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DIFFERENTIATING EXERCISE-INDUCED CARDIAC BIOMARKER ELEVATION FROM ACUTE CORONARY SYNDROME: A LITERATURE REVIEW ON RELEASE KINETICS AND WASHOUT DURATION

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ABSTRACT

Background: Cardiac troponin elevation after strenuous exercise can mimic the biochemical profile of acute coronary syndrome (ACS), risking misdiagnosis in athletes and active individuals presenting to the emergency department. This review synthesises 31 sources to establish an evidence base on release kinetics and washout duration of cardiac biomarkers after exercise relative to ACS.

Methods: A narrative synthesis was performed on publications from Circulation, the Journal of the American College of Cardiology, the European Heart Journal, Clinical Chemistry, the Journal of the American Heart Association, the American Journal of Physiology, and BMJ Open Sport & Exercise Medicine, focusing on release mechanisms, modifying factors, differential diagnosis, and clinical management.

Results: Troponin elevation above the 99th-percentile upper reference limit (URL) was observed in approximately 36% of individuals after exercise overall, rising to 57–93% with high-sensitivity assays after endurance exercise lasting 3–6 hours. The kinetic pattern is characteristic: concentrations peak at 2–6 hours and return toward baseline within 24–72 hours, contrasting with ACS, which peaks at 10–24 hours and remains elevated for 4–10 days. Cardiovascular magnetic resonance evidence consistently shows no late gadolinium enhancement after exercise, supporting reversible membrane leakage rather than irreversible necrosis. The relationship between post-exercise troponin elevation and subclinical coronary artery disease remains inconsistent across studies.

Conclusion: Differentiating exercise-induced biomarker elevation from ACS requires integrating clinical history, electrocardiography, serial kinetic patterns, and imaging, rather than a single value above the URL. Athlete-specific reference values, standardised sampling protocols, and long-term cohort studies remain key research gaps.

Keywords: Cardiac Troponin; Exercise; Acute Coronary Syndrome; Biomarker Kinetics; Myocardial Injury

1 INTRODUCTION

Public participation in high-intensity endurance sport continues to grow, as reflected in the rise in marathon finishers in the United States from approximately 25,000 in 1976 to nearly 470,000 in 2008 [1]. This growth in participation has been accompanied by a parallel risk of acute cardiovascular events, including sudden cardiac arrest, which is estimated to occur in six to eight marathon runners annually in the United States as a result of the combination of occult cardiac disease and superimposed physical and environmental stress [1].

A far more frequently encountered, yet clinically confusing, phenomenon is the rise in cardiac troponin concentration observed in otherwise healthy individuals after strenuous physical activity, in the absence of true myocardial infarction. A meta-analysis of 45 studies by Sedaghat-Hamedani et al. found that troponin T (cTnT) exceeded the diagnostic cut-off in 51% of participants after endurance exercise, with mean increases of +40 ng/L for troponin I (cTnI) and +26 ng/L for high-sensitivity troponin T (hs-cTnT) from baseline [2]. A recent clinical review further reported that 74–96% of marathon finishers exhibit high-sensitivity troponin concentrations above the 99th-percentile upper reference limit (URL) [3]. Should such individuals present to the emergency department with symptoms resembling angina—whether coincidental or related to post-race fatigue—this elevated biomarker profile risks being misinterpreted as acute coronary syndrome (ACS), prompting unnecessary hospitalisation or invasive catheterisation, or conversely, masking genuine ischaemia in individuals with subclinical coronary artery disease (CAD) who happen to engage in strenuous exercise [4,5].

This issue has become increasingly salient since cardiac troponin, whether cTnI or cTnT, was established as the gold-standard biomarker for diagnosing acute myocardial infarction (AMI) under the Universal Definition of Myocardial Infarction, superseding creatine kinase-MB (CK-MB), which has a narrower diagnostic window and lower specificity in the context of skeletal muscle injury [6,7]. The Fourth Universal Definition of Myocardial Infarction explicitly requires a rise and/or fall pattern in troponin concentration, with at least one value above the 99th-percentile URL, accompanied by clinical evidence of acute myocardial ischaemia, as the criterion for infarction; troponin elevation without evidence of ischaemia is instead classified as myocardial injury alone [7]. This ambiguity lies at the heart of the clinical dilemma in athletes: troponin can rise sharply after exercise without accompanying ischaemia, yet the pattern of elevation may superficially overlap with mild-to-moderate ACS, particularly in the era of high-sensitivity assays capable of detecting picogram-per-millilitre concentrations [8,9].

This literature review was undertaken to address this gap in understanding, focusing on three principal themes: (1) the physiological mechanisms and kinetics of biomarker release—specifically troponin I/T and CK-MB—within the framework of physiological strain versus pathological necrosis; (2) differential-diagnosis patterns based on washout kinetics distinguishing exercise-induced elevation from ACS; and (3) clinical management, triage, and return-to-play (clearance) approaches. By synthesising onset, peak time, and washout duration data across study designs—ranging from field studies following marathon completion and controlled laboratory exercise trials to international consensus guidelines—this review aims to provide a practical framework for clinicians to distinguish benign, reversible biomarker elevation from genuine myocardial injury.

2 MATERIALS AND METHODS

This review is narrative in design and was constructed from 31 unique literature sources (out of 32 files screened, one of which was a duplicate) identified from the materials provided, encompassing original research, prospective cohort studies, controlled laboratory trials, meta-analyses, systematic reviews, and consensus documents or guidelines from international cardiology and clinical chemistry professional bodies (Figure 1). Sources were prioritised according to relevance to the three core themes outlined above and methodological quality, with emphasis placed on publications in *Circulation*, the *Journal of the American College of Cardiology*, the *European Heart Journal*, *Clinical Chemistry*, the *Journal of the American Heart Association*, the *American Journal of Physiology-Heart and Circulatory Physiology*, the *Journal of Applied Physiology*, and *BMJ Open Sport & Exercise Medicine*. Of the 31 sources, 25 were reviewed as full text, whereas the remaining six (references 10–15, corresponding to Aakre & Omland, Laugaudin et al., Serrano-Ostáriz et al., Skadberg et al., Valenzuela et al., and Sharma et al.) were available only as structured abstracts, such that synthesis of these sources was limited to the information contained therein. Synthesis was performed critically and comparatively, rather than as a sequential summary of individual studies, with emphasis on points of convergence, divergence, and plausible explanations for discrepant findings across studies.

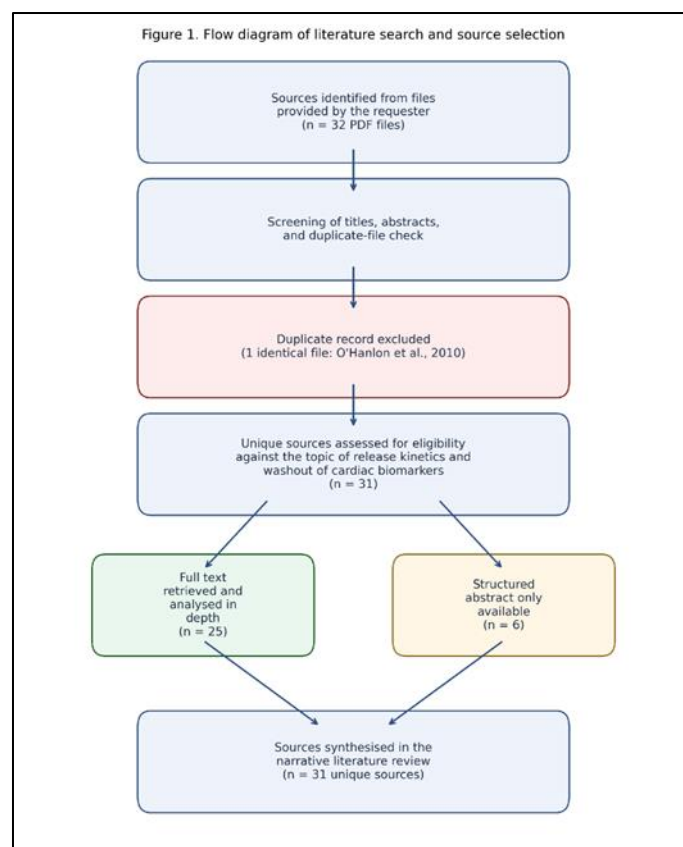


Figure 1: Flow diagram of literature search and source selection for this review.

3 RESULTS AND DISCUSSION

3.1 Definitions and Epidemiology of Exercise-Induced Cardiac Biomarker Elevation versus Acute Coronary Syndrome

The Fourth Universal Definition of Myocardial Infarction defines myocardial injury as a cardiac troponin concentration exceeding the 99th-percentile URL of a healthy reference population, irrespective of the underlying mechanism [7]. Myocardial injury is classified as acute only when a rise and/or fall pattern is observed on serial measurement, and can only be termed myocardial infarction when this pattern is accompanied by clinical evidence of acute ischaemia— ischaemic symptoms, new ischaemic ECG changes, new loss of viable myocardium or new regional wall-motion abnormality on imaging, or identification of an intracoronary thrombus on angiography or autopsy [7]. Type 1 myocardial infarction arises from atherosclerotic plaque rupture or erosion with intracoronary thrombosis, whereas type 2 infarction results from an imbalance between myocardial oxygen supply and demand without acute atherothrombosis, as may occur with severe tachyarrhythmia, anaemia, or vasospasm [7]. This distinction is important because the mechanism of exercise-induced troponin elevation more closely resembles a question of normal physiological limits than either of these two infarction subtypes [16].

The large High-STEACS cohort study, which implemented a high-sensitivity troponin assay in 48,282 patients with suspected ACS, demonstrated that application of this definition increased the diagnosis of type 1 infarction by 11%, type 2 infarction by 22%, and acute and chronic myocardial injury by 36% and 43%, respectively [16]. This finding underscores that increased analytical sensitivity of troponin assays enlarges the proportion of individuals classified as having myocardial injury without true infarction—a phenomenon conceptually paralleling what occurs in the post-exercise context.

3.1.1 Prevalence of Post-Exercise Troponin Elevation

The prevalence of troponin elevation above the URL after exercise varies considerably across studies, depending on sport type, duration, intensity, and the assay employed. A recent meta-analysis and meta-regression of studies on post-exercise troponin elevation reported a pooled prevalence of 36% overall, rising sharply to 57.8% when measured using high-sensitivity assays compared with 26% for conventional assays; troponin T also exceeded the URL more frequently (44.6%) than troponin I (29.8%) [17]. The TREAT cohort study of 1,011 long-distance walkers, cyclists, and runners demonstrated a similar pattern: hs-cTnT concentration rose from a median baseline of 5.8 ng/L to 14.3 ng/L post-

exercise, with 51.3% of participants exceeding the URL, whereas hs-cTnI rose from 2.0 ng/L to 7.4 ng/L with only 15.9% exceeding the URL—confirming that assay choice substantially influences prevalence estimates [18]. The design of this prospective cohort, encompassing reference-value determination, a nested imaging sub-study comparing high and low troponin responders, and long-term outcome follow-up, is detailed in its published protocol [19].

Sedaghat-Hamedani et al. also reported, via their meta-analysis of 45 studies, that other biomarkers rise after strenuous exercise, including B-type natriuretic peptide (BNP, +10 ng/L), N-terminal pro-BNP (NT-proBNP, +67 ng/L), and D-dimer (+262 ng/mL)—a pattern that can clinically mimic the profile of acute pulmonary embolism in addition to ACS, underscoring the need for a broader diagnostic vigilance that extends beyond troponin alone [2].

With respect to sport type, the meta-regression by Stekelenburg et al. showed the highest prevalence in triathlon (49%), followed by cycling (40%) and running (41%), with the lowest prevalence observed in contact sports (6%) and walking (8%) [17]. Exercise duration demonstrated a non-linear relationship with prevalence, peaking at a duration of 3–6 hours (52–55%) before slightly declining at more extreme durations—a pattern consistent with the concept that cumulative cardiac workload, rather than absolute duration alone, is the principal determinant of biomarker release [17,4].

3.1.2 Demographic Characteristics and Epidemiological Significance

Notably, recent meta-regression did not identify age, sex, or training status as significant population-level predictors of troponin-elevation prevalence, although prevalence appeared to peak non-linearly in middle-aged individuals (40–50 years) [17]—an age group that also, epidemiologically, carries an increased prevalence of subclinical CAD, such that this age overlap further compounds the complexity of clinical interpretation (discussed further in Section 3.3.4). The epidemiological significance of this phenomenon lies in the sheer size of the population at risk: with millions of marathon finishers and other mass-participation event entrants annually, even a prevalence of 15–50% troponin elevation above the URL represents a substantial population potentially subject to unwarranted additional cardiac work-up if clinicians do not appreciate the physiological context underlying such findings [3,20].

3.1.3 Summary of Key Source Characteristics

Table 1 summarises the design and population characteristics of several key studies underpinning the synthesis of kinetics and prevalence in this review.

Table 1: Summary of design, population, and key findings from the principal studies synthesised in this review.

Study (Year)	Design	Population/Sample	Exercise Type	Key Findings on Prevalence/Kinetics
Sedaghat-Hamedani et al. [2]	Meta-analysis (45 studies)	Heterogeneous; all endurance studies, 1997–2014	Running, triathlon, cycling	cTnT exceeded cut-off in 51% of participants; hs-cTnT +26 ng/L, cTnI +40 ng/L from baseline
Stekelenburg et al. [17]	Meta-analysis & meta-regression	Pooled post-exercise troponin-elevation studies	Mixed (7 sport categories)	Pooled prevalence 36%; highest in triathlon (49%); non-linear relationship with duration, peaking at 3–6 h
Janssen et al. [18]/TREAT	Prospective cohort	1,011 walkers/cyclists/runners aged 40–70 y	Walking ≥20 km, cycling ≥100 km, running ≥15 km	hs-cTnT >URL in 51.3%; hs-cTnI >URL in 15.9%; no difference in subclinical-CAD prevalence between high and low responders
Trivax et al. [1]	Prospective cohort with CMR	25 healthy marathon runners (38.7±9.0 y)	Full marathon	cTnI rose significantly post-race (p<0.001); no LGE; transient RV dysfunction
O'Hanlon et al. [21]	Prospective cohort with CMR	17 recreational athletes (33.5±6.5 y)	Full marathon	11/17 had TnI above the AMI threshold at 6 h post-race; no LGE, oedema, or myocardial hyperaemia

Aengevaeren et al. [22], JAHA	Field time-series study	12 male runners ≥ 45 y	Amsterdam Marathon	cTnI peaked at 4 ± 2 h post-race, returned to baseline at 2 weeks; correlated with myocardial water diffusivity on CMR
Skadberg et al. [13], NEEDED	Prospective cohort	97 recreational cyclists (43 ± 10 y)	91-km mountain-bike race	Median cTnI peaked at 69.3 ng/L at 3 h, falling to 14.2 ng/L at 24 h; 3 cases of obstructive CAD among the highest troponin responders
Janssen et al. [23], AJP	Controlled laboratory trial	58 male athletes, 61 y (control/high CACS/ $\geq 50\%$ stenosis)	Stationary cycling to volitional exhaustion	hs-cTnT/hs-cTnI rose similarly across all three groups; no difference by CAD status up to 180 min post-exercise
Laugaudin et al. [11]	Prospective cohort	106 STEMI patients post-percutaneous coronary intervention	Not applicable (ACS population)	First peak at ~ 10 – 12 h; hs-cTnT exhibited a biphasic curve with a second peak at 76.9 h
Airaksinen et al. [24]	Comparative troponin study	Marathon runners vs. myocardial infarction patients	Marathon vs. ACS	Long-form cTnT ratio distinguished runners (0.17) from AMI (0.62); AUC 0.857

3.2 Anatomy, Pathophysiology, and Mechanisms of Myocardial Biomarker Leakage

The troponin complex is the regulatory unit of the thin filament within the sarcomere, comprising three subunits: troponin C (TnC), which binds calcium; troponin I (TnI), which inhibits actin-myosin interaction; and troponin T (TnT), which anchors the complex to tropomyosin [5,8]. Cardiac troponin I (cTnI) is a single isoform of approximately 23–24 kDa with only around 40% sequence homology to the skeletal-muscle isoform, conferring high cardiac specificity [8]. Cardiac troponin T (cTnT) has three isoforms encoded by distinct genes in cardiac muscle, fast-twitch skeletal muscle, and slow-twitch skeletal muscle, with 56–58% sequence homology to the skeletal isoform—theoretically rendering it more susceptible to cross-reactivity, although clinical evidence shows that the specificity of fourth-generation cTnT assays remains high under most conditions [8,6].

Most troponin is tightly bound within the contractile apparatus (the structurally bound pool), but a small proportion circulates freely in the cytosol as a cytosolic pool that is readily released upon disruption of membrane integrity. This cytosolic pool is estimated at 6–8% for cTnT and 2–4% (up to 8% in some sources) for cTnI [8,25]. This difference in cytosolic-pool proportion between the two isoforms partly explains why cTnT more frequently exceeds the URL than cTnI after exercise—the larger early release of cTnT allows the assay to detect elevation in a higher proportion of individuals [17].

3.2.1 Membrane-Permeability Leakage versus Irreversible Ischaemic Necrosis

In ACS, coronary occlusion causes prolonged myocardial ischaemia (generally >15 – 20 minutes), which disrupts aerobic cellular metabolism, depletes adenosine triphosphate reserves, and ultimately causes irreversible disruption of sarcolemmal integrity, triggering cardiomyocyte necrosis and proteolytic degradation of the contractile apparatus that releases troponin massively and over a prolonged period into the circulation [7,26]. By contrast, the mechanistic framework proposed by the European Society of Cardiology biomarker working group identifies three non-exclusive hypotheses underlying post-exercise troponin release: (1) reversible increased membrane permeability (cell wounds or membrane blebbing) due to mechanical and metabolic strain during intense cardiac work; (2) mild cardiomyocyte apoptosis; and (3) minimal-degree myocyte necrosis [4].

Evidence supporting the reversible permeability mechanism comes from cardiovascular magnetic resonance (CMR) imaging studies. Aengevaeren et al. demonstrated that myocardial water diffusivity (MD) on CMR increased significantly after marathon running (from 1.54 ± 0.08 to 1.67 ± 0.18 mm^2/s) and correlated with cTnI concentration ($r=0.66$) and single-molecule-counting cTnI ($r=0.71$), yet returned to baseline within two weeks—coinciding with troponin normalisation [22]. This finding is consistent with a reversible leakage model that does not involve permanent cell death. Correspondingly, animal-model apoptosis studies have reported a transient increase in apoptotic rate after strenuous exercise, possibly mediated by calpain activation and non-necrotic troponin degradation [4].

The strongest argument against widespread post-exercise necrosis comes from a series of CMR studies using the late gadolinium enhancement (LGE) technique, which have consistently failed to detect fibrosis or acute myocardial scarring in athletes after marathon running despite troponin concentrations exceeding the diagnostic threshold for infarction. O'Hanlon et al. found no LGE, myocardial oedema (myocardium-to-skeletal-muscle T2 ratio), or regional hyperaemia in any of 17 post-marathon participants, even though 11 (65%) had cTnI above the AMI threshold at 6 hours post-race [21]. Trivax et al. obtained similar results in 25 marathon runners: although cTnI and BNP rose significantly, no LGE was found in any cardiac chamber, leading the authors to conclude that the observed right atrial and ventricular dilation was more likely attributable to increased volume and pressure load (preload-afterload) than to ischaemia or infarction [1]. It is nonetheless important to note that CMR has limited spatial resolution for detecting very small foci of necrosis; theoretically, damage to as little as 40 mg of rat myocardial tissue is sufficient to produce a troponin concentration exceeding the human URL, such that a negative CMR does not entirely exclude minimal microscopic necrosis [4].

3.2.2 Molecular Composition Evidence: Troponin-Fragment-Based Differentiation

Beyond differences in temporal kinetics, recent research reveals that the molecular composition of circulating troponin differs between the post-exercise state and acute myocardial infarction, opening the possibility of differential diagnosis based on structural characterisation rather than concentration alone. Wu et al. first used gel-filtration chromatography to characterise troponin released into the circulation after infarction as a ternary cTnT-I-C complex, a binary cTnI-C complex, and free cTnT, with no meaningful quantity of free cTnI detected [27]. Damen et al. summarised that in AMI, cTnI circulates predominantly in complexed form (75–100%), while cTnT undergoes progressive proteolytic cleavage from the intact 37-kDa form to 29-kDa and subsequently 16–14-kDa fragments over time post-infarction [28].

Airaksinen et al. directly compared cTnT fragment composition between marathon runners and patients with type 1 myocardial infarction, finding that the “long-form” cTnT ratio relative to total cTnT was significantly lower in marathon runners (median 0.17) than in infarction patients (median 0.62; $p < 0.001$), with an area under the curve (AUC) of 0.857 for distinguishing the two conditions [24]. This indicates that troponin released after exercise is dominated by small fragments (<18 kDa), consistent with release from a partially degraded cytosolic pool, in contrast to troponin released through necrosis and degradation of the more structurally organised myofibrillar apparatus seen in infarction [24,28]. As an additional comparator, end-stage renal disease—another non-ischaemic condition also producing chronic troponin elevation—shows an even lower long-form ratio (approximately 0.03), illustrating that the troponin fragment profile has the potential to serve as an aetiology-specific biochemical “fingerprint” [28]. Although promising, the assay technology required to measure this ratio remains investigational and is not yet widely commercially available.

3.2.3 Influence of Exercise Load Characteristics on Release Magnitude

The magnitude of post-exercise troponin release is strongly influenced by the combination of exercise intensity and duration, which together determine cumulative cardiac workload. Serrano-Ostáriz et al., in a crossover trial of 21 subjects running for 45, 90, and 180 minutes at 85% and 95% of individual anaerobic threshold, found that peak post-exercise cTnI concentration was significantly associated with both duration ($p = 0.003$) and intensity ($p = 0.037$), whereas NT-proBNP was associated only with duration ($p = 0.049$) and not intensity ($p = 0.451$)—suggesting that these two biomarkers may partly reflect distinct physiological processes [12].

Direct comparison of high-intensity interval training (HIIT) and longer-duration moderate-intensity endurance exercise indicates that cTnT tends to be higher after high-intensity exercise than after longer, moderate-intensity exercise at an equivalent cardiac workload, implying that peak momentary intensity contributes disproportionately relative to total duration [4]. Conversely, recent meta-regression shows a non-linear relationship between duration and troponin-elevation prevalence, peaking at 3–6 hours and tending to decline at more extreme durations [17]—possibly because very long ultra-endurance exercise tends to be performed at a lower relative intensity, such that momentary cardiac workload does not reach the level seen in moderate-duration, high-intensity exercise [4].

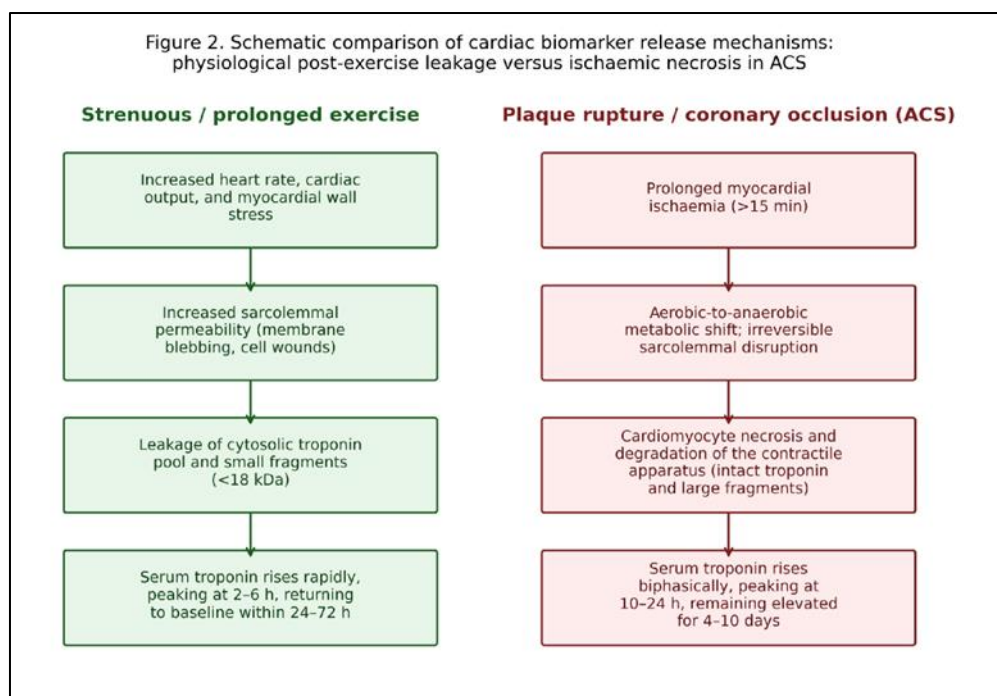


Figure 2: Schematic comparison of cardiac biomarker release mechanisms between strenuous physical exercise (reversible physiological leakage) and acute coronary syndrome (irreversible ischaemic necrosis), synthesised from Aengevaeren et al. [4], Shave et al. [26], and Thygesen et al. [7].

3.3 Risk Factors and Modifiers of Post-Exercise Cardiac Biomarker Release

Inter-individual variability in the degree of post-exercise troponin release is substantial, even under relatively uniform exercise loads. This section groups the identified modifying factors into four categories, summarised in Table 2.

3.3.1 Demographic Factors and Fitness Status

Age shows a non-linear relationship with the prevalence of post-exercise troponin elevation, peaking in middle-aged individuals (40–50 years), although age is not a consistent independent predictor at the population meta-regression level [17]. Similarly, sex and training status did not emerge as significant predictors in aggregate meta-regression, although individual studies have reported contrary patterns—for instance, less well-trained runners have been reported to show greater troponin increases than trained runners at the same event, as cited in the review by Stavroulakis and George [5]. Long-term training status appears to act through chronic cardiovascular adaptation: two controlled training studies summarised by Aengevaeren et al. showed that a 12–14-week training programme increased both baseline and post-exercise troponin concentrations at the same absolute workload, but not at the same workload relative to the now-increased aerobic capacity—suggesting that training effects are complex and depend on how exercise load is normalised, rather than simply on cumulative training volume [4].

3.3.2 Exercise Characteristics

As outlined in Section 3.2.4, intensity and duration are the principal determinants of the magnitude of troponin release, their interaction forming the concept of cumulative cardiac workload [12,4]. Sport type further modifies risk: the meta-regression by Stekelenburg et al. shows a prevalence gradient from triathlon and cycling (highest) to contact sports and walking (lowest), likely reflecting differences in the pattern of cardiovascular loading relative to maximal capacity across modalities [17]. Regarding the repeated-bout effect—a protective skeletal-muscle adaptation to repeated exercise-induced injury—direct evidence for cardiac troponin remains limited; however, the indirect findings from the controlled training studies above may be interpreted as a partial analogue of this phenomenon in the cardiac context, although caution is warranted, as skeletal-muscle and myocardial adaptation mechanisms are not identical and cardiac-specific evidence still requires confirmation through targeted longitudinal studies.

3.3.3 Metabolic and Physiological Profile

Several secondary physiological mechanisms have also been proposed as contributors to post-exercise troponin release, including oxidative stress, intracellular calcium dysregulation, mitochondrial permeability-transition disturbance, and activation of inflammatory pathways such as interleukin-6 and nuclear factor kappa-B [3]. The contribution of haemoconcentration from dehydration, or transient reduction in renal function during strenuous exercise, is thought

to be relatively minor relative to the total magnitude of troponin increase observed, given that haemodilution is, in fact, more commonly observed after prolonged endurance exercise, and transient reductions in renal clearance are insufficient to account for the multi-fold increases in concentration that can occur [4]. As a comparative context from the ACS population, higher body-mass index has been reported to be associated with differing peak high-sensitivity troponin concentrations in patients with non-ST-elevation myocardial infarction, although this evidence derives from a pathological context and cannot be directly extrapolated to the physiological post-exercise setting [29].

3.3.4 Comorbidity and Subclinical Coronary Artery Disease: A Critical Synthesis

One of the most clinically important—and most contested—questions is whether a high magnitude of post-exercise troponin elevation can serve as an indirect marker of previously undiagnosed subclinical CAD. The NEEDED study by Skadberg et al. in 97 recreational cyclists found that the three participants with the highest cTnI concentrations (>370 ng/L) at 3 and 24 hours post-race were all subsequently confirmed to have obstructive CAD on coronary angiography, suggesting that extreme post-exercise troponin elevation may signal occult coronary pathology [13]. This finding, however, has not been consistently replicated in subsequent, more tightly controlled studies.

Janssen et al. conducted a controlled laboratory trial in 58 male athletes stratified by coronary artery calcium score (CACS) and stenosis severity, and found no significant difference in the magnitude or kinetic pattern of hs-cTnT and hs-cTnI between control (CACS=0), high-CACS, and significant-stenosis ($\geq 50\%$) groups during a cycling test to volitional exhaustion with sampling up to 180 minutes post-exercise [23]. Consistent with this, the TREAT study by Janssen et al., comparing 68 athletes with the highest troponin response to 34 athletes with the lowest response—matched for age, sex, and sport type—found no significant difference in the prevalence (67.6% vs. 50.0%; $p=0.18$) or magnitude of CAD on cardiac computed tomography (CACS 9 AU vs. 2 AU; $p=0.58$), and although regression associations between troponin concentration and CAD-RADS score reached statistical significance, they explained only a very small proportion of variance (R^2 4–8%) [18].

The discrepancy between the NEEDED study and the two Janssen studies is most plausibly explained by differences in sampling time: NEEDED detected an association at 24 hours post-race, whereas the Janssen et al. laboratory study sampled only up to 180 minutes post-exercise—a window that, by the authors' own account, may not have captured the true peak concentration, given that the troponin curve was still rising at the final observation point. A further possible explanation is selection bias, as participants with significant stenosis in the Janssen et al. study were included only after being cleared for unrestricted exercise by pharmacological stress testing, likely under-representing individuals with haemodynamically meaningful demand ischaemia. This critical synthesis suggests that a slow rise-and-fall pattern or persistent elevation on delayed sampling (24 hours) may be more informative for detecting subclinical CAD than an early peak value, although current evidence remains insufficient to recommend routine coronary work-up based on isolated, asymptomatic post-exercise troponin elevation [4].

3.3.5 Iatrogenic and Analytical Factors

Beyond biological factors, the choice of troponin assay is an important, semi-iatrogenic determinant of clinical interpretation. As noted in Section 3.1.2, the prevalence of elevation above the URL is systematically higher with high-sensitivity assays than conventional assays, and higher for cTnT than cTnI [17]. This is partly explained by the difference in cytosolic-pool size between isoforms (Section 3.2.1), but also by variation in 99th-percentile URL derivation methodology across assay manufacturers, which use reference populations with differing exclusion criteria [8,9]. Renal function further influences troponin clearance, with cTnT reported to be more strongly affected by glomerular filtration rate than cTnI, such that interpretation of troponin in individuals with renal impairment requires additional caution [25].

Table 2: Summary of modifying factors influencing post-exercise cardiac biomarker release.

Category	Factor	Direction of Effect on Troponin Release	Source
Demographic/fitness	Age	Non-linear; prevalence peaks at 40–50 y; not a consistent independent predictor in meta-regression	[17]
Demographic/fitness	Sex	Not significant in aggregate population meta-regression	[17]
Demographic/fitness	Training status	Not significant in aggregate; chronic training may shift the threshold at absolute workload	[17,4]

Exercise characteristics	Intensity	Positively associated with cTnI; stronger contribution with HIIT vs. longer moderate-intensity exercise	[12,4]
Exercise characteristics	Duration	Non-linear; prevalence peaks at 3–6 h duration	[17,12]
Exercise characteristics	Sport type	Highest in triathlon/cycling/running; lowest in contact sports/walking	[17]
Metabolic/physiological	Oxidative stress & inflammation (IL-6, NF- κ B)	Presumed contributor to membrane permeability; evidence remains mechanistic	[3]
Metabolic/physiological	Hydration/haemoconcentration	Contribution estimated to be minor relative to overall magnitude	[4]
Comorbidity	Subclinical CAD (CACS/stenosis)	Inconsistent: positive association with 24-h sampling (NEEDED); no association with $\leq$ 180-min sampling (Janssen studies)	[13,23,18]
Iatrogenic/analytical	Assay type (hs vs. conventional; cTnT vs. cTnI)	Prevalence >URL higher with hs assays and with cTnT relative to cTnI	[17,8]
Iatrogenic/analytical	Renal function	Affects clearance, particularly for cTnT	[25]

3.4 Clinical Manifestations and Differential-Diagnosis Approach

3.4.1 Clinical Manifestations: Discrepancy Between Biomarker and Symptoms

The most striking clinical feature of post-exercise troponin elevation is the absence of accompanying ischaemic symptoms in the majority of cases. Trivax et al. reported no signs or symptoms of myocardial ischaemia or significant arrhythmia during or after marathon completion in all 25 participants, despite a significant rise in cTnI [1]. O'Hanlon et al. likewise found no correlation between troponin elevation and clinical symptoms in their cohort [21]. This discrepancy between an alarming biochemical profile and a clinically reassuring presentation is the crux of the diagnostic challenge: a clinician relying solely on the troponin value without considering the context of recent physical activity risks misclassifying a healthy individual as having ACS [20,4].

3.4.2 Kinetics as a Differential-Diagnosis Tool

Temporal pattern is the single most informative distinguishing feature between post-exercise troponin elevation and ACS (Table 3, Figure 3). In ACS, particularly ST-elevation myocardial infarction (STEMI) managed with primary percutaneous coronary intervention, Laugaudin et al. found a first peak biomarker concentration at 10.2–11.8 hours post-onset for hs-cTnT, hs-cTnI, and creatine kinase, with a log-linear decline for troponin I and creatine kinase, but a characteristic biphasic curve for hs-cTnT with a second peak at 76.9 hours—a behaviour directly relevant to the interpretation of serial troponin when reinfarction is suspected [11]. Overall, troponin concentrations in ACS remain significantly elevated for 4–10 days post-onset, reflecting continued release from the degrading structural pool as necrosis progresses [4,26].

By contrast, post-exercise kinetics show a far more rapid onset and resolution. Aengevaeren et al. found that all biomarkers measured (cTnI, single-molecule-counting cTnI, hs-cTnT, and cardiac myosin-binding protein C) peaked at 4 ± 2 hours post-marathon and returned toward baseline at the 1–2-day follow-up sample, with complete normalisation at two weeks [22]. Skadberg et al., in the context of a 91-km cycling race, found median cTnI rising from a baseline of 3.4 ng/L to 50.5 ng/L immediately post-race, peaking at 69.3 ng/L at 3 hours, and falling sharply to 14.2 ng/L at 24 hours—illustrating markedly faster clearance than the ACS pattern [13]. The controlled laboratory study by Janssen et al. further confirmed a similar trend, although at 180 minutes post-exercise concentrations had not yet fully returned to baseline, indicating that the true washout phase had only just begun beyond that time point [23].

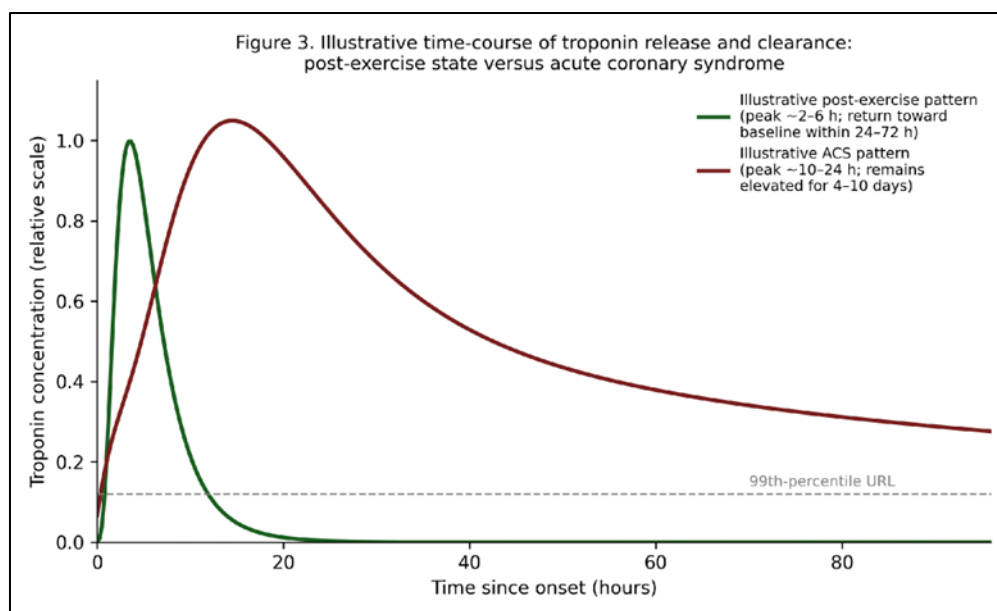


Figure 3: Illustrative comparison of the time-course of troponin release and clearance between the post-strenuous-exercise state and acute coronary syndrome, synthesised from descriptive data in Laugaudin et al. [11], Aengevaeren et al. [4,22], and Skadberg et al. [13]. The curves are schematic illustrations and not a reproduction of raw data from the original studies.

3.4.3 Delta Criteria and Serial Sampling

The Fourth Universal Definition of Myocardial Infarction recommends the use of change (delta) criteria on serial troponin measurement to distinguish acute from chronic myocardial injury: absolute change is preferred over relative (percentage) change when the baseline concentration is not, or only marginally, elevated above the URL, whereas for chronic elevation above the URL, the absence of significant change (generally a threshold of <20%) indicates chronic rather than acute myocardial injury [7]. Sandoval et al., in a critical appraisal of the 2021 AHA/ACC guidelines, emphasise that the high-sensitivity troponin rule-in/rule-out algorithms at 0/1-hour, 0/2-hour, and 0/3-hour recommended by the European Society of Cardiology require a thorough understanding of assay-specific limit of detection (LoD) and limit of quantitation (LoQ), as well as sex-specific 99th-percentile thresholds [9]. This delta principle is directly relevant to the post-exercise context: the absence of significant change on repeat sampling several hours later, or a pattern of rapid decline consistent with physiological clearance, strengthens the suspicion of benign elevation, whereas a persistent, progressively rising pattern is more suggestive of an ongoing pathological process [7,9].

3.4.4 Role of Electrocardiography and Non-Invasive Imaging

In addition to biomarker kinetics, the absence of new ischaemic ECG changes and the absence of regional wall-motion abnormality or LGE on imaging are essential components for excluding true ACS, as repeatedly demonstrated in post-marathon CMR studies [21,1] and formalised in the Universal Definition criteria [7]. The European Society of Cardiology sports cardiology guidelines further emphasise that in athletes with suspected myocarditis or pericarditis, whether post-infection or post-strenuous exercise, CMR with T1/T2 mapping and LGE protocols plays a central role in confirming or excluding active inflammation [30].

3.4.5 Differential Diagnosis Beyond Acute Coronary Syndrome

Sedaghat-Hamedani et al. caution that the rise in D-dimer and natriuretic peptides after strenuous exercise can also mimic the profile of acute pulmonary embolism, such that clinical evaluation of athletes presenting with post-exercise dyspnoea or chest pain should ideally consider a broader differential diagnosis beyond ACS alone [2]. Other relevant differential diagnoses include transient right ventricular dysfunction due to increased pulmonary arterial pressure load during prolonged endurance exercise [31,1], subclinical myocarditis, atrial-remodelling-related arrhythmia, and—in rarer cases—genuine demand ischaemia from occult CAD in middle-aged athletes [15,14].

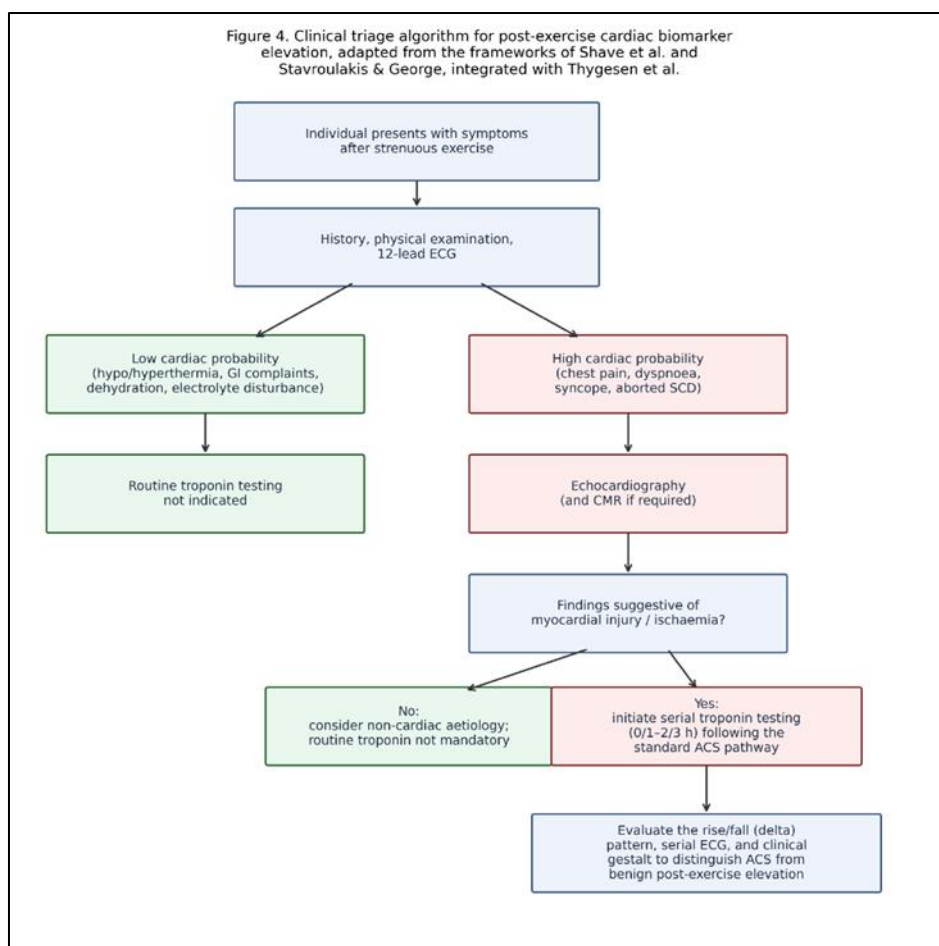


Figure 4: Clinical triage algorithm for the evaluation of post-exercise cardiac biomarker elevation, conceptually adapted from the frameworks of Shave et al. [26] and Stavroulakis & George [5], integrated with the delta criteria of Thygesen et al. [7] and the high-sensitivity troponin algorithm of Sandoval et al. [9].

Table 3: Comparative summary of release and clearance kinetic parameters of cardiac biomarkers between the post-exercise state and acute coronary syndrome.

Kinetic Parameter	Post-Strenuous-Exercise State	Acute Coronary Syndrome	Key Source
Onset of detectable increase	During exercise to shortly after (<1 h)	2–4 h post-symptom onset (hs assay)	[22,9]
Time to peak	2–6 h (broad range 3–24 h depending on modality)	10–24 h; hs-cTnT may show a second peak at ~77 h (biphasic pattern)	[22,13,11]
Curve pattern	Unimodal, relatively symmetrical rise and fall	Often biphasic (particularly hs-cTnT), slower decline	[11]
Washout duration	Returns toward baseline within 24–72 h	Remains elevated for 4–10 days	[4,22]
Dominant molecular composition	Small fragments (<18 kDa); low long-form cTnT ratio (median 0.17)	Higher proportion of intact complex/large fragments; high long-form cTnT ratio (median 0.62)	[24,28,27]
Correlation with imaging	Correlates with myocardial water diffusivity (reversible permeability marker), without LGE	Correlates with infarct size, positive LGE, wall-motion abnormality	[22,21,7]

3.5 Clinical Management and Risk Evaluation in Athletes and Active Individuals

3.5.1 Triage Algorithm and Serial Biomarker Monitoring

Stavroulakis and George propose a tiered triage algorithm for individuals presenting to the emergency department after endurance exercise, beginning with assessment of the clinical probability of a cardiac aetiology [5]. In individuals with low probability—characterised by non-specific complaints such as hypo/hyperthermia, gastrointestinal disturbance, dehydration, or electrolyte derangement—history, physical examination, and 12-lead ECG are generally sufficient to exclude cardiac involvement without the need for routine troponin testing. Conversely, in individuals with high probability—characterised by chest pain, dyspnoea, syncope, or a history of aborted cardiac arrest—further evaluation with echocardiography is required, and troponin testing is initiated only if findings suggestive of myocardial injury or ischaemia are identified [5,26]. This tiered approach is philosophically consistent with the high-sensitivity troponin rule-in/rule-out algorithms at 0/1-hour and 0/2-hour recommended by ESC guidelines and critically reviewed by Sandoval et al. for the general ACS population, with the caveat that a single value below the limit of detection in late presenters (>3 hours post-symptom onset) carries a high negative predictive value for excluding infarction [9].

Once troponin has been measured and found to be elevated, serial monitoring at 1–3-hour intervals becomes essential to assess the delta pattern: the absence of significant change, or a downward trend, is more consistent with physiological clearance, whereas a progressively rising trend raises suspicion of an active pathological process requiring escalation along the standard ACS pathway [7,9].

3.5.2 Integration of Non-Invasive Investigations

Serial ECG remains a core component for detecting dynamic ischaemic changes. Echocardiography provides rapid information on left and right ventricular function and regional wall-motion abnormality; several studies have documented transient reduction in right ventricular ejection fraction after prolonged endurance exercise that recovers rapidly without structural sequelae [1,31]. CMR serves as the definitive modality in equivocal cases, particularly to exclude LGE (indicating fibrosis/necrosis), oedema (indicating active inflammation), or regional perfusion abnormality [21,30]. In the context of suspected myocarditis, the ESC sports cardiology guideline recommends CMR as an integral part of the evaluation before a return-to-play decision is made [30].

3.5.3 Clinical Decision-Making for Return-to-Play (Clearance)

The 2020 ESC Guidelines on Sports Cardiology and Exercise in Patients with Cardiovascular Disease provide a detailed framework for specific conditions relevant to this context. For suspected or confirmed myocarditis, the guideline recommends abstention from competitive sport during the recovery period (generally 3–6 months), with return-to-play criteria including normalisation of troponin and inflammatory markers, normal left ventricular function on echocardiography and CMR, absence of active inflammation or new fibrosis on CMR, and absence of complex arrhythmia on Holter monitoring or exercise testing [30]. For pericarditis, similar recommendations require abstention until symptom resolution and normalisation of inflammatory markers, with duration ranging from approximately 30 days for mild cases to 3 months for severe cases [30].

For isolated post-exercise troponin elevation—asymptomatic, without ischaemic ECG change, and without imaging abnormality—the reviewed literature does not identify a standardised mandatory abstention period. Instead, the consensus emerging from Shave et al. and Stavroulakis and George emphasises that routine troponin testing in asymptomatic post-exercise individuals is, in fact, not indicated, and that clinical focus should be directed at identifying clinical red flags rather than an absolute troponin value—so as to avoid an unnecessary cascade of investigation and hospitalisation [26,5].

3.5.4 Cardiovascular Risk Evaluation and Prognostic Considerations

Evidence regarding the long-term prognostic significance of post-exercise troponin elevation remains inconsistent. On one hand, a long-term cohort study of 725 long-distance walkers (referenced within the discussion framework of Aengevaeren et al.) reported that post-exercise cTnI elevation above the URL after long-distance walking was independently associated with increased mortality and major cardiovascular events in older individuals during follow-up. On the other hand, the NEEDED cycling cohort did not confirm this association, with a low event rate and relatively short follow-up further limiting statistical power to detect such an association [4]. This critical synthesis indicates that, although post-exercise troponin may represent a marker of cardiovascular vulnerability in certain subgroups (particularly older individuals with a higher cardiovascular risk-factor burden), current evidence is not yet mature enough to be used as a routine tool for individual risk stratification, and clinical decisions should continue to rest on comprehensive evaluation rather than a single troponin value [4,18].

Table 4: Summary of clinical management strategies and return-to-play (clearance) considerations by clinical scenario.

Clinical Scenario	Primary Diagnostic Step	Clearance Criteria/Consideration	Source
Asymptomatic troponin elevation, normal ECG, no red flags	Careful history and physical examination; ECG; routine troponin not mandatory	No standardised abstention period required; clinical education and observation	[5,26]
Troponin elevation with suggestive symptoms (chest pain, syncope)	Serial ECG, echocardiography, serial troponin with delta criteria	Follow the standard ACS pathway (0/1–2/3 h); escalate if delta is significant	[7,9]
Suspected post-exercise/post-infective myocarditis	CMR (LGE, T1/T2 mapping), troponin, Holter monitoring	Abstain from competition for 3–6 months; return when troponin is normal, LV function is normal, no active inflammation on CMR, and no complex arrhythmia	[30]
Suspected pericarditis	Echocardiography, inflammatory markers	Abstain until resolution (30 days for mild cases – 3 months for severe cases)	[30]
Suspected subclinical CAD in higher-risk, middle-aged athletes	Consider individualised coronary calcium CT when additional risk factors are present; not indicated routinely based on isolated troponin	Individualised approach; no indication for routine screening based on post-exercise troponin alone	[23,18,4]

3.6 Clinical Challenges and Evidence Gaps

Although two decades of accumulated evidence have clarified the general physiological nature of post-exercise troponin elevation, several important gaps continue to hinder precise clinical application.

- Absence of athlete-specific and sport-specific reference values: the 99th-percentile URL used clinically is derived from a healthy reference population that is generally sedentary, so its application to athletes produces a high false-positive rate (reaching 74–96% with some hs assays) [3]. Large cohort studies such as TREAT [18] are expected to yield more contextually relevant reference values, although external validation across populations is still required.
- Variability in post-exercise sampling-time protocols: the time window for post-exercise sampling varies considerably across studies—from immediately after exercise to 24 hours or more—obscuring the true prevalence estimate and potentially missing the actual peak concentration, as identified in the limitations of the Janssen et al. study, which stopped sampling at 180 minutes despite the curve not yet having peaked [17].
- Lack of long-term longitudinal studies in representative young-athlete populations: most prognostic evidence derives from older or middle-aged cohorts with limited follow-up, such that the long-term cardiac health implications of repeated troponin elevation in young competitive athletes remain unanswered [4,3].
- Incomplete standardisation across troponin assays: differences in antibody epitope, calibration, and 99th-percentile threshold across cTnI assay manufacturers hinder direct comparison of results across studies and centres [8,7].
- Need for large-scale validation of fragment/composition-based troponin assays: although the long-form cTnT ratio shows promising discriminatory potential (AUC 0.857) [24], this technology remains investigational, with limited sample sizes, and requires large-scale prospective validation and commercial availability before routine clinical application [28].
- Inconsistent findings regarding the relationship between post-exercise troponin and subclinical CAD: as discussed in Section 3.3.4, contradictory findings between early- and delayed-sampling studies underscore the need for prospective studies with standardised sampling protocols (including a 24-hour time point) and larger sample sizes to clarify the role of troponin as an indirect marker of occult CAD [13,23,18].
- Limited representation of women: the majority of key studies reviewed—including the CMR study by O'Hanlon et al. [21] and the controlled laboratory study by Janssen et al. [23]—enrolled only male participants, such that sex-specific reference values and kinetic patterns still require further investigation, given that troponin is known to have a different 99th-percentile threshold between men and women in the ACS context [9].

- Methodological heterogeneity in meta-analyses: the very wide range of prevalence across individual studies included in meta-analyses (from a few per cent to nearly all participants) reflects substantial heterogeneity in design, population, and cut-off definitions, such that generalisation of pooled results warrants caution [17,2].

4 CONCLUSION

This literature review synthesises evidence from 31 unique sources to establish that elevation of cardiac troponin concentration after strenuous physical exercise is a common phenomenon—with prevalence ranging from 15% to over 90% depending on assay type, sport, and duration—yet is mechanistically and kinetically distinct from ACS. Evidence from CMR imaging studies consistently shows the absence of late gadolinium enhancement after exercise, supporting a dominant mechanism of reversible sarcolemmal membrane-permeability increase and/or mild apoptosis, rather than the irreversible cardiomyocyte necrosis characteristic of myocardial infarction [4,22,21,1].

From a kinetic perspective, the pattern of peak time and washout duration constitutes the most practical and front-line-applicable distinguishing feature: typical post-exercise troponin elevation peaks within 2–6 hours and returns toward baseline within 24–72 hours, whereas ACS shows a later peak (10–24 hours, with a possible biphasic pattern for hs-cTnT) and elevation persisting for 4–10 days [11,22,13]. Characterisation of troponin molecular composition—particularly the ratio of long-form fragments to total troponin—emerges as a promising additional marker for distinguishing these two conditions based on their underlying release mechanisms, although its routine clinical application still requires further validation [24,28].

The principal clinical implication of this review is that a diagnosis of ACS in an individual after strenuous exercise should not be based on a single troponin value above the URL, but rather requires comprehensive integration of history and the context of recent physical activity, physical examination, serial ECG, the pattern of troponin change (delta criteria) on repeat sampling, and non-invasive imaging where required. A tiered triage approach that distinguishes low from high clinical probability before initiating troponin testing has the potential to reduce unnecessary investigation in healthy individuals without compromising the safety of detecting genuine ACS [5,26,9].

From a research perspective, anticipated future outcomes include the establishment of troponin reference values specific to athlete populations and sport type, standardised post-exercise sampling protocols across studies, large-scale prospective validation of molecular-composition-based biomarkers, and longitudinal cohort studies capable of clarifying the long-term prognostic significance of repeated troponin elevation in competitive and recreational athletes. Achieving these outcomes has direct implications for improving emergency-department efficiency, reducing unnecessary hospitalisation, and simultaneously heightening clinical awareness of the small but meaningful possibility that post-exercise troponin elevation may serve as an early detection window for occult cardiovascular disease in certain high-risk subgroups [4,18].

As a final methodological note, the synthesis in this review is based on 31 unique sources, of which 25 were reviewed as full text and the remaining six only as structured abstracts (Section 2); readers intending to use this review as a basis for clinical decisions or further manuscript development are advised to verify the methodological and numerical detail of the original sources, particularly for the six sources available only as abstracts.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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