGING TREATMENT PARADIGM



# EPIDEMIOLOGY OF RECURRENT PERICARDITIS IN THE UNITED STATES<sup>1,2</sup>

- **Up to 30% of individuals** with an initial episode of pericarditis will experience a recurrence within 18 months
- **Approximately 40,000 patients** in the United States seek treatment for recurrent pericarditis annually
- **An estimated 14,000 individuals** have 2 or more recurrences
  - There is estimated to be a nearly 50% turnover in this population annually, with approximately 7000 patients coming in and out of the pool each year



**References:** 1. Data on file #1. Kiniksa Pharmaceuticals (UK), Ltd. 2. Cremer PC, Kumar A, Kontzias A, et al. Complicated pericarditis: understanding risk factors and pathophysiology to inform imaging and treatment. *J Am Coll Cardiol.* 2016;68(21):2311-2328.

# PATIENT CHALLENGES ARE MORE THAN JUST PHYSICAL

**Patients living with recurrent pericarditis may face many challenges, including<sup>1,2</sup>:**

- Chest pain
- Anxiety
- Inability to perform physical activities
- Fatigue
- Depression
- Missed work time

**Patients not currently experiencing a flare reported living in fear of their next one.<sup>1\*</sup>**

- Nearly all (95%) reported living in fear of their next recurrence, with more than 50% reporting that it negatively impacts their lifestyle

\*A survey of 83 adult patients with recurrent pericarditis, 75% of whom were not experiencing a recurrence at that time.

**References:** 1. LeWinter M, Kontzias A, Lin D, et al. Burden of recurrent pericarditis on health-related quality of life. *Am J Cardiol.* 2021;141:113-119. doi:10.1016/j.amjcard.2020.11.018 2. Pericarditis. Cleveland Clinic website. May 3, 2019. Accessed October 27, 2021. <https://my.clevelandclinic.org/health/diseases/17353-pericarditis>



“  
The biggest challenge for me with [recurrent] pericarditis is not knowing when it’s going to come on.”

Jill, 50  
Person living with recurrent pericarditis.

# RECURRENT PERICARDITIS IMPACTS HEALTH-RELATED QUALITY OF LIFE

## Impaired physical functioning and mental well-being, and reduced sleep quality<sup>1</sup>

- Mean T-score for PROMIS Physical Health (37.6) and PROMIS Mental Health (42.8) were considerably lower than US general population (mean=50.0, SD=10)
- Patient-reported sleep disturbance was greater [worse] in recurrent pericarditis than in scores previously reported by other patients for chronic pain, multiple sclerosis, and spinal cord injury

## Patients report fear, anxiety, and depression<sup>1</sup>

- Unknown cause and unpredictability of recurrent pericarditis episodes are among the most bothersome aspects of the disease
- 95% of respondents reported fear of their next flare
- More than one third reported depression and anxiety

## Restricts activities of daily living

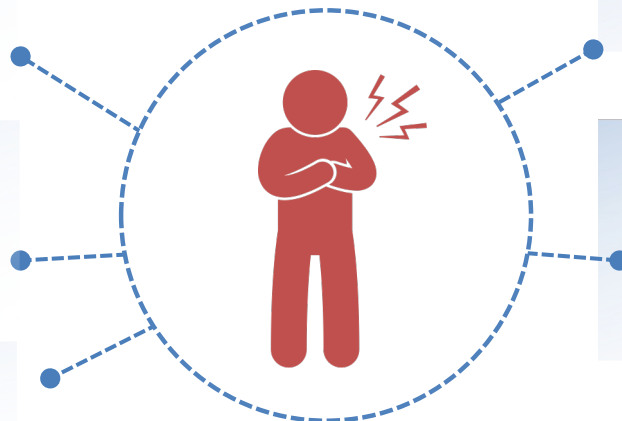
- Impact on daily activities and ability to work<sup>1</sup>
- Clinical guidelines recommend exercise restriction in athletes and non-athletes until resolution of pericarditis<sup>2</sup>

## Flares often result in hospitalizations, ER visits, outpatient visits, procedures, and pharmacotherapy<sup>3</sup>

- Patients with  $\geq 2$  recurrences had 74% higher healthcare costs than patients with 1 episode
- Overall healthcare costs driven by higher hospitalization rates

## Indirect costs include absenteeism and impaired work productivity

- More than 50% of patients with recurrent pericarditis report overall work impairment<sup>1</sup>
- Patients with  $\geq 2$  recurrences had 4 times greater work loss costs than patients with a single episode<sup>3</sup>



ER, emergency room; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, standard deviation; US, United States.

**References:** 1. LeWinter M, Kontzias A, Lin D, et al. Burden of recurrent pericarditis on health-related quality of life. *Am J Cardiol.* 2021;141:113-119. doi:10.1016/j.amjcard.2020.11.018 2. Adler Y, Charron P, Imazio M, et al. 2015 ESC guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC). *Eur Heart J.* 2015;36(42):2921-2964. 3. Lin D, Laliberté F, Majeski C, et al. Disease and economic burden associated with recurrent pericarditis in a privately insured United States population. *Adv Ther.* 2021;38(10):5127-5143. doi:10.1007/s12325-021-01868-7

# RISK FACTORS FOR DEVELOPMENT OF RECURRENT PERICARDITIS



## Inadequate treatment of the first episode<sup>1,2</sup>

- Rapid tapering of anti-inflammatory therapy
- Early use of corticosteroids (rapid tapering or use of short courses of high-dose corticosteroids)

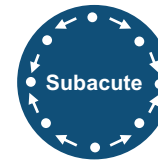


## Idiopathic etiology<sup>1,3</sup>

- Presumed to be the result of an underlying autoinflammatory pathophysiology driven by interleukin-1 (IL-1)



## Incomplete response to anti-inflammatory therapy<sup>1</sup>



## Subacute presentation<sup>4</sup>



## Persistently elevated high-sensitivity C-reactive protein (CRP)<sup>2</sup>



## Younger age<sup>4</sup>

**References:** 1. Chiabrando JG, Bonaventura A, Vecchié A et al. Management of acute and recurrent pericarditis. *J Am Coll Cardiol.* 2020;75:76-92. 2. Cremer PC, Kumar A, Kontzias A, et al. Complicated pericarditis: understanding risk factors and pathophysiology to inform imaging and treatment. *J Am Coll Cardiol.* 2016;68(21):2311-2328. 3. Vecchié A, Chiabrando JG, Dell MS, et al. Clinical presentation and outcomes of acute pericarditis in a large urban hospital in the United States of America. *Chest.* 2020;158(6):2556-2567. 4. Del Buono MG, Vecchié A, Damonte JI, et al. Pericarditis recurrence after initial uncomplicated clinical course. *Am J Cardiol.* 2021;160:112-116.

# ESC GUIDELINES ON DIAGNOSTIC CRITERIA FOR PERICARDITIS<sup>1</sup>

- Based on the 2015 European Society of Cardiology (ESC) guidelines, a clinical diagnosis of a first episode of pericarditis can be made with 2 of the following criteria:
  - Pericardial chest pain
  - Pericardial rubs
  - New widespread ST elevation or PR depression on ECG
  - Pericardial effusion (new or worsening)
- Diagnosis of a recurrence is established according to the same criteria as those above
  - Recurrent pericarditis may be diagnosed after a documented first episode of pericarditis and a symptom-free period of 4 to 6 weeks

ECG, electrocardiogram.

**Reference:** 1. Adler Y, Charron P, Imazio M, et al. 2015 ESC guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC). *Eur Heart J.* 2015;36(42):2921-2964.

# RECURRENT PERICARDITIS CAN BE CHALLENGING TO DIAGNOSE

- Clinical presentation **may not meet the established diagnostic criteria**<sup>1</sup>

- Pericardial chest pain may be the only clinical finding
- May lead to delay in diagnosis and care

A recent study found that  
**~50% of patients** had a less  
clear presentation of recurrence<sup>1\*</sup>

- When diagnosis of recurrent pericarditis is not clear, **additional tests may be done to lessen the uncertainty and time to diagnosis**<sup>2</sup>

- Support for diagnosis of pericarditis includes:

- Elevated markers of inflammation such as **CRP**, erythrocyte sedimentation rate (ESR), and white blood cell count
- Evidence of pericardial inflammation and neo-vessel formation using imaging techniques such as **computed tomography (CT), cardiac magnetic resonance (CMR), and late gadolinium enhancement**

\*A pericardial expert (Dr Allan Klein) adjudicated if a patient was having a recurrence based on expert judgment. Patients were only adjudicated as having a recurrence if they also required an increased dose or additional anti-inflammatory agent to treat an ongoing recurrence (N=67).

**References:** 1. Kumar A, Sato K, Verma BR, et al. Quantitative assessment of pericardial delayed hyperenhancement helps identify patients with ongoing recurrences of pericarditis. *Open Heart*. 2018;5(2):e000944. 2. Adler Y, Charron P, Imazio M, et al. 2015 ESC guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC). *Eur Heart J*. 2015;36(42):2921-2964.



# RECURRENT PERICARDITIS AND A FIRST EPISODE ARE DISTINCT, WITH DIFFERENT TREATMENT NEEDS

Recurrent pericarditis and a single or first episode differ in:

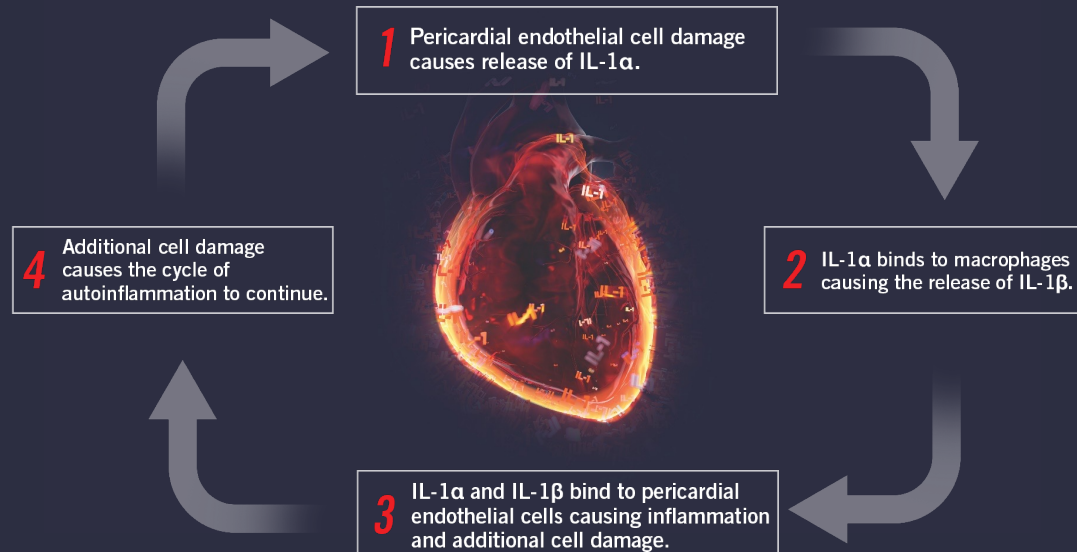
- Pathophysiology<sup>1</sup>
- Duration of disease<sup>1,2</sup>
- Risk of additional recurrences<sup>3</sup>
- Risk of serious complications<sup>3</sup>

**References:** 1. Chiabrando JG, Bonaventura A, Vecchie A, et al. Management of acute and recurrent pericarditis. *J Am Coll Cardiol.* 2020;75(1):76-92. 2. Lin D, Laliberté F, Majeski C, et al. Disease and economic burden associated with recurrent pericarditis in a privately insured United States population. *Adv Ther.* 2021;38(10):5127-5143. doi:10.1007/s12325-021-01868-7 3. Klein A, Cremer P, Kontzias A, et al. US database study of clinical burden and unmet need in recurrent pericarditis. *J Am Heart Assoc.* 2021;10:e018950. doi:10.1161/JAHA.120.018950



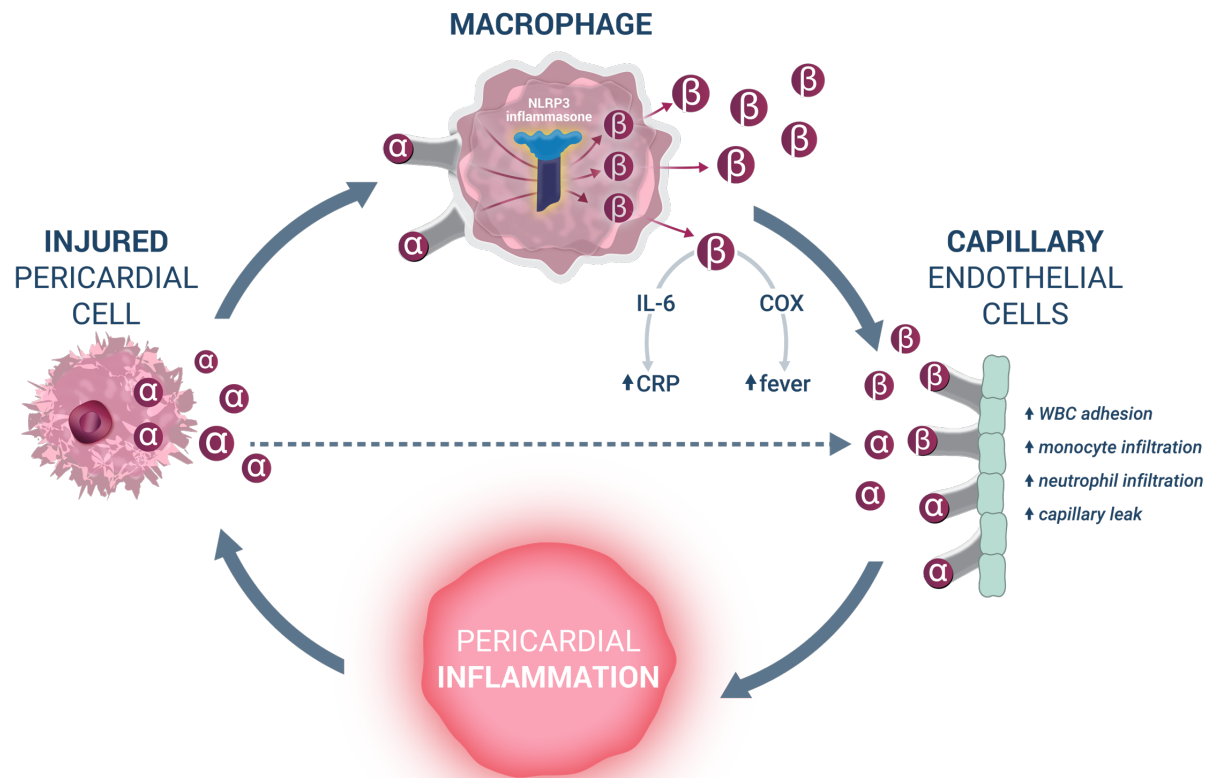
# RECURRENT PERICARDITIS IS DRIVEN BY AN UNCONTROLLED CYCLE OF INTERLEUKIN-1 (IL-1)–MEDIATED AUTOINFLAMMATION

While the etiology of single- or first-episode pericarditis may be caused by several factors, including viral illness and post-cardiac injury, the pathogenesis of recurrent pericarditis is a self-perpetuating cycle of IL-1–mediated autoinflammation<sup>1,2</sup>



**References:** 1. Chiabrando JG, Bonaventura A, Vecchié A, et al. Management of acute and recurrent pericarditis. *J Am Coll Cardiol.* 2020;75(1):76-92. 2. Dinarello CA, Simon A, van der Meer JWM. Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. *Nat Rev Drug Discov.* 2012;11(8):633-652. doi:10.1038/nrd3800

# THE SELF-PERPETUATING CYCLE OF IL-1-MEDIATED AUTOINFLAMMATION IN RECURRENT PERICARDITIS<sup>1-3</sup>



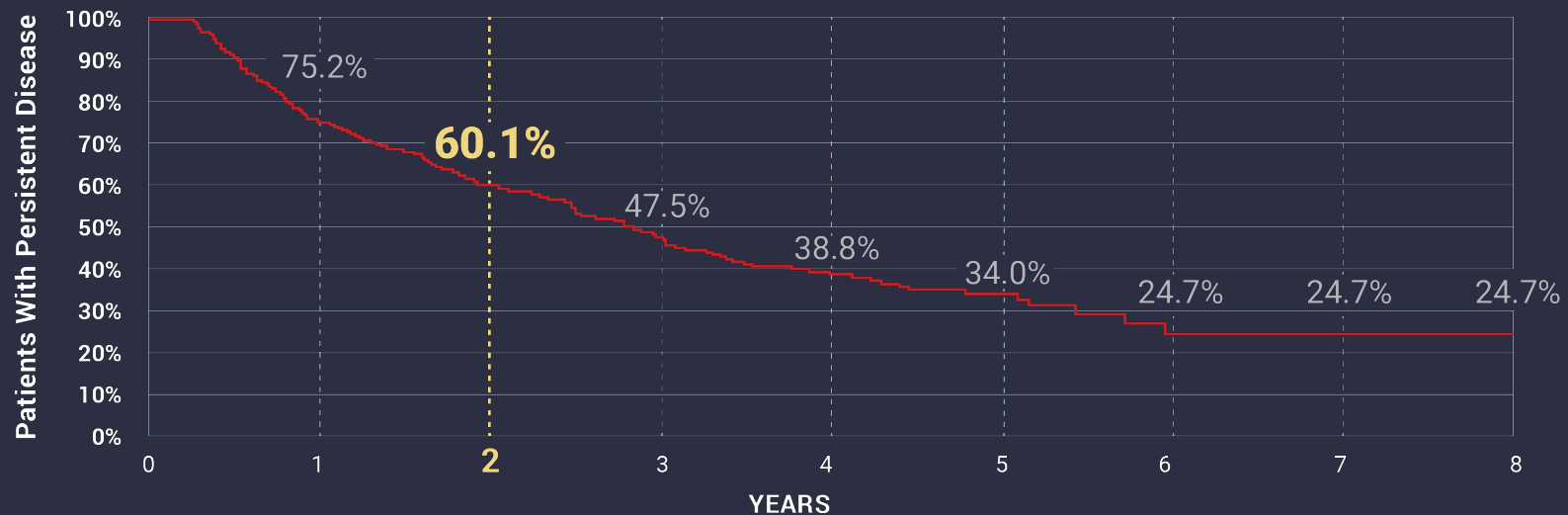
COX, cyclooxygenase; CRP, C-reactive protein; NLRP3, NLR family pyrin domain-containing 3; WBC, white blood cell.

**References:** 1. Dinarello CA, Simon A, van der Meer JWM. Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. *Nat Rev Drug Discov.* 2012;11(8): 633-652. doi:10.1038/nrd3800 2. Brucato A, Emmi G, Cantarini L, et al. Management of idiopathic recurrent pericarditis in adults and in children: a role for IL-1 receptor antagonism. *Intern Emerg Med.* 2018;13:475-489. <https://doi.org/10.1007/s11739-018-1842-x> 3. Ridker PM. From C-reactive protein to interleukin-6 to interleukin-1: moving upstream to identify novel targets for atheroprotection. *Circ Res.* 2016;118(1):145-156. doi:10.1161/CIRCRESAHA.115.306656

# RECURRENT PERICARDITIS IS ASSOCIATED WITH LONGER DURATION OF DISEASE

While the duration of single- or first-episode pericarditis lasts up to 4 to 6 weeks, for those with  $\geq 2$  recurrences, this disease may last for years<sup>1,2</sup>

60% of patients with  $\geq 2$  recurrences suffer for at least 2 years<sup>2</sup>



Data from Optum Health Care Solutions, Inc., collected from January 1, 2007, through March 31, 2017, were analyzed for this observational study (N=375 patients with  $\geq 2$  recurrences of recurrent pericarditis).

**References:** 1. Chiabrando JG, Bonaventura A, Vecchié A, et al. Management of acute and recurrent pericarditis. *J Am Coll Cardiol.* 2020;75(1):76-92. 2. Lin D, Laliberté F, Majeski C, et al. Disease and economic burden associated with recurrent pericarditis in a privately insured United States population. *Adv Ther.* 2021;38(10):5127-5143. doi:10.1007/s12325-021-01868-7

# WITH EACH EPISODE OF PERICARDITIS, THE RISK OF ADDITIONAL EPISODES INCREASES<sup>1</sup>

## RISK OF RECURRENCE

Risk of recurrence **nearly doubles** after the first recurrence

AFTER THE 1st EPISODE

**28%**

(2096 of 7502 patients)

AFTER 1st RECURRENCE

**47%**

(994 of 2096 patients)

AFTER 2nd RECURRENCE

**54%**

(541 of 994 patients)

With multiple events, **risk of recurrence increases** while **time to recurrence decreases**.

Data from the PharMetrics Plus database, collected between January 1, 2013, and March 31, 2018, were used for this retrospective analysis (N=7502 patients with pericarditis, 2096 of whom experienced ≥1 recurrence).

**Reference:** 1. Klein A, Cremer P, Kontzias A, et al. US database study of clinical burden and unmet need in recurrent pericarditis. *J Am Heart Assoc.* 2021;10:e018950. doi:10.1161/JAHA.120.018950

# RISK OF SERIOUS COMPLICATIONS IS 2 TO 3 TIMES HIGHER IN PATIENTS WITH RECURRENT PERICARDITIS<sup>1</sup>

COMPLICATION	FIRST EPISODE OF PERICARDITIS (n=7502)	RECURRENT PERICARDITIS (n=2096)	LEVEL OF RISK
Pericardial effusion, %	18.1	49.7	~3x greater
Cardiac tamponade, %	5.1	8.9	~2x greater
Constrictive pericarditis, %	1.7	3.9	~2x greater

Data from the PharMetrics Plus database, collected between January 1, 2013, and March 31, 2018, were used for this retrospective analysis (N=7502 patients with pericarditis, 2096 of whom experienced ≥1 recurrence).

**Reference:** 1. Klein A, Cremer P, Kontzias A, et al. US database study of clinical burden and unmet need in recurrent pericarditis. *J Am Heart Assoc.* 2021;10:e018950. doi:10.1161/JAHA.120.018950

# POTENTIAL LIMITATIONS WITH TRADITIONAL THERAPIES PRESCRIBED FOR RECURRENT PERICARDITIS

## Traditional therapies<sup>1-4</sup>:

- Have insufficient efficacy and patients continue to suffer from recurrences despite treatment (eg, patients treated with colchicine have about 25% risk of recurrence)
- Do not target the IL-1–mediated cycle of autoinflammation specifically
- Are associated with AEs that can make them suboptimal for long-term treatment
  - Strategies to lessen AEs may unmask the underlying IL-1–driven disease and result in recurrence

Treatment Option(s)	Mode of Action	Possible AEs*
NSAIDs <sup>1,5,6</sup>	Nonspecifically reduce pain and inflammation	<ul style="list-style-type: none"> <li>• Gastrointestinal (GI) disturbances</li> <li>• Potential for serious GI bleeding</li> <li>• Heart attack</li> <li>• Stroke</li> </ul>
Colchicine <sup>1,5</sup>	Blocks tubulin polymerization, nonspecifically disrupting several functions in immune cells	<ul style="list-style-type: none"> <li>• GI disturbances are a major cause of dose reduction. They include:               <ul style="list-style-type: none"> <li>– Diarrhea (often dose-limiting)</li> <li>– Nausea</li> <li>– Cramping</li> <li>– Abdominal pain</li> <li>– Vomiting</li> </ul> </li> </ul>
Corticosteroids <sup>1,5</sup>	Nonspecifically reduce inflammation	<ul style="list-style-type: none"> <li>• Mood change</li> <li>• Mental health problems</li> <li>• Fatty deposits in the face (moon face)</li> <li>• Osteoporosis</li> <li>• Acne</li> <li>• Diabetes</li> </ul>

\*Not a complete list of possible AEs across drug class.

**References:** 1. Klein A, Cremer P, Kontzias A, et al. Clinical burden and unmet need in recurrent pericarditis: a systematic literature review. *Cardiol Rev.* 2022;30(2):59-69. doi:10.1097/CRD.0000000000000356 2. Imazio M, Brucato A, Cemin R, et al; CORP (Colchicine for Recurrent Pericarditis) Investigators. Colchicine for recurrent pericarditis (CORP): a randomized trial. *Ann Intern Med.* 2011;155(7):409-414. doi:10.7326/0003-4819-155-7-201110040-00359 3. Chiabrando JG, Bonaventura A, Vecchié A, et al. Management of acute and recurrent pericarditis. *J Am Coll Cardiol.* 2020;75(1):76-92. 4. Vecchié A, Del Buono MG, Mauro AG, et al. Advances in pharmacotherapy for acute and recurrent pericarditis. *Expert Opin Pharmacother.* 2022;23(6):681-691. 5. Imazio M, Lazaros G, Brucato A, Gaita F. Recurrent pericarditis: new and emerging therapeutic options. *Nat Rev Cardiol.* 2016;13(3):99-105. 6. FDA Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes. US Food and Drug Administration. July 9, 2015. Updated February 26, 2018. Accessed December 6, 2022. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-strengthens-warning-non-aspirin-nonsteroidal-anti-inflammatory>

# EMERGING EVIDENCE SUGGESTS THAT RECURRENT PERICARDITIS REQUIRES A NEW TREATMENT PARADIGM<sup>1,2</sup>

## Historical treatment approach:

Reliance on therapies with broad anti-inflammatory actions associated with adverse events (AEs)

Premature cessation of therapy to minimize AEs may unmask the underlying autoinflammatory process and result in a recurrence

New understanding of pathophysiology drives a culture shift

## Emerging approach:

Specifically targeting the IL-1 pathway could represent a new paradigm for breaking the cycle of autoinflammation and treating recurrent pericarditis:

- With the goal to relieve pain, reduce inflammation, and prevent recurrences

**References:** 1. Vecchié A, Del Buono MG, Mauro AG, et al. Advances in pharmacotherapy for acute and recurrent pericarditis. *Expert Opin Pharmacother.* 2022;23(6):681-691. 2. Lin D, Laliberté F, Majeski C, et al. Disease and economic burden associated with recurrent pericarditis in a privately insured United States population. *Adv Ther.* 2021;38(10):5127-5143. doi:10.1007/s12325-021-01868-7



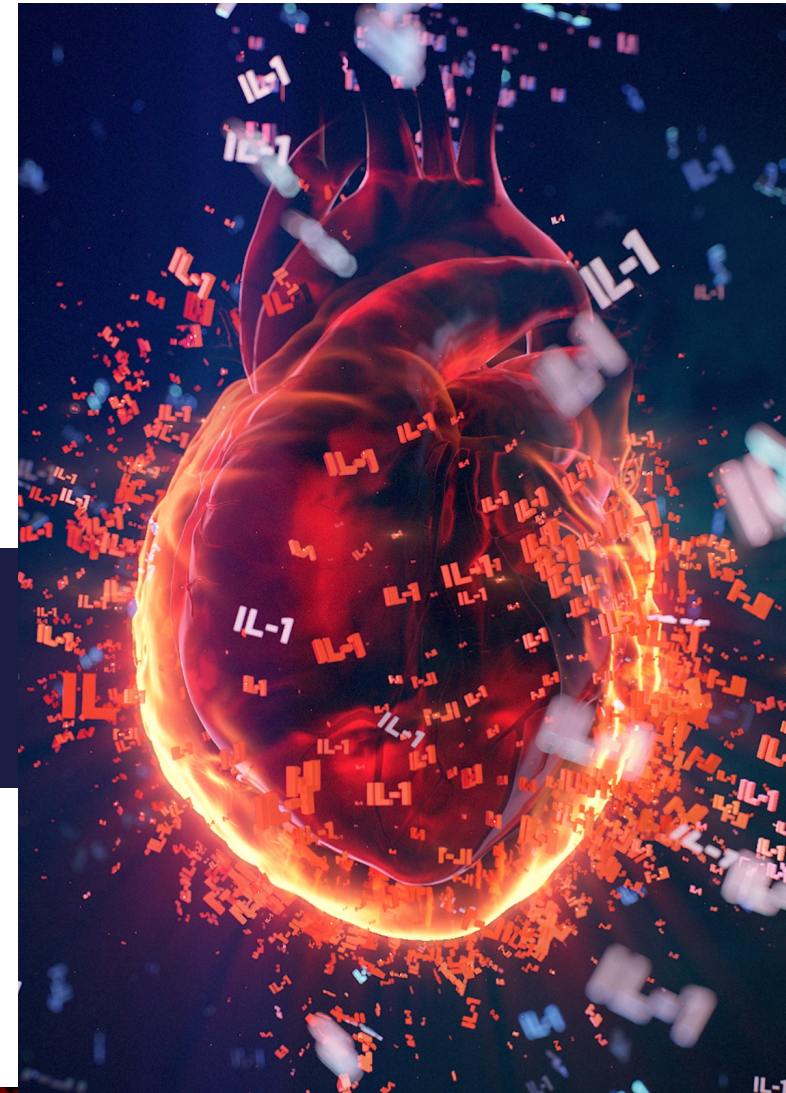
## SUMMARY

- Approximately 40,000 patients in the United States seek treatment for recurrent pericarditis annually, with about 14,000 patients suffering from  $\geq 2$  recurrences<sup>1</sup>
- Diagnosing recurrences is challenging, and delay in diagnosis may lead to increased patient morbidity<sup>2</sup>
- A first episode and recurrent pericarditis are distinct, necessitating a different treatment approach<sup>3-5</sup>
- Recurrent pericarditis is driven by an ongoing cycle of IL-1-mediated autoinflammation<sup>4,6</sup>

Specifically targeting the IL-1 pathway could represent a new paradigm for breaking the cycle of autoinflammation and treating recurrent pericarditis<sup>4,6</sup>:

- With the goal to relieve pain, reduce inflammation, and prevent recurrences

**References:** 1. Data on file #1. Kiniksa Pharmaceuticals (UK), Ltd. 2. Kumar A, Sato K, Verma BR, et al. Quantitative assessment of pericardial delayed hyperenhancement helps identify patients with ongoing recurrences of pericarditis. *Open Heart*. 2018;5(2):e000944. 3. Chiabrando JG, Bonaventura A, Vecchié A, et al. Management of acute and recurrent pericarditis. *J Am Coll Cardiol*. 2020;75(1):76-92. 4. Lin D, Laliberté F, Majeski C, et al. Disease and economic burden associated with recurrent pericarditis in a privately insured United States population. *Adv Ther*. 2021;38(10):5127-5143. doi:10.1007/s12325-021-01868-7 5. Dinarello CA, Simon A, van der Meer JWM. Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. *Nat Rev Drug Discov*. 2012;11(8):633-652. doi:10.1038/nrd3800 6. Vecchié A, Del Buono MG, Mauro AG, et al. Advances in pharmacotherapy for acute and recurrent pericarditis. *Expert Opin Pharmacother*. 2022;23(6):681-691.





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