

# Measuring Heart Rate Variability in Patients Admitted with ST-Elevation Myocardial Infarction for the Prediction of Subsequent Cardiovascular Events: A Systematic Review

Crischientian Brinza<sup>1,2,†</sup> , Mariana Floria<sup>2,3,†</sup>, Adrian Covic<sup>2,4,\*</sup> and Alexandru Burlacu<sup>1,2,5,\*</sup> 

<sup>1</sup> Institute of Cardiovascular Diseases, 700503 Iasi, Romania; crischientian-branza@email.umfiasi.ro

<sup>2</sup> Faculty of Medicine, University of Medicine and Pharmacy, 700115 Iasi, Romania; floria.mariana@umfiasi.ro

<sup>3</sup> Military Emergency Clinical Hospital, 700483 Iasi, Romania

<sup>4</sup> Nephrology Clinic, Dialysis and Renal Transplant Center, University Hospital, 700503 Iasi, Romania

<sup>5</sup> Medical Sciences Academy, 700503 Iasi, Romania

\* Correspondence: adrian.covic@umfiasi.ro (A.C.); alexandru.burlacu@umfiasi.ro (A.B.);

Tel.: +40-744488580 (A.B.)

† Both authors contributed equally.

**Abstract:** *Background and objectives:* Ischemic heart disease represents the leading cause of death, emphasizing risk stratification and early therapeutic intervention. Heart rate variability (HRV), an indirect marker of autonomic nervous system activity, was investigated extensively as a risk factor for adverse cardiovascular events following acute myocardial infarction. Thus, we systematically reviewed the literature to investigate the association of HRV parameters with mortality and adverse cardiovascular events in patients presenting with ST-elevation myocardial infarction (STEMI). *Materials and methods:* Following the search process in the MEDLINE (PubMed), Embase, and Cochrane databases, nine studies were included in the final analysis. *Results:* Lower time-domain HRV parameters and a higher ratio between power in the low-frequency (LF) band and power in the high-frequency (HF) band (LF/HF) were associated with higher all-cause mortality during follow-up, even in patients treated mainly with percutaneous coronary interventions (PCI). Although most studies measured HRV on 24 h ECG recordings, short- and ultra-short-term measures (1 min and 10 s, respectively) were also associated with an increased risk of all-cause mortality. Although data were discrepant, some studies found an association between HRV and cardiac mortality, reinfarction, and other major adverse cardiovascular events. *Conclusions:* In conclusion, HRV measurement in patients with STEMI could bring crucial prognostic information, as it was associated with an increased risk of all-cause mortality documented in clinical studies. More and larger clinical trials are required to validate these findings in contemporary patients with STEMI in the context of the new generation of drug-eluting stents and current antithrombotic and risk-modifying therapies.

**Keywords:** heart rate variability; ST-elevation myocardial infarction; prognosis; autonomic nervous system; risk assessment



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## 1. Introduction

Heart rate variability (HRV) can be briefly characterized as the physiological variation of RR intervals between successive depolarizations of the sinus node. HRV can be considered an indirect marker of autonomic nervous system activity, which allows a relatively superficial insight into the complex structure of heart–brain connection [1].

HRV reflects the psycho-emotional status linked to different disorders such as stress or anxiety [2,3]. Interestingly, HRV represents not only a consequence of the action of various factors on the brain–heart connection, but it also can modulate the nervous system function. HRV biofeedback represents a respiratory training intervention that modifies the activity of different brain regions with beneficial effects documented in clinical studies on autonomic markers, stress levels, and anxiety, even in healthy individuals [4–7].

However, HRV constitutes more than a simple variation of RR intervals, as it can be expressed by different parameters using time-domain, frequency-domain, or nonlinear methods of measurement [8]. Four time-domain parameters were recommended for HRV assessment by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, namely standard deviation of all NN intervals (SDNN), HRV triangular index, the standard deviation of the average NN interval over short time divisions (SDANN), and the square root of the mean squared differences of consecutive NN intervals (RMSSD). Low-frequency power (LF), high-frequency power (HF), and the LF/HF ratio represent the most used frequency-derived parameters endorsed by the guidelines [9].

One of the earliest clinical applications of HRV measurement is represented by mortality risk stratification in patients with acute myocardial infarction (AMI). One study published in 1987 involving 808 patients with AMI observed that an SDNN less than 50 ms was associated with a 4-fold increase in mortality risk compared to patients with an SDNN more than 100 ms (34% vs. 9%, respectively) during a 4-year follow-up period. The usefulness of HRV for mortality stratification remained statistically significant after multivariable analysis. Moreover, HRV was associated with left ventricular function and segmental contraction abnormalities, as well as clinical and radiographic signs of pulmonary congestion [10].

HRV measurement is also helpful for mortality risk assessment in patients with end-stage kidney disease and chronic hemodialysis. A meta-analysis published in 2021 observed that both time- and frequency-domain parameters (SDNN, SDANN, and LF/HF ratio) were associated with increased all-cause death and cardiovascular mortality in hemodialysis patients [11].

Although most studies investigated HRV measured by 24 h electrocardiographic (ECG) recordings, many parameters were also validated in case of shorter time intervals. In one study that recruited 900 patients without coronary heart disease, HRV was measured using 2 min ECG strips. Patients with the lowest SDNN values had an increased risk of all-cause death and cardiovascular mortality. Other time-domain parameters such as RMSSD and pNN50 were also linked to increased mortality [12].

A recent meta-analysis involving patients with known cardiovascular diseases documented that patients with lower HRV exhibited a higher risk of all-cause death and cardiovascular events, an effect maintained in a subgroup analysis in participants with AMI. Although this meta-analysis also included studies that recruited patients with AMI, it was not focused on the specific population presenting with ST-elevation myocardial infarction (STEMI) [13].

We aimed to systematically review the literature to investigate the association of HRV parameters with mortality and adverse cardiovascular events in patients presenting with STEMI.

## 2. Materials and Methods

The present systematic review was conducted according to the updated Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) checklist [14].

### 2.1. Data Sources and Search Strategy

We performed a literature search in the MEDLINE (PubMed), Embase, and Cochrane databases from the inception until 20 August 2021, without using time intervals or language filters. Whenever possible, the search was restricted to studies that enrolled humans. As recommended by the PRISMA checklist, to find additional studies, we also screened cited articles, the Google Scholar search engine, and the [ClinicalTrials.gov](https://www.clinicaltrials.gov) database of clinical trials. The following MeSH terms and keywords were used to retrieve references from the mentioned databases: “heart rate variability”, “myocardial infarction”, “ST-elevation myocardial infarction”, “cardiovascular events”, “risk assessment”, and “mortality”. The search process is provided in Table S1.

## 2.2. Eligibility Criteria and Outcomes

Obtained citations from prespecified databases were considered for inclusion in the present systematic review if they met several criteria: (1) humans  $\geq 18$  years old were included for the analysis; (2) patients presenting with STEMI were enrolled; (3) standard HRV parameters endorsed by the guidelines were investigated [9]; (4) HRV was measured during the hospitalization for STEMI or at a distance from the index event; and (5) original data regarding the association between HRV parameters and the risk of adverse cardiovascular events or mortality in patients presenting with STEMI were reported. In addition, studies available only in abstracts, editorials, letters, case reports, conference papers, unpublished data, and meta-analyses were excluded from the analysis. In addition, studies were excluded due to the inability to extract data. Two independent investigators analyzed the eligibility criteria, and disagreements were solved by consensus.

## 2.3. Data Collection

Two independent investigators extracted the following data: the first author, publication year, number of patients included, their age, HRV parameters evaluated, clinical setting, follow-up period, reported outcomes, timing, and methods for HRV measurements. When available, data were presented as numbers, percentages, median or mean values, hazard ratio (HR), and odds ratio (OR), and the corresponding confidence intervals (*p*-values).

## 2.4. Quality Assessment

The quality of observational studies without a control group was appraised using a tool provided by the National Institutes of Health (NIH). It contained 14 key questions that guided the overall evaluation of the studies' quality [15].

## 3. Results

Our search in the databases mentioned above and in additional sources identified 2995 references. Subsequently, duplicate citations and those based on title or abstract were excluded, thus leaving 124 studies for eligibility assessment. After full-text examination, nine studies were included in the present systematic review. The search process is detailed in Figure S1 and Table S1.

General characteristics of clinical studies, including the number of patients and their age, HRV parameters evaluated, timing and methods of measurement, and outcomes investigated, are provided in Table S2. In addition, results reported in studies are illustrated in Table 1.

**Table 1.** The results reported in clinical studies.

Author, Year	Outcomes	Parameters	Results
Balanescu et al., 2004	1-year total mortality	RMSSD, ms	Nonsurvivors vs. survivors 9.6 $\pm$ 3.1 vs. 32.6 $\pm$ 10.9 <i>p</i> < 0.001
		SDNN, ms	37 $\pm$ 10.3 vs. 144 $\pm$ 41 <i>p</i> < 0.001
		LF, ms <sup>2</sup>	1409 $\pm$ 143 vs. 1241 $\pm$ 131 <i>p</i> < 0.001
		HF, ms <sup>2</sup>	443 $\pm$ 105 vs. 883 $\pm$ 184 <i>p</i> < 0.001
		LF/HF > 2	80.9% of patients who died vs. 8.1% patients who survived <i>p</i> < 0.0001
Boskovic et al., 2014	Sudden cardiac death at 1-year follow-up	RMSSD, ms	Nonsurvivors vs. survivors 9.3 $\pm$ 2.5 vs. 30.2 $\pm$ 2.5 <i>p</i> < 0.001
		SDNN, ms	36.7 $\pm$ 10 vs. 133 $\pm$ 51 <i>p</i> < 0.001
		LF, ms <sup>2</sup>	1382 $\pm$ 152 vs. 1260 $\pm$ 142 <i>p</i> < 0.001
		HF, ms <sup>2</sup>	451 $\pm$ 112 vs. 836 $\pm$ 223 <i>p</i> < 0.001
		LF/HF > 2	81% of deceased patients vs. 15.6% survivors <i>p</i> < 0.0001
Boskovic et al., 2014	All-cause mortality at 1 year	SDNN, ms	Nonsurvivors vs. survivors 60.55 $\pm$ 12.84 vs. 98.38 $\pm$ 28.21 <i>p</i> < 0.001
		Mean RR interval, ms	695.82 $\pm$ 65.87 vs. 840.07 $\pm$ 93.97 <i>p</i> < 0.001
		RRmax-RRmin, ms	454.36 $\pm$ 111.00 vs. 600.99 $\pm$ 168.72 <i>p</i> = 0.006

**Table 1.** Cont.

Author, Year	Outcomes	Parameters	Results
Chakrovortty et al., 2011	Correlation between HRV and TIMI risk score	SDNN, ms	Low-risk group (TIMI 0–2) vs. intermediate-risk group (TIMI 3–7) vs. high-risk group (TIMI ≥ 8) 120.0 ± 19.8 vs. 71.0 ± 20.5 vs. 40.9 ± 6.4 <i>p</i> < 0.001
		Mean RR interval, ms	836.8 ± 121.0 vs. 776.7 ± 130.3 vs. 649.7 ± 75.5 <i>p</i> < 0.001
Compostella et al., 2017	Major clinical events	SDNN, ms	10 events from 52 patients in the lowest SDNN quartile vs. 21 events from 150 patients in the other quartiles ( <i>X</i> <sup>2</sup> = 0.813) <i>p</i> = 0.367
	All-cause death	SDNN, ms	3 of 4 deaths occurred in the lowest SDNN quartile <i>p</i> = 0.010
	Cardiac mortality	SDNN, ms	2 of 3 deaths occurred in the lowest SDNN quartile <i>p</i> = 0.055
Coviello et al., 2013	Major clinical events	Mean RR, ms	Predischarge HRV parameters, univariate analysis HR 0.99 (95% CI, 0.98–1.00) <i>p</i> = 0.06
		SDNN, ms	HR 0.97 (95% CI, 0.95–0.99) <i>p</i> = 0.009
		SDNNi, ms	HR 0.97 (95% CI, 0.93–1.00) <i>p</i> = 0.08
		VLF, ms	HR 0.94 (95% CI, 0.89–0.98) <i>p</i> = 0.007
		LF, ms	HR 0.88 (95% CI, 0.80–0.96) <i>p</i> = 0.006
		HF, ms	HR 0.88 (95% CI, 0.77–1.00) <i>p</i> = 0.05
		Mean RR, ms	HRV parameters at 6 months (no MCE vs. MCE) 916.4 ± 122.6 vs. 867.6 ± 68.6 <i>p</i> = 0.29
		SDNN, ms	139.1 ± 38.2 vs. 141.4 ± 41.4 <i>p</i> = 0.88
		SDNNi, ms	58.6 ± 21.6 vs. 52.7 ± 16.5 <i>p</i> = 0.48
		VLF, ms	53.8 ± 39.9 vs. 43.9 ± 12.1 <i>p</i> = 0.11
	LF, ms	26.1 ± 10.5 vs. 21.9 ± 7.0 <i>p</i> = 0.30	
	HF, ms	18.2 ± 12.1 vs. 14.2 ± 5.8 <i>p</i> = 0.18	
		SDNN, ms	Predischarge HRV parameters, multivariate analysis HR 0.97 (95% CI, 0.952–0.996) <i>p</i> = 0.02
		LF, ms	HR 0.90 (95% CI, 0.819–0.994) <i>p</i> = 0.04
	Reinfarction	SDNN, ms	Predischarge HRV parameters, multivariate analysis HR 0.96 (95% CI, 0.936–0.991) <i>p</i> = 0.009
		LF, ms	HR 0.90 (95% CI, 0.81–1.009) <i>p</i> = 0.07
Ablonskyte-Dudoniene et al., 2012	1-year mortality	RMSSD (≤20.9 ms)	HR 9.69 (95% CI, 1.88–49.95) <i>p</i> = 0.007
	5-year all-cause mortality	SDNN (≤100.42 ms)	HR 4.36 (95% CI, 1.68–11.35) <i>p</i> = 0.003
	5-year cardiac mortality	SDANN (≤85.41 ms)	HR 9.65 (95% CI, 1.27–73.4) <i>p</i> = 0.029
	Recurrent nonfatal MI	SDNN (≤123.43 ms)	HR 4.1 (95% CI, 1.54–11.32) <i>p</i> = 0.005
Erdogan et al., 2008	All-cause mortality	SDNN, ms	102 ± 39 (survivors) vs. 81 ± 33 (nonsurvivors) OR 0.95 (95% CI, 0.95–1)–multivariate analysis <i>p</i> = 0.1
	4-year survival	SDNN, ms	80% (SDNN < 50) vs. 92% (SDNN > 50) <i>p</i> < 0.001
Karp et al., 2009	2-year mortality	SDNN, ms (admission)	OR 2.9 (95% CI, 1.12–7.56) <i>p</i> = 0.028
	Reinfarction	SDNN, ms (admission)	3.1 ± 0.9 (reinfarction) vs. 3.0 ± 0.9 (no reinfarction) <i>p</i> = 0.7
Katz et al., 1999	All-cause mortality	RRmax–RRmin, beats/min	OR 1.38 (95% CI, 1.13–1.63) <i>p</i> = 0.028
		SDANN, ms	All patients who died ( <i>n</i> = 10) had SDANN < 50 ms

HF = power in high-frequency range; HRV = heart rate variability; LF = power in low-frequency range; RMSSD = the square root of the mean of the sum of the squares of differences between adjacent NN intervals; RRmax–RRmin = difference between the longest RR interval and the shortest RR interval; SDANN = standard deviation of the averages of NN intervals in all 5 min segments of the entire recording; SDNN = standard deviation of all NN intervals; SDNNi = mean of the standard deviations of all NN intervals for all 5 min segments of the entire recording; TIMI = thrombolysis in myocardial infarction; VLF = power in very-low-frequency range.

All analyzed studies had an observational, nonrandomized design [16–24]. Most of the studies ( $n = 5$ ) investigated patients prospectively [16,17,20,21,24], while three studies were retrospective [19,22,23], and one was cross-sectional [18]. In the majority of cases, HRV was measured based on 24 h ECG recordings [16–22], while two studies measured short or ultra-short time recordings (10 s and 1 min) [23,24]. Concerning myocardial reperfusion therapy, four studies enrolled mainly patients treated with primary percutaneous coronary intervention (pPCI) [19–22]. As all included studies had an observational design, the quality was judged to be fair, as guided by the NIH assessment tool (Table S3).

Concerning all-cause mortality, clinical studies found an association with both time- and frequency-domain HRV parameters. Balanescu et al. documented significantly lower SDNN and RMSSD values ( $p < 0.001$ ) in patients who died at 1-year follow-up compared to those who survived. In addition, deceased patients exhibited higher LF and lower HF values ( $p < 0.001$  for both), most likely denoting an increased sympathetic tone. Importantly, 80.9% of patients who died had an LF/HF ratio value greater than 2. Moreover, an LF/HF ratio  $> 2$  displayed good sensitivity, specificity, and a negative predictive value, but a low positive predictive value (80%, 83%, 96%, and 45%, respectively), in comparison to SDNN  $< 50$  ms, which had better specificity and a positive prediction value (98% and 85%, respectively), but lower sensitivity and a negative prediction value (58% and 93%, respectively) [16].

Boskovic et al. observed similar results, with reduced time-domain parameters (SDNN, mean RR interval, RRmax–RRmin) in patients who died in the 1-year follow-up, providing additional prognostic value to classic risk markers [17]. Compostella et al. found that patients with the lowest SDNN values had a higher risk of all-cause mortality ( $p = 0.010$ ), even in patients with a high successful percutaneous coronary intervention (PCI) rate (94%), an effect that was not maintained in the case of RMSSD [19]. Ablonskyte-Dudoniene et al. revealed that patients with a reduced RMSSD had an almost 10-fold higher 1-year mortality risk, and those with low SDNN values had a 4-fold higher 5-year mortality risk [21].

In contrast to the studies mentioned earlier, when HRV was measured on 24 h ECG recordings, Karp et al. observed that measurement during an ultra-short time (10 s) also had important prognostic implications. Patients with low SDNN values at admission (before reperfusion) exhibited an almost 3-fold higher risk of 2-year mortality, even after multivariate analysis [23]. Katz et al. also investigated the utility of HRV measured on a short ECG strip (1 min), but during deep breathing. The authors observed that all patients who died during follow-up had reduced SDANN values [24].

In comparison with all-cause mortality, data regarding cardiac mortality were discrepant across studies. Balanescu et al. observed that patients who experienced sudden cardiac death within one year of follow-up had lower RMSSD, SDNN, and HF values, but a higher LF and LF/HF ratio, thus reflecting a high sympathetic tone in deceased patients. As prognostic markers for sudden cardiac death, an LF/HF ratio  $> 2$  showed an excellent negative predictive value (98%), but with lower sensitivity (81%), specificity (74%), and positive predictive value (14%). A similar negative predictive value was found in the case of patients with SDNN less than 50 ms (97%), with reduced sensitivity (63%), specificity (87%), and poor positive predictive value (21%) [16].

Although depressed SDNN values had an independent predictive value for cardiac mortality ( $p < 0.01$ ), Boskovic et al., observed that it was not associated with an increased risk of sudden cardiac death ( $p > 0.05$ ) [17]. Compostella et al. did not find an association between low SDNN values and cardiac mortality ( $p = 0.055$ ), even though it was statistically significant in the case of all-cause mortality [19]. Nevertheless, Ablonskyte-Dudoniene et al. documented an almost 10-fold higher risk of 5-year cardiac mortality in patients with low SDANN thresholds treated mainly with PCI [21].

Data regarding the correlation between HRV and the risk of major clinical events (MCE) were also discrepant in the literature. Coviello et al. observed that patients with MCE (death, new AMI) exhibited reduced SDNN and HF values, while LF was higher when compared to patients without MCE. After multivariate analysis, both predischarge

SDNN and LF were associated with a significantly higher risk of MCE and reinfarction [20]. SDNN was also linked to a 4-fold higher risk of nonfatal MI, and an almost 5-fold risk of revascularization at 5-year follow-up [21]. In addition, HRV (SDNN, mean RR interval) was correlated with a higher thrombolysis in myocardial infarction (TIMI) score [18]. However, Compostella et al. found different results, as SDNN values were not linked to an increase in MCE risk ( $p = 0.367$ ), and were associated only with all-cause death [19]. Moreover, Karp et al. did not report any difference in reinfarction risk, coronary artery bypass graft (CABG) surgery incidence, and risk of hospitalizations for cardiac causes regarding SDNN values at admission [23].

#### 4. Discussion

To our knowledge, our systematic literature review was the first one focused on the utility of HRV measurement in patients admitted with STEMI.

Published guidelines regarding HRV measurement standards have recognized since 1996 the importance of HRV assessment in various pathological conditions, including hypertension, congestive heart failure, MI, cardiac arrest, and supraventricular and ventricular arrhythmias [9].

Nevertheless, HRV seemed to be forgotten in the next decade, as it was not adopted for risk stratification by any guidelines on STEMI, non-ST segment elevation myocardial infarction (NSTEMI), or chronic coronary syndromes [25–29]. The enthusiasm for HRV evaluation was raised once more advanced technology became available, including different sensors and wearable devices, allowing a more straightforward measurement of various HRV parameters, even in a contactless way [30–32].

Ischemic heart disease represents the leading cause of death, emphasizing the importance of risk stratification and early therapeutic intervention [33]. A recently published meta-analysis involving patients with coronary artery disease revealed that HRV parameters were associated with an increased risk of overall mortality, including sudden cardiac death, sudden cardiac arrest, nonsudden cardiac death, and noncardiac death ( $p < 0.001$ ). In addition, diminished SDNN values were linked to other established risk factors, such as reduced left ventricular ejection fraction [34]. The great merit of this study was that it consolidated and confirmed the hypothesis of the (general) correlation of ischemic coronary heart disease and HRV, but it did not mention specifically acute coronary events or STEMI.

Moreover, HRV could be used to predict cardiovascular events even in a healthy population. One meta-analysis involving patients without known cardiovascular disease documented impressive results, as reduced HRV values were associated with a 40% higher risk of a first cardiovascular event. This meta-analysis included studies that measured HRV on different duration strips, from 10 s to 24 h evaluation [35]. Thus, HRV assessment could provide important prognostic information for cardiovascular risk stratification.

Mortality in patients with STEMI remains high, although it decreased significantly once PCI became available and more invasive secondary prevention measures were implemented in daily clinical practice. In one study that enrolled patients with STEMI who underwent primary PCI, the authors observed a 13.7% mortality rate during a mean follow-up of 3.5 years [36]. Therefore, risk stratification still represents a crucial step for each patient presenting with STEMI.

However, none of the risk scores available confers a perfect prediction power for adverse events, including TIMI, Global Registry of Acute Coronary Events (GRACE), Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC), and Primary Angioplasty in Myocardial Infarction (PAMI) scores [37,38]. Inclusion of a supplementary marker such as HRV in traditional risk scores may improve the detection of high-risk patients, thus ensuring an early therapeutic intervention. Furthermore, HRV could be incorporated in future risk stratification computational models based on artificial intelligence to increase accuracy.

Overall, HRV appeared to be a helpful marker in stratifying the risk of all-cause mortality in patients with STEMI. In particular, lower SDNN and RMSSD values and

higher LF/HF ratios were observed in high-risk patients [16,17,19,21–24]. However, these results should be interpreted cautiously, as many factors can impact HRV measurements: nonmodifiable factors (age, gender), environmental factors, physiological and pathological factors, lifestyle, and neuropsychological factors [39]. Although an increased LF/HF ratio was associated with worse clinical outcomes, a lower LF/HF ratio was observed in patients in prolonged lying positions due to various pathological conditions ( $p < 0.001$ ) [40]. This could be of particular interest in patients with STEMI and low physical activity limited by heart failure symptoms.

Moreover, long-term treatment with beta-blockers recommended in patients presenting with STEMI can also impact HRV assessment. Beta-blockers can increase time- and frequency-domain parameters (HF) by reducing the activity of the sympathetic autonomic nervous system, thus improving clinical outcomes [17,41,42]. However, there are limited data concerning patients whose HRV parameters remained unchanged under treatment with beta-blockers. Thus, more clinical trials are required to elucidate if this could be a sign of a poor prognosis. Consequently, awareness is required when evaluating HRV parameters in patients treated with beta-blockers, as they could have higher values.

Although 24 h ECG monitoring was used in most of the clinical studies analyzed, there was also supportive evidence for the utility of short and ultra-short time-recording evaluations (<5 min) [23,24]. HRV measured even on a 10 s ECG strip before revascularization therapy was associated with significantly increased 2-year mortality [23].

Nonetheless, studies analyzed in the present systematic review were observational, with different PCI rates than myocardial reperfusion treatment, limiting the results in the contemporary cohort of patients with STEMI in the context of the new generation of drug-eluting stents and current antithrombotic and risk-modifying therapies. Hence, large clinical trials are required to confirm the utility of HRV assessment for risk stratification in contemporary patients with STEMI.

## 5. Conclusions

HRV facile measurement in patients with STEMI can provide major prognostic information, as it is associated with an increased risk of all-cause mortality documented in clinical studies. Currently, the available evidence supports the integration of HRV parameters in future prediction models to identify high-risk patients who would benefit from more aggressive or invasive preventive measures. Although data were discrepant, some studies found an association between HRV and cardiac mortality, reinfarction, and other major adverse cardiovascular events. More and larger clinical trials are required to validate these findings in contemporary patients with STEMI.

**Supplementary Materials:** The following are available online at <https://www.mdpi.com/article/10.3390/medicina57101021/s1>, Figure S1: Flow diagram of selected studies in the present systematic review. Table S1: Databases and search strategies used in the present systematic review. Table S2: General characteristics of studies included in the present systematic review. Table S3: Quality assessment using the NIH tool designed for observational studies.

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## References

1. Cygankiewicz, I.; Zareba, W. Chapter 31—Heart rate variability. In *Handbook of Clinical Neurology*; Buijs, R.M., Swaab, D.F., Eds.; Elsevier: Amsterdam, The Netherlands, 2013; Volume 117, pp. 379–393.
2. Kim, H.-G.; Cheon, E.-J.; Bai, D.-S.; Lee, Y.H.; Koo, B.-H. Stress and heart rate variability: A meta-analysis and review of the literature. *Psychiatry Investig.* **2018**, *15*, 235–245. [[CrossRef](#)]
3. Chalmers, J.A.; Quintana, D.S.; Abbott, M.J.A.; Kemp, A.H. Anxiety disorders are associated with reduced heart rate variability: A meta-analysis. *Front. Psychiatry* **2014**, *5*, 80. [[CrossRef](#)] [[PubMed](#)]
4. Deschodt-Arsac, V.; Lalanne, R.; Spiluttini, B.; Bertin, C.; Arsac, L.M. Effects of heart rate variability biofeedback training in athletes exposed to stress of university examinations. *PLoS ONE* **2018**, *13*, e0201388. [[CrossRef](#)] [[PubMed](#)]
5. Goessel, V.C.; Curtiss, J.E.; Hofmann, S.G. The effect of heart rate variability biofeedback training on stress and anxiety: A meta-analysis. *Psychol. Med.* **2017**, *47*, 2578–2586. [[CrossRef](#)] [[PubMed](#)]
6. Lehrer, P.; Kaur, K.; Sharma, A.; Shah, K.; Huseby, R.; Bhavsar, J.; Zhang, Y. Heart rate variability biofeedback improves emotional and physical health and performance: A systematic review and meta analysis. *Appl. Psychophysiol. Biofeedback* **2020**, *45*, 109–129. [[CrossRef](#)]
7. Schumann, A.; de la Cruz, F.; Köhler, S.; Brotte, L.; Bär, K.-J. The influence of heart rate variability biofeedback on cardiac regulation and functional brain connectivity. *Front. Neurosci.* **2021**, *15*, 775. [[CrossRef](#)]
8. Shaffer, F.; Ginsberg, J.P. An overview of heart rate variability metrics and norms. *Front. Public Health* **2017**, *5*, 1–17. [[CrossRef](#)]
9. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: Standards of measurement, physiological interpretation and clinical use. *Circulation* **1996**, *93*, 1043–1065. [[CrossRef](#)]
10. Kleiger, R.E.; Miller, J.P.; Bigger, J.T., Jr.; Moss, A.J. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am. J. Cardiol.* **1987**, *59*, 256–262. [[CrossRef](#)]
11. Yang, L.; Zhao, Y.; Qiao, B.; Wang, Y.; Zhang, L.; Cui, T.; Fu, P. Heart rate variability and prognosis in hemodialysis patients: A meta-analysis. *Blood Purif.* **2021**, *50*, 298–308. [[CrossRef](#)]
12. Dekker, J.M.; Crow, R.S.; Folsom, A.R.; Hannan, P.J.; Liao, D.; Swenne, C.A.; Schouten, E.G. Low heart rate variability in a 2-minute rhythm strip predicts risk of coronary heart disease and mortality from several causes: The ARIC Study. *Circulation* **2000**, *102*, 1239–1244. [[CrossRef](#)]
13. Fang, S.C.; Wu, Y.L.; Tsai, P.S. Heart rate variability and risk of all-cause death and cardiovascular events in patients with cardiovascular disease: A meta-analysis of cohort studies. *Biol. Res. Nurs.* **2020**, *22*, 45–56. [[CrossRef](#)]
14. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* **2021**, *372*, n71. [[CrossRef](#)] [[PubMed](#)]
15. Ma, L.L.; Wang, Y.Y.; Yang, Z.H.; Huang, D.; Weng, H.; Zeng, X.T. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: What are they and which is better? *Mil. Med. Res.* **2020**, *7*, 7. [[CrossRef](#)] [[PubMed](#)]
16. Balanescu, S.; Corlan, A.D.; Dorobantu, M.; Gherasim, L. Prognostic value of heart rate variability after acute myocardial infarction. *Med. Sci. Monit.* **2004**, *10*, Cr307–Cr315. [[PubMed](#)]
17. Bošković, A.; Belada, N.; Knežević, B. Prognostic value of heart rate variability in post-infarction patients. *Vojnosanit. Pregl.* **2014**, *71*, 925–930. [[CrossRef](#)]
18. Chakrovorty, S.; Khan, M.; Kundu, S.; Barua, S.; Dutta, B.; Uddin, M.; Islam, A.K.M.M.; Ullah, M.; Majumder, A. Correlation of heart rate variability and 24-hour mean heart rate with TIMI risk score in acute ST-segment elevation myocardial infarction. *Cardiovasc. J.* **2012**, *4*, 8–12. [[CrossRef](#)]
19. Compostella, L.; Lakusic, N.; Compostella, C.; Truong, L.V.S.; Iliceto, S.; Bellotto, F. Does heart rate variability correlate with long-term prognosis in myocardial infarction patients treated by early revascularization? *World J. Cardiol.* **2017**, *9*, 27–38. [[CrossRef](#)]
20. Coviello, I.; Pinnacchio, G.; Laurito, M.; Stazi, A.; Battipaglia, I.; Barone, L.; Mollo, R.; Russo, G.; Villano, A.; Sestito, A.; et al. Prognostic role of heart rate variability in patients with ST-segment elevation acute myocardial infarction treated by primary angioplasty. *Cardiology* **2013**, *124*, 63–70. [[CrossRef](#)]
21. Ablonskytė-Dūdonienė, R.; Bakšytė, G.; Čeponienė, I.; Kriščiukaitis, A.; Drėgūnas, K.; Ereminienė, E. Impedance cardiography and heart rate variability for long-term cardiovascular outcome prediction after myocardial infarction. *Medicina* **2012**, *48*, 350–358. [[CrossRef](#)]
22. Erdogan, A.; Coch, M.; Bilgin, M.; Parahuleva, M.; Tillmanns, H.; Waldecker, B.; Soydan, N. Prognostic value of heart rate variability after acute myocardial infarction in the era of immediate reperfusion. *Herzschrittmachertherapie Elektrophysiologie* **2008**, *19*, 161–168. [[CrossRef](#)]
23. Karp, E.; Shiyovich, A.; Zahger, D.; Gilutz, H.; Grosbard, A.; Katz, A. Ultra-short-term heart rate variability for early risk stratification following acute ST-elevation myocardial infarction. *Cardiology* **2009**, *114*, 275–283. [[CrossRef](#)]
24. Katz, A.; Liberty, I.F.; Porath, A.; Ovsyshcher, I.; Prystowsky, E.N. A simple bedside test of 1-minute heart rate variability during deep breathing as a prognostic index after myocardial infarction. *Am. Heart J.* **1999**, *138*, 32–38. [[CrossRef](#)]
25. Ibanez, B.; James, S.; Agewall, S.; Antunes, M.J.; Bucciarelli-Ducci, C.; Bueno, H.; Caforio, A.L.P.; Crea, F.; Goudevenos, J.A.; Halvorsen, S.; et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur. Heart J.* **2018**, *39*, 119–177. [[CrossRef](#)] [[PubMed](#)]



26. O’Gara, P.T.; Kushner, F.G.; Ascheim, D.D.; Casey, D.E., Jr.; Chung, M.K.; de Lemos, J.A.; Ettinger, S.M.; Fang, J.C.; Fesmire, F.M.; Franklin, B.A.; et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the american college of cardiology foundation/american heart association task force on practice guidelines. *Circulation* **2013**, *127*, e362–e425. [[CrossRef](#)] [[PubMed](#)]
27. Collet, J.P.; Thiele, H.; Barbato, E.; Barthélémy, O.; Bauersachs, J.; Bhatt, D.L.; Dendale, P.; Dorobantu, M.; Edvardsen, T.; Folliguet, T.; et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur. Heart J.* **2021**, *42*, 1289–1367. [[CrossRef](#)] [[PubMed](#)]
28. Amsterdam, E.A.; Wenger, N.K.; Brindis, R.G.; Casey, D.E., Jr.; Ganiats, T.G.; Holmes, D.R., Jr.; Jaffe, A.S.; Jneid, H.; Kelly, R.F.; Kontos, M.C.; et al. 2014 AHA/ACC guideline for the management of patients with non-st-elevation acute coronary syndromes: A report of the american college of cardiology/american heart association task force on practice guidelines. *J. Am. Coll. Cardiol.* **2014**, *64*, e139–e228. [[CrossRef](#)] [[PubMed](#)]
29. Knuuti, J.; Wijns, W.; Saraste, A.; Capodanno, D.; Barbato, E.; Funck-Brentano, C.; Prescott, E.; Storey, R.F.; Deaton, C.; Cuisset, T.; et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur. Heart J.* **2020**, *41*, 407–477. [[CrossRef](#)]
30. Bakhtiyari, K.; Beckmann, N.; Ziegler, J. Contactless heart rate variability measurement by IR and 3D depth sensors with respiratory sinus arrhythmia. *Procedia Comput. Sci.* **2017**, *109*, 498–505. [[CrossRef](#)]
31. Schuurmans, A.A.T.; de Loeff, P.; Nijhof, K.S.; Rosada, C.; Scholte, R.H.J.; Popma, A.; Otten, R. Validity of the empatica E4 wristband to measure heart rate variability (HRV) parameters: A Comparison to Electrocardiography (ECG). *J. Med. Syst.* **2020**, *44*, 190. [[CrossRef](#)]
32. Hochstadt, A.; Chorin, E.; Viskin, S.; Schwartz, A.L.; Lubman, N.; Rosso, R. Continuous heart rate monitoring for automatic detection of atrial fibrillation with novel bio-sensing technology. *J. Electrocardiol.* **2019**, *52*, 23–27. [[CrossRef](#)]
33. Nowbar, A.N.; Gitto, M.; Howard, J.P.; Francis, D.P.; Al-Lamee, R. Mortality from ischemic heart disease. *Circulation Cardiovasc. Qual. Outcomes* **2019**, *12*, e005375. [[CrossRef](#)]
34. Vuoti, A.O.; Tulppo, M.P.; Ukkola, O.H.; Junttila, M.J.; Huikuri, H.V.; Kiviniemi, A.M.; Perkiömäki, J.S. Prognostic value of heart rate variability in patients with coronary artery disease in the current treatment era. *PLoS ONE* **2021**, *16*, e0254107. [[CrossRef](#)]
35. Hillebrand, S.; Gast, K.B.; de Mutsert, R.; Swenne, C.A.; Jukema, J.W.; Middeldorp, S.; Rosendaal, F.R.; Dekkers, O.M. Heart rate variability and first cardiovascular event in populations without known cardiovascular disease: Meta-analysis and dose–response meta-regression. *EP Eur.* **2013**, *15*, 742–749. [[CrossRef](#)]
36. Doost Hosseiny, A.; Moloi, S.; Chandrasekhar, J.; Farshid, A. Mortality pattern and cause of death in a long-term follow-up of patients with STEMI treated with primary PCI. *Open Heart* **2016**, *3*, e000405. [[CrossRef](#)] [[PubMed](#)]
37. Kao, Y.-T.; Hsieh, Y.-C.; Hsu, C.-Y.; Huang, C.-Y.; Hsieh, M.-H.; Lin, Y.-K.; Yeh, J.-S. Comparison of the TIMI, GRACE, PAMI and CADILLAC risk scores for prediction of long-term cardiovascular outcomes in Taiwanese diabetic patients with ST-segment elevation myocardial infarction: From the registry of the Taiwan Society of Cardiology. *PLoS ONE* **2020**, *15*, e0229186. [[CrossRef](#)] [[PubMed](#)]
38. Chen, Y.-H.; Huang, S.-S.; Lin, S.-J. TIMI and GRACE risk scores predict both short-term and long-term outcomes in Chinese patients with acute myocardial infarction. *Acta Cardiol. Sin.* **2018**, *34*, 4–12. [[CrossRef](#)] [[PubMed](#)]
39. Fatissou, J.; Oswald, V.; Lalonde, F. Influence diagram of physiological and environmental factors affecting heart rate variability: An extended literature overview. *Heart Int.* **2016**, *11*, e32–e40. [[CrossRef](#)] [[PubMed](#)]
40. Yoshida, Y.; Furukawa, Y.; Ogasawara, H.; Yuda, E.; Hayano, J. Longer lying position causes lower LF/HF of heart rate variability during ambulatory monitoring. In Proceedings of the 2016 IEEE 5th Global Conference on Consumer Electronics, Kyoto, Japan, 11–14 October 2016; pp. 1–2.
41. Aronson, D.; Burger, A.J. Effect of beta-blockade on heart rate variability in decompensated heart failure. *Int. J. Cardiol.* **2001**, *79*, 31–39. [[CrossRef](#)]
42. Brembilla-Perrot, B.; Houriez, P.; Claudon, O.; Beurrier, D.; Preiss, J.P. Different action of beta-blockers on daytime and nighttime heart rate variability. *Ann. Noninvasive Electrocardiol.* **2000**, *5*, 158–165. [[CrossRef](#)]