Original Article

Heart Rate Turbulence Is a Powerful Predictor of Cardiac Death and Ventricular Arrhythmias in Postmyocardial Infarction and Heart Failure Patients

A Systematic Review and Meta-Analysis

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Background—Heart rate turbulence (HRT) has been proposed as a candidate marker of altered autonomic tone, and some studies showed its prognostic value for both cardiac death (CD) and sudden death. Nevertheless, HRT is not currently used in the clinical practice.

Methods and Results—We performed a systematic review and meta-analysis of the predictive value of HRT for the end points of total mortality, CD, and fatal and nonfatal ventricular arrhythmias in postacute myocardial infarction and heart failure patients. MEDLINE and The Cochrane Library databases were systematically searched to identify studies, which analyzed the predictive value of abnormal HRT for the defined end points. Twenty studies (25 cohorts: 12 832 patients) were identified by the systematic review, and 15 studies (20 cohorts: 11 499 patients) were included in the meta-analyses. Abnormal HRT was a predictive marker for all the end points in heart failure patients and more markedly in postacute myocardial infarction patients, where 9 out of the 10 cohorts had an ejection fraction >30%. In postacute myocardial infarction patients, HRT had pooled risk ratios of 3.53 (95% confidence interval [CI], 2.54–4.90), 4.82 (95% CI, 3.12–7.45), and 4.48 (95% CI, 3.04–6.60), and positive likelihood ratios of 3.5 (95% CI, 2.6–4.8), 4.1 (95% CI, 3.0–5.7), and 2.7 (95% CI, 2.2–3.3) for total mortality, CD, and arrhythmic events, respectively. The combination of abnormal HRT and T-wave alternans (5 cohorts: 1516 patients) increased the predictive power for CD and arrhythmic events.

Conclusions—HRT is a powerful predictor of both CD and arrhythmic events, particularly in postacute myocardial infarction patients with ejection fraction >30%. HRT power increases in combination with T-wave alternans analysis. (***Circ Arrhythm Electrophysiol*. 2016;9:e004610. DOI: 10.1161/CIRCEP.116.004610.**)

Key Words: autonomic nervous system ■ heart failure ■ implantable cardioverter-defibrillator ■ myocardial infarction ■ sudden cardiac death ■ ventricular tachycardia/fibrillation

In the current guidelines,[1] a left ventricular ejection fraction (EF) ≤35% is the major determinant to recommend an implantable cardioverter–defibrillator (ICD) in sudden cardiac death (SCD) primary prevention. However, low EF has limited sensitivity and specificity as a risk marker of SCD.[2] Most patients implanted with an ICD according to the current guidelines do not actually benefit from it[3,4] and may experience side effects.[4] By contrast, several patients who are at risk of SCD are not identified by the EF marker because the main part of SCD patients exhibits just mildly depressed EF.[5] Therefore, in recent years, efforts have been made to identify new markers or combinations of markers,[6] to improve the prognostic stratification of SCD.

Numerous experimental and clinical observations have shown that alterations of the autonomic nervous system, such as sympathetic activation and reduced vagal modulation, may have important proarrhythmic effects and may facilitate the onset of ventricular tachycardia/fibrillation.[2] Despite the plethora of methods proposed for the study of autonomic tone, their clinical use in the prognostic stratification of SCD is still limited. In 1999, heart rate turbulence (HRT) has been proposed as a new marker of altered autonomic tone.[7] HRT describes the short-term changes of heart rate induced by a premature ventricular beat and typically consists of a brief heart rate acceleration followed by a gradual heart rate deceleration. The HRT acceleration and deceleration phases are quantified by 2 numeric descriptors, HRT onset (TO) and HRT slope (TS).[8] The biphasic HRT curve is the result of a complex physiological reflex, mostly mediated by the baroreflex; however, other mechanisms, such as postextrasystolic potentiation, have been proposed.[8,9] Following the seminal work of Schmidt et al,[7] subsequent studies have confirmed HRT prognostic value

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WHAT IS KNOWN

- The current guidelines for the indication of an ICD in primary prevention of SCD are mostly based on the EF, which is a suboptimal predictor of SCD.
- Autonomic tone alterations can facilitate the onset of ventricular tachycardia/fibrillation leading to SCD and can be noninvasively measured by HRT.

WHAT THE STUDY ADDS

- This meta-analysis of a large number of studies shows that HRT is a powerful predictor of both CD and SCD in post-AMI and HF patients.
- HRT is particularly predictive in post-AMI patients with mildly depressed EF, and its performance can be improved in combination with TWA.
- The combination of HRT and TWA, easily assessable by a 24-hour Holter recording, could be considered in a polyparametric evaluation of arrhythmic risk to improve the patient selection for ICD therapy.

for both cardiac death (CD) and SCD.[9] In addition, a recent editorial by Rizas and Bauer[10] suggested the use of HRT to improve ICD implantation in high-risk postmyocardial infarction patients. Nevertheless, HRT is not currently used in the clinical practice. This systematic review and meta-analysis aims to assess the role of HRT in the prognostic stratification of major adverse cardiac events (total mortality [TM], CD, SCD, and ventricular tachyarrhythmias) in a large population of patients in postacute myocardial infarction (post-AMI) and heart failure (HF) conditions.

Methods

The systematic review and the meta-analysis were conducted following the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement.[11]

Eligibility Criteria

The literature search was performed to identify studies assessing HRT predictive value in the prognostic stratification of major adverse cardiac events (TM, CD, SCD, and ventricular tachyarrhythmias defined as arrhythmic events [AEs]) in post-AMI and HF patients. Both ischemic and nonischemic dilated cardiomyopathy causes of HF were considered, although other cardiomyopathies were excluded. Additional inclusion criteria were a sample size >100 and an average follow-up longer than 1 year. Consistently with HRT guidelines,[8] only studies based on Holter recordings of at least 18 to 24 hours and using standard TS and TO measures were included. The search was restricted to articles published in English in peer-reviewed journals. Abstracts and session presentations were excluded.

Information Sources, Search Strategy, Study Selection, and Data Collection

MEDLINE and The Cochrane Library electronic databases were systematically searched by 2 reviewers (M.D. and M.M.) to identify primary references from 1999 to March 2016. The following search terms were used: (cardiomyopathy OR ischemic OR idiopathic OR nonischemic OR heart failure OR myocardial infarction OR acute myocardial infarction OR coronary syndrome OR implantable cardioverter–defibrillator) AND (mortality OR cardiac mortality OR cardiac death OR death OR sudden cardiac death OR survival OR adverse cardiac events OR arrhythmias) AND (heart rate turbulence OR turbulence slope OR turbulence onset).

The database search was followed by a review of the citations from eligible studies. Studies were selected based on title and abstract. Selected studies were read thoroughly to identify those suitable for the qualitative analysis and the quantitative analysis (meta-analysis). Studies analyzing the association of HRT with other markers of SCD risk, such as deceleration capacity[12] and Holter T-wave alternans (TWA),[13] were also considered. Two reviewers (M.D. and M.M.) independently extracted the demographic and clinical outcome data from the selected studies. When disagreement occurred, they reviewed the papers together to reach joint conclusions. The methodological quality of the studies was evaluated by applying the Newcastle-Ottawa Scale checklist for cohort studies.[14]

Statistical Analysis

When available, patient characteristics were expressed as numbers or percentages, mean±SD or median (interquartile range), as appropriate. Whenever possible, raw counts of true positives, false positives, false negatives, and true negatives for the available outcomes were extracted from each study. When raw data were not reported, proportions of positive cases, risk ratios, odds ratios, sensitivity, specificity, and Cohen κ coefficient data were used to calculate raw numbers with an approximation error <5%.

Six meta-analyses were performed, subdividing the studies according to the population type and the 3 considered outcomes. An additional meta-analysis was performed on the studies combining HRT with deceleration capacity. Pooled risk ratios (RRs) and 95% confidence intervals (CIs) were estimated by a random effects model based on DerSimonian and Laird method.[15] Data heterogeneity among studies was estimated by Chi^2, I^2, and Tau^2 statistics, which were calculated by an inverse-variance fixed-effect model. Sensitivity analysis was performed to evaluate the influence of individual studies on the pooled RRs. Small study effects were assessed by the Harbord modified test.[16] For each of the end points and subgroups of patients, the performance of a binary classification test based on HRT was assessed in terms of pooled sensitivity, specificity, positive, and negative likelihood ratios (LRs). Specifically, pooled values were calculated using a bivariate model fitted by a generalized linear mixed model approach, to consider the correlation between sensitivity and specificity values across the studies.[17] When the small number of studies precluded the identification of the bivariate model, raw specificity and sensitivity values were reported. A 2-tailed P value <0.05 indicated statistical significance. All analyses were performed using the Cochrane Collaboration Software Review Manager 5 (version 5.2) and STATA 13.1 Statistics/Data analysis (StataCorp, College Station, TX).

Results

Study Selection

The database search identified 193 relevant references, which were complemented by 4 references from the study citations (Figure 1). A total of 144 references were excluded after reading title and abstract, and 53 were retrieved for further evaluation. Of these, 33 studies were excluded because they did not fulfill the inclusion criteria. In particular, the ISAR-HRT study (Innovative Stratification of Arrhythmic Risk–Heart Rate Turbulence; 1445 patients),[18] the first prospective study to validate HRT in a large cohort of the reperfusion era was excluded because of population overlap with the ISAR-Risk study (Improve Stratification of Autonomic Regulation–Risk).[12] The CAST study (Cardiac Arrhythmia Suppression Trial; 744 patients)[19] was excluded because of methodological differences in HRT parameter computation with respect to HRT guidelines.[8] Twenty studies[7,12,20–37] were left for the subsequent qualitative synthesis and 15 for the meta-analyses.[7,12,20–26,29,31–35]

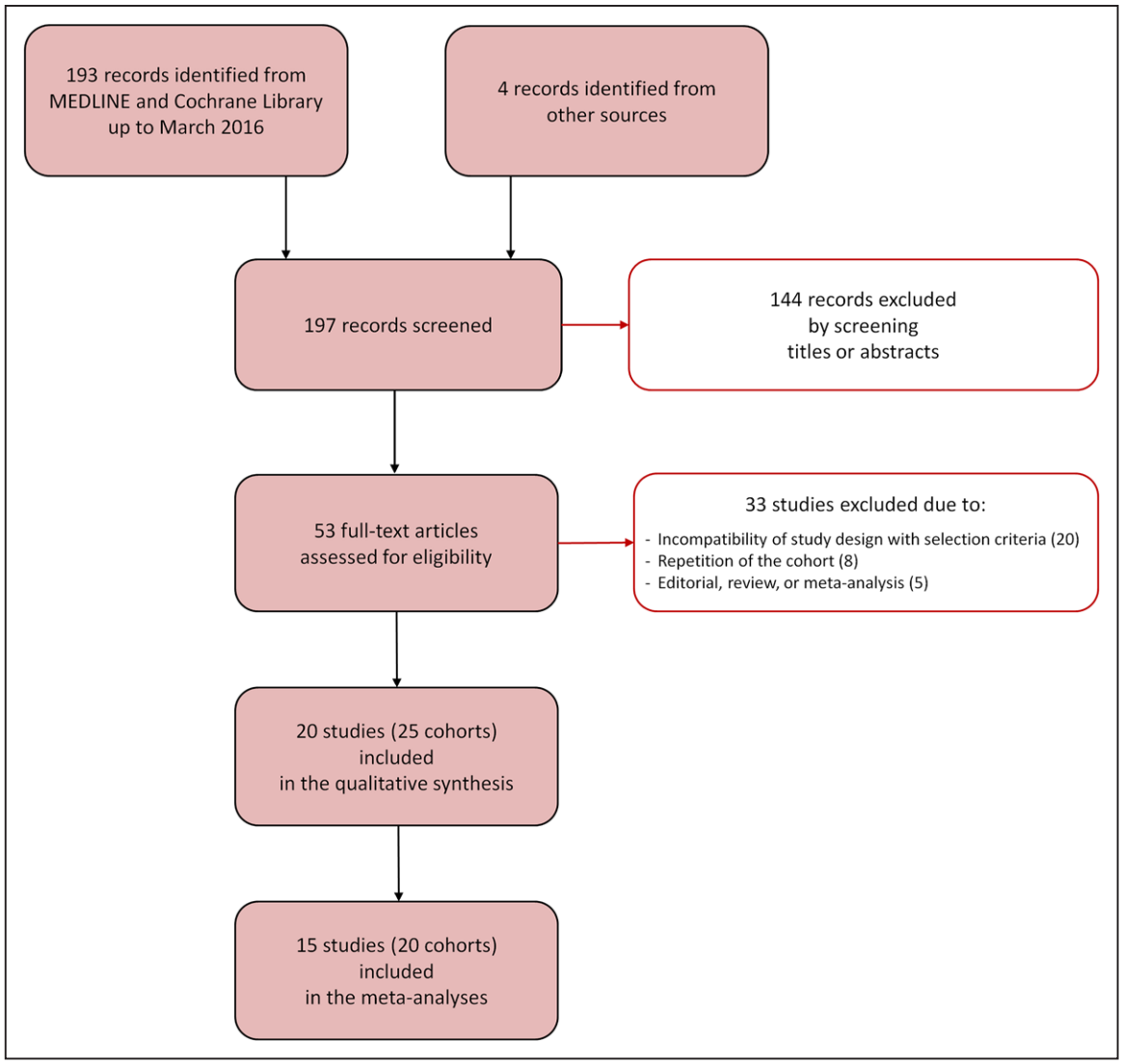

Figure 1. Selection process for the studies included in the systematic review and meta-analysis. The Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) flow diagram depicts the number of records identified, included and excluded, and the reasons for exclusion, through the different phases of the systematic review and meta-analysis.

Of these, 2 studies[7,12] performed a post hoc analysis of previous trials on different cohorts of patients.[38–41] Overall, a total of 25 and 20 cohorts of patients were included in the qualitative and quantitative analysis, respectively. Despite they met eligibility criteria, 5 studies[27,28,30,36,37] were not included in the meta-analysis because of heterogeneity in data presentation (raw data were not available nor derivable). The end points varied in the different cohorts, including TM and CD and AE (Table 1). To avoid data repetition, some cohorts were meta-analyzed only for some of the available end points.

Study Characteristics

The 25 cohorts were divided into post-AMI patients (16 cohorts) and HF patients (9 cohorts), as reported in Tables 1 and 2. In HRT assessment, TO and TS were defined as abnormal according to the thresholds proposed by Schmidt et al.[7] (TS≤2.5 ms/ventricular interval and TO ≥0%). When using both HRT parameters for classification, patients were categorized as HRT0, when both HRT parameters were normal; HRT1, when one parameter was abnormal; and HRT2, when both parameters were abnormal.[7] The combination of HRT2 and abnormal deceleration capacity (≤4.5 ms) was defined as severe autonomic failure (SAF)[12] and was evaluated in a total of 5 cohorts. HRT in combination with Holter TWA was evaluated in 5 cohorts, with some differences in Holter TWA assessment methods (in 3 cohorts,[25,26,28] the Modified Moving Average method[13] was used). The quality of the selected studies was generally good with Newcastle-Ottawa Scale scores ranging between 6 and 9 (Table 1). There were no randomized studies. Sixteen cohorts were analyzed prospectiv ely,[12,21–24,26–36] 1 retrospectively,[25] and 8 cohorts represented post hoc analyses of previous trials.[20,36,38–41]

Predictive Power of HRT

Ten cohorts of post-AMI patients were included in the first group of meta-analyses. The characteristics of the cohorts and patients are reported in Tables 1 and 2. All cohorts but one[7] had patients with an average EF >30%. The prevalence

Table 1. Characteristics of the 25 Cohorts Identified by the Systematic Review, Subgrouped According to Patient Type

Cohorts	Year	Study Type	NOS Score	Patients, n	End Points	Follow-Up, mo	HRT Category	HRT Timing
Cohorts including patients after myocardial infarction								
Schmidt et al (a)[7]	1999	Post hoc	3, 1, 2	577	TM	22*	HRT2	Early
Schmidt et al (b)[7]	1999	Post hoc	3, 2, 2	614	TM	21 [12–24]	HRT2	Early
Ghuran et al[20]	2002	Post hoc	3, 2, 2	981	CD†	21	HRT2	Early
Mäkikallio et al[21]	2005	Prospective	4, 2, 3	2130	SCD	33 (25–47)	TS	Early
Bauer et al (a)[12]	2009	Prospective	4, 2, 3	2343	TM	59 (34–60)	HRT2; SAF	Early
Huikuri et al[22]	2009	Prospective	3, 2, 3	234	VF/VT	22±6	TS	Late
Stein et al[23]	2009	Prospective	3, 1, 2	342	CD	12	HRT2	Early
Miwa et al[24]	2011	Prospective	4, 2, 3	222	CD‡	29±14	HRT2	Late
Sulimov et al[25]	2012	Retrospective	3, 1, 2	111	TM, CD, SCD	=12	HRT2; HRT2+TWA	Late
Hoshida et al[26]	2013	Prospective	4, 2, 3	313	CD, SCD	39±14	HRT2; HRT2+TWA	Late
Exner et al[27]§	2007	Prospective	3, 2, 3	322	CD, SCD, a.SCD	47 (37–56)	HRT1+TWA	Late
Li-na et al[28]§	2012	Prospective	4, 2, 2	173	CD	19±5	HRT2+TWA	Early
Bauer et al (b)[12]	2009	Post hoc	4, 1, 2	679	TM	36	SAF	Early
Bauer et al (c)[12]	2009	Post hoc	3, 2, 2	633	TM	21 [12–24]	SAF	Early
Bauer et al (d)[12]	2009	Post hoc	3, 2, 2	625	TM	21 [12–24]	SAF	Early
Bauer et al (e)[12]	2009	Post hoc	4, 1, 3	597	TM	24	SAF	Early
Cohorts including heart failure patients								
Grimm et al[29]	2003	Prospective	4, 1, 3	242 (0–242)	TM†, AE	41±23	HRT2	…
Moore et al[30]§	2006	Prospective	4, 1, 2	358 (265–93)	TM, CD, SCD	60	TS	…
Cygankiewicz et al[31]	2008	Prospective	4, 2, 2	592 (296–296)	TM, CD, SCD	44*	HRT2	…
Miwa et al[32]	2009	Prospective	4, 2, 2	292 (186–106)	CD	15±7	HRT2	…
Sredniawa et al[33]	2010	Prospective	4, 2, 2	110 (63–47)	TM†	70±16	HRT2	…
Miwa et al[34]	2012	Prospective	4, 2, 3	282 (177–105)	AE	32±15	HRT2	…
La Rovere et al[35]	2012	Prospective	3, 1, 3	194 (97–97)	AE	47 (39–52)	TS+creatinine‖	…
Au-Yeung et al[36]§	2015	Post hoc	3, 1, 3	475 (252–223)	AE	46 [24–73]	TS	…
Ramírez et al[37]§	2015	Prospective	4, 2, 2	597 (299–298)	CD, SCD	48	TS+TWA	…

Studies performing sole HRT analysis or HRT analysis in combination with deceleration capacity (severe autonomic failure) or T-wave alternans analysis are included. Schmidt et al[7] (a): patients of MPIP study (Multicentre Post-Infarction Program) 1983[38]; Schmidt et al[7] (b): patients of EMIAT (European Myocardial Infarction Amiodarone Trial) placebo arm 1997[39]; Bauer et al[12] (a): patients of ISAR-Risk study (Improve Stratification of Autonomic Regulation–Risk) 2009[12]; Bauer et al[12] (b): patients of SGHMS study (St George's Hospital Medical School) 1996[40]; Bauer et al[12] (c): patients of EMIAT placebo arm 1997[39]; Bauer et al[12] (d): patients of EMIAT amiodarone arm 1997[39]; and Bauer et al[12] (e): patients of MRFAT study (Multiple Risk Factor Analysis Trial) 2003.[41] Data are numbers (n), mean±SD or median (interquartile range) or median [range], as available. a.SCD indicates aborted sudden cardiac death; AE, arrhythmic events; CD, cardiac death; Early, <4 wk; HRT, heart rate turbulence; HRT1, either turbulence onset or slope abnormal; HRT2, both turbulence onset and slope abnormal; Late, >4 wk; NOS, Newcastle-Ottawa Scale for quality assessment of nonrandomized studies (selection, comparability, outcome; range: 0–4, 0–2, and 0–3); SAF, severe autonomic failure; SCD, sudden cardiac death; M, total mortality; TS, turbulence slope; TWA, Holter T-wave alternans; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*Median, interquartile range not available.

†Including heart transplant.

‡Including nonfatal cardiac events.

§Studies not included in the meta-analysis.

‖TS ≤2.5 ms/ventricular interval and creatinine >1.21 mg/dL.

of positive HRT test ranged between 4% and 28% among cohorts. Individual and pooled RRs for the 3 different end points are reported in the forest plots of Figure 2. The pooled RRs for TM, CD, and AE were 3.53 (95% CI, 2.54–4.90), 4.82 (95% CI, 3.12–7.45), and 4.48 (95% CI, 3.04–6.60), respectively. Heterogeneity was not statistically significant. Sensitivity analysis, performed for the study with 100% of diabetic patients[24] and for the study with average EF of 30%,[7] showed that the exclusion of individual studies did not affect the strength of the association between HRT and the end points. The Harbord modified test was not significant.

Six cohorts of HF patients were included in the second group of meta-analyses (Tables 1 and 2). Four of the cohorts had patients with an average EF >30%.[31,32,34,35] Individual and pooled RRs for the 3 different end points are reported in the forest plots of Figure 3. The pooled RRs for TM, CD, and AE

Table 2. Characteristics of the Patients Included in the 25 Cohorts Identified by the Systematic Review, Subgrouped According to Patient Type

Cohorts	Males, %	Age, y	LVEF, %	Diabetes Mellitus, %	β-Blockers, %	PCI, %	HRT+ Prevalence, %
Cohorts including patients after myocardial infarction							
Schmidt et al (a)[7]	78	57±9	45±15	NA	32	0	12
Schmidt et al (b)[7]	85	61±9	30±9	17	44	0	13
Ghuran et al[20]	87	57±10	49±12	17	20	0	4
Mäkikallio et al[21]	78	59±10	>35% in 89%	19	94	66	22
Bauer et al (a)[12]	80	59 (51–67)	55 (45–62)	18	94	92	8
Huikuri et al[22]	77	65±11	35±10	20	89	14	28
Stein et al[23]	72	62	35	24	NA	NA	26
Miwa et al[24]	76	71±11	46±11	100	83	93	19
Sulimov et al[25]	76	64±11	47±12	18	77	NA	20
Hoshida et al[26]	74	70±12	47±11	38	72	87	19
Exner et al[27]*	85	62 (53–70)	47 (37–56)	22	92	66	30†
Li-na et al[28]*	63	65	46	45	77	74	22
Bauer et al (b)[12]	79	54±9	>30 in 85%	NA	52	0	7
Bauer et al (c)[12]	85	60±9	30±8	17	45	0	12
Bauer et al (d)[12]	84	60±10	30±7	17	44	0	15
Bauer et al (e)[12]	74	62±10	NA	24	97	24	22
Cohorts including heart failure patients							
Grimm et al[29]	77	48±12	30±10	NA	26	…	29
Moore et al[30]*	74	63±10	41±17	NA	8	…	NA
Cygankiewicz et al[31]	72	63±12	37±14	38	70	…	20
Miwa et al[32]	70	66±15	34±5	26	66	…	28
Sredniawa et al[33]	85	55±10	30±10	24	95	…	25
Miwa et al[34]	73	67±15	34±7	34	79	…	24
La Rovere et al[35]	82	65±10	38±6	NA	69	…	53‡
Au-Yeung et al[36]*	78	60 (19–90)	≤35	NA	69	…	NA
Ramírez et al[37]*	71	65 (17)	≤35 in 56%	38	71	…	47

Studies performing sole HRT analysis or HRT analysis in combination with deceleration capacity or T-wave alternans analysis are included. For the original cohorts included in the studies of Schmidt et al[7] and Bauer et al[12] see the footnote of Table 1. HRT+ indicates abnormal heart rate turbulence; LVEF, left ventricular ejection fraction; NA, not available; PCI, percutaneous coronary intervention for acute myocardial infarction; TS, turbulence slope; and TWA, T-wave alternans.

*Studies not included in the meta-analysis.

†Abnormal HRT and TWA.

‡TS ≤2.5 ms/ventricular interval and creatinine >1.21 mg/dL.

were 2.21 (95% CI, 1.76–2.78), 3.73 (95% CI, 1.65–8.43), and 2.51 (95% CI, 1.55–406), respectively. Heterogeneity was not statistically significant, except for the end point CD (P=0.04; I^2=76%), where only 2 studies were available for analysis. Sensitivity analysis, performed for 1 study with 100% of non-ischemic cardiomyopathy patients,[29] showed that the exclusion of the study did not affect the strength of the association between HRT and the analyzed end points. The Harbord modified test was not significant. Two studies (833 patients) in HF patients[30,36] were not included in the meta-analysis because of the statistical analysis of the data. One study[36] showed a hazard ratio of 1.53 (P<0.01) for AE and the other[30] a significant correlation of HRT with CD (hazard ratio, 0.84; P<0.001, for every 10% increase of TS), but not with AE.

The sensitivity, specificity, positive, and negative LRs of HRT in predicting the 3 end points in post-AMI and HF patients are reported in Table 3. HRT showed high specificity and high positive LR, especially in post-AMI patients.

Predictive Power of HRT in Combination With Other Arrhythmic Markers

To study the predictive value of SAF, 5 cohorts of post-AMI patients were included in the meta-analysis, as reported in Tables 1 and 2. All cohorts were analyzed by Bauer et al,[12]

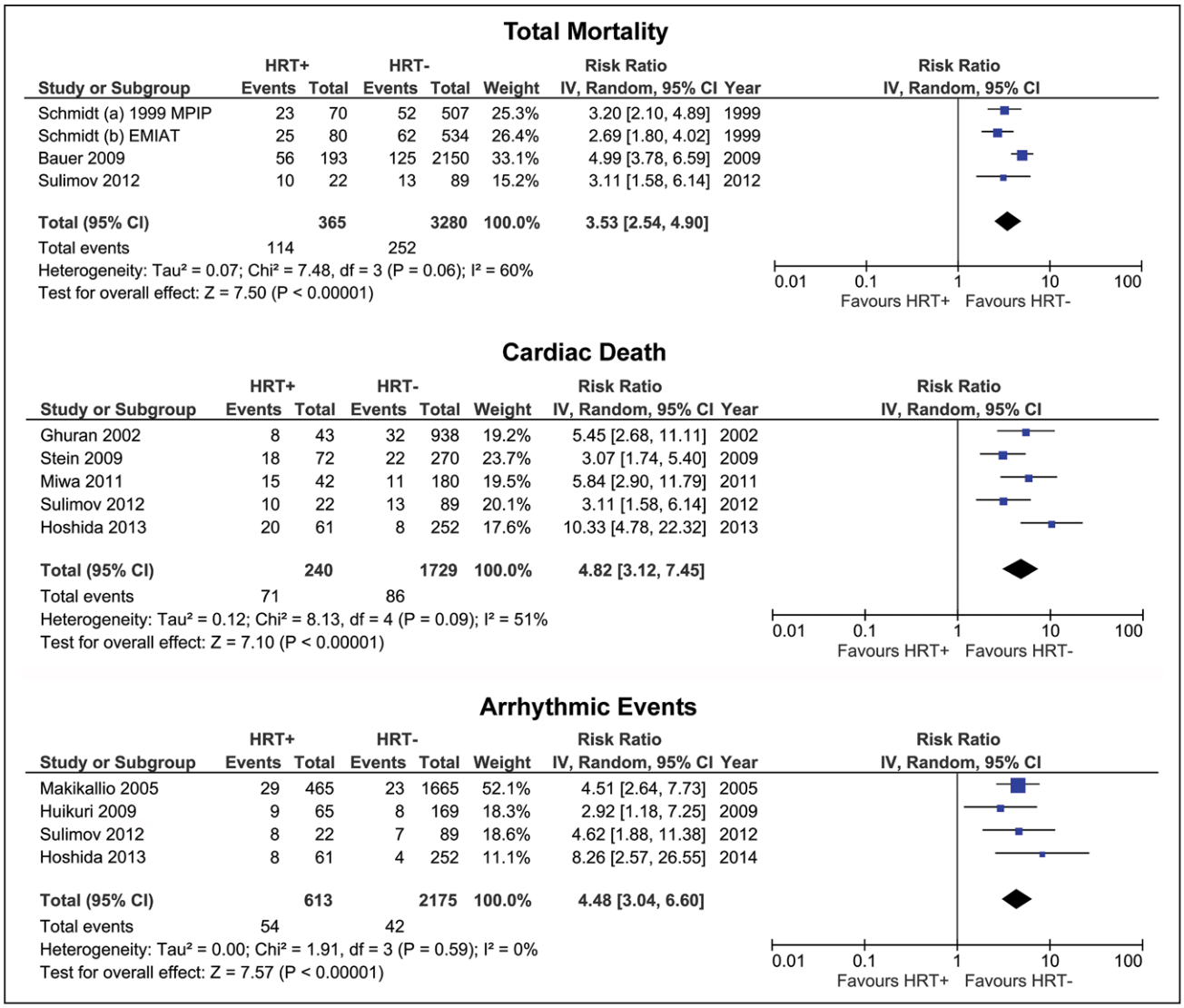

Figure 2. Individual and pooled risk ratios (RRs) of heart rate turbulence (HRT) for the 3 different end points in postacute myocardial infarction (post-AMI) patients. Forest plots comparing total mortality (**top**), cardiac death (**center**), and arrhythmic events (**bottom**) end points in patients with positive (HRT+) and negative test (HRT–). The original cohorts included in the studies of Schmidt et al[7] are listed in the footnote of Table 1. Raw data in the study by Bauer et al[12] were obtained from Zuern et al.[42] CI indicates confidence interval; and IV, inverse-variance.

but 4 referred to post hoc analysis of previous trials.[39–41] The average EF was >30% in 2 cohorts, 30% in 2, and not available in 1 (Table 2). The end point analyzed in these cohorts was TM. The individual and pooled RRs are reported in the forest plot of Figure 4. The pooled RR (3.87; 95% CI, 2.81–5.33) was slightly higher than that of HRT alone. Statistically significant heterogeneity was present (P=0.01; I^2=68%), probably due to the recent prospective cohort of Bauer et al[12] with higher RR than the older, post hoc analyzed cohorts. The Harbord modified test was not significant. Only the large study (2343 patients) of Bauer et al[12] analyzed the predictive power of SAF for the CD and SCD end points. The study showed a high predictive power of SAF for both CD and SCD, with RRs of 9.01 (95% CI, 6.55–12.38) and 5.91 (95% CI, 3.57–9.81), respectively.

The predictive power of HRT in combination with TWA was evaluated in a total of 5 cohorts, whose characteristics are reported in Tables 1 and 2. Four cohorts (all with EF>30%) analyzed post-AMI patients[25–28] and 1 HF patients.[37] Data were not meta-analyzed because of heterogeneities in data reporting and statistical analysis. In all 5 cohorts and for both CD and AE end points, the RRs/HRs (Table 4) displayed a consistent increase when the TWA marker was added to HRT (in post-AMI patients the RRs/HRs increased by a factor ranging from 1.4–4.9).

Discussion

By analyzing a large population (12 832 patients) of post-AMI and HF patients, this systematic review and the meta-analysis demonstrated that the autonomic imbalance measured by HRT was a predictor of all the analyzed end points (TM, CD, and AE) in both populations. However, the pooled RRs were higher in post-AMI patients compared with HF patients (Figures 2 and 3) for all the end points.

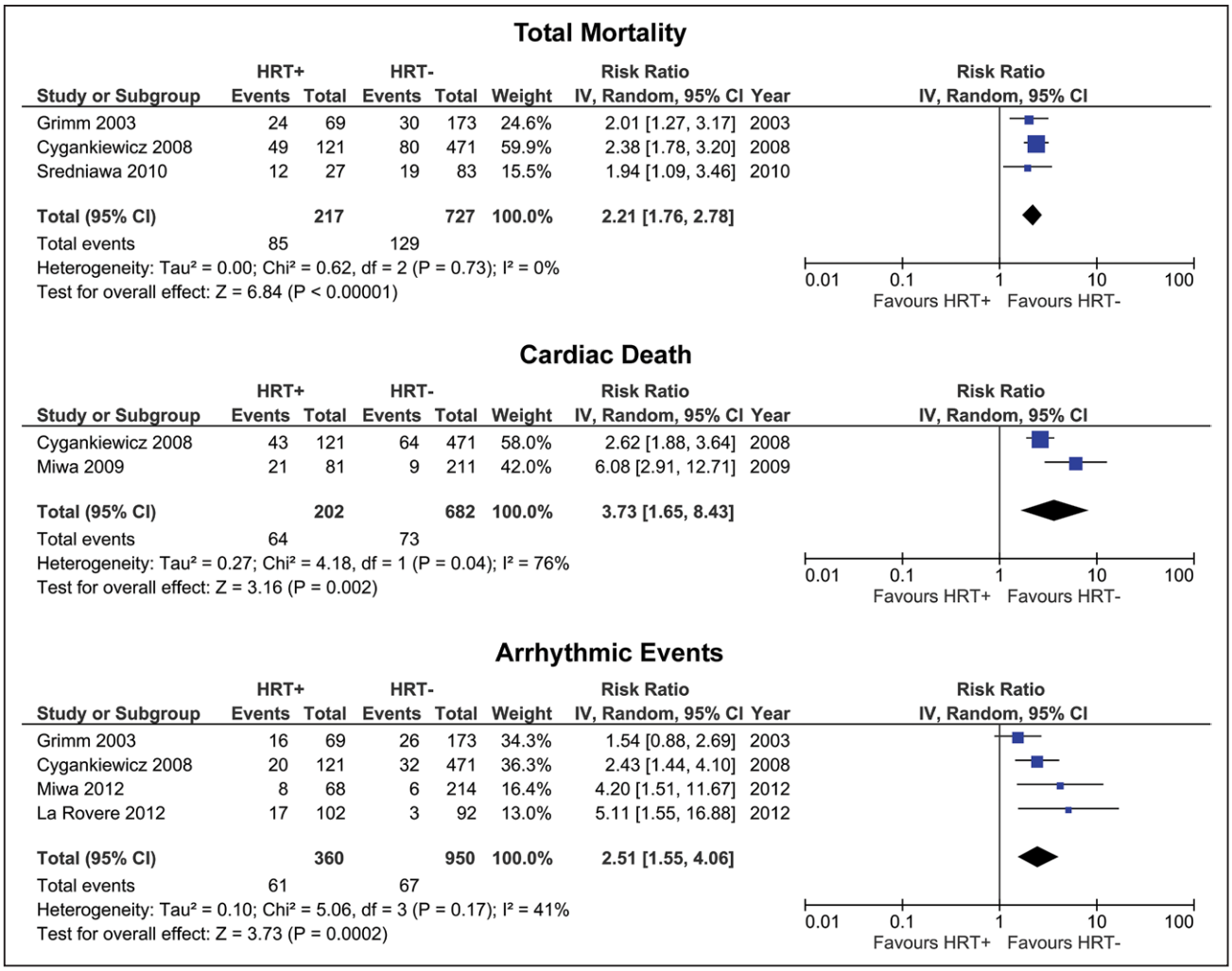

Figure 3. Individual and pooled risk ratios (RRs) of heart rate turbulence (HRT) for the 3 different end points in heart failure patients. Forest plots comparing total mortality (**top**), cardiac death (**center**), and arrhythmic events (**bottom**) end points in patients with positive (HRT+) and negative test (HRT–). CI indicates confidence interval; and IV, inverse-variance.

Post-AMI Patients

In post-AMI patients, HRT was a powerful predictor of all the end points and especially of CD and AE. In the meta-analyses, 9 out of the 10 cohorts had an average EF >30%, thus the results are mainly related to a population with moderately depressed EF. The positive LRs were higher than 2 for all the end points. For CD, they reached a maximum of 4.1, which could influence the therapeutic approach.

In 2 cohorts,[22,27] HRT was predictive of the end points only if measured late from AMI (>4 weeks). However, HRT

Table 3. Performance of HRT Test in Predicting the 3 Different End Points in the 2 Patient Subgroups

End Points	Cohorts, n	Patients, n	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
HRT performance in patients after myocardial infarction						
Total mortality	4	2454	31 (26–37)	91 (88–93)	3.5 (2.6–4.8)	0.75 (0.70–0.82)
Cardiac death	5	1969	46 (31–62)	89 (82–93)	4.1 (3.0–5.7)	0.61 (0.47–0.79)
Arrhythmic events	4	2788	56 (46–66)	79 (78–81)	2.7 (2.2–3.3)	0.55 (0.44–0.69)
HRT performance in heart failure patients						
Total mortality	3	944	40 (33–47)*	82 (79–85)*	2.2 (1.8–2.8)*	0.74 (0.66–0.82)*
Cardiac death	2	884	47 (38–55)*	82 (79–84)*	2.5 (2.0–3.2)*	0.65 (0.56–0.77)*
Arrhythmic events	4	1310	53 (32–74)	72 (60–82)	1.9 (1.5–2.4)	0.64 (0.45–0.92)

Parameters were estimated by a bivariate generalized linear mixed model. CI indicates confidence interval; HRT, heart rate turbulence; and LR, likelihood ratio.
*Raw estimate from number of events, bivariate model fitting not possible because of the limited number of studies.

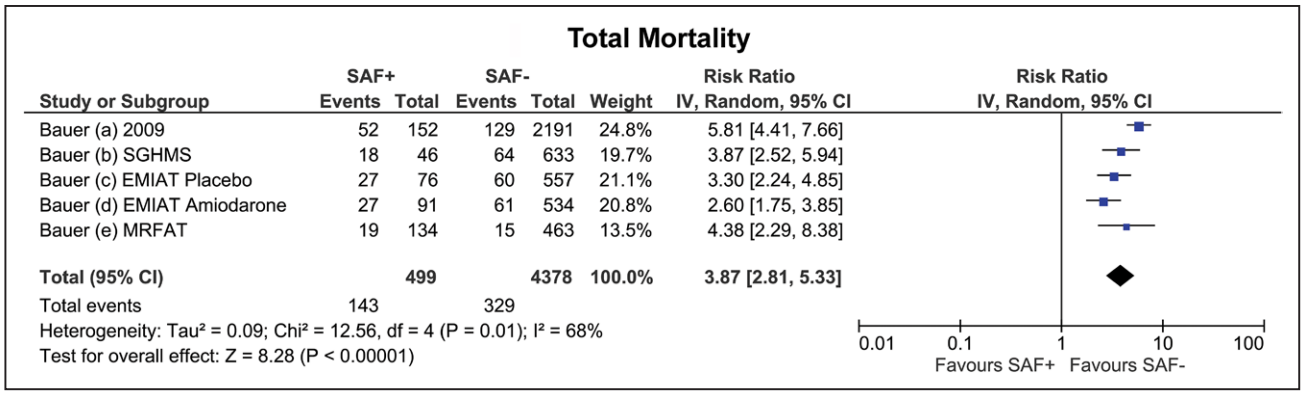

Figure 4. Individual and pooled risk ratios (RRs) of total mortality end point for severe autonomic failure (SAF) in postacute myocardial infarction (post-AMI) patients. Forest plots comparing total mortality end point in patients with positive (SAF+) and negative test (SAF–). The original cohorts included in the study of Bauer et al[12] are listed in the footnote of Table 1. CI indicates confidence interval; and IV, inverse-variance.

recording was performed early (within 4 weeks) in 6 out of the 10 analyzed cohorts, without significant differences in the prognostic value. Although the optimal time for HRT recording remains to be determined, from a pathophysiological point of view, a late registration seems more appropriate because of the slow recovery of autonomic tone after AMI. Furthermore, failure to recover normal HRT values at a distance from AMI was proven to be a powerful predictor of both CD and SCD.[43] The modern approach to AMI treatment did not significantly affect HRT predictive value. Similar results were indeed obtained in populations enrolled before and after 2000 and, thus, characterized by different prevalence of β-blocker treatment and percutaneous coronary interventions. Also the concomitant presence of diabetes mellitus did not significantly affect the predictive value of HRT, though an abnormal HRT was reported as more frequent in patients with diabetes mellitus.[44]

It is to notice that although current guidelines do not recommend ICD therapy in patients with moderately depressed EF, also these patients may experience SCD. Thus, highly specific risk markers are needed to identify true positive for arrhythmic risk in this population. Our results suggest that HRT is able to select among post-AMI patients with moderately depressed EF and treated with modern therapy, those at increased risk of CD and AE. In particular, the HRT test displays high specificity and high positive LR and could, therefore, be helpful in identifying patients at increased arrhythmic risk, but currently excluded from ICD therapy.

Table 4. Comparison of Risk Evaluation, Assessed by HRT Alone, Holter TWA Alone, and HRT and Holter TWA Analysis in Combination

Cohorts	Patients, n	Clinical Classification	Risk Evaluation 95% CI	Abnormal HRT	Abnormal Holter TWA	Abnormal HRT and Holter TWA
Cardiac death end point						
Li-na et al[28]	173	Post-AMI	aHR	5.01 (1.33–18.85)	7.44 (0.8–67.6)	9.08 (2.21–37.2)
Hoshida et al[26]	313	Post-AMI	aHR	5.7 (2.1–15.9)	3.6 (1.3–10.4)*	11.4 (4.6–28.6)
Sulimov et al[25]	111	Post-AMI	RR	5.8 (2.0–12.8)	6.8 (6.7–21.2)†	28.5 (3.7–172.5)
Ramírez et al[37]‡	597	Heart failure	RR	4.30 (2.38–7.75)	Not significant	5.27 (2.65–10.50)
Total	1194					
Arrhythmic events end point						
Exner et al[27]§	322	Post-AMI	aHR	2.91 (1.13–7.48)	2.94 (1.10–7.87)	4.18 (2.06–8.32)
Hoshida et al[26]	313	Post-AMI	aHR	10.1 (3.0–33.3)*	5.8 (1.6–20.8)	13.9 (3.0–66.7)
Sulimov et al[25]	111	Post-AMI	RR	18.3 (6.5–59.3)	14.3 (5.1–58.2)†	58.4 (7.2–474.3)
Total	746					

Studies are subgrouped based on the end points (cardiac death and arrhythmic events). Two studies evaluated both the end points. aHR indicates adjusted hazard ratio; AMI, acute myocardial infarction; CI, confidence interval; HRT, abnormal heart rate turbulence (HRT2, both turbulence onset and slope abnormal, in the studies of Li-na et al,[28] Hoshida et al,[26] and Sulimov et al[25]; HRT1, either turbulence onset or slope abnormal, in the study of Exner et al[27]; abnormal turbulence slope in the study of Ramírez et al[37]); Holter TWA, abnormal Holter T-wave alternans (Modified Moving Average method in the studies of Li-na et al[28], Hoshida et al,[26] and Sulimov et al[25]); and RR, risk ratio.

*Univariate hazard ratio.

†Analysis in combination with left ventricular ejection fraction.

‡The end point is only pump failure death.

§Composite end point: cardiac nonarrhythmic death (5 patients), cardiac arrhythmic death (17 patients), and resuscitated cardiac arrest (7 patients).

On the other hand, our data are insufficient to draw conclusions on patients with EF ≤30%. In patients with severely depressed EF, other tests, such as late gadolinium enhancement cardiac magnetic resonance imaging, may be suitable to improve the appropriateness of ICD implantation. Complementarily to HRT, thanks to its high sensitivity and low negative LR, late gadolinium enhancement imaging may help to identify among patients with EF ≤30% a lower-risk group unlikely to benefit from ICD.[45]

HF Patients

HRT was predictive of all the end points also in HF patients, although with lower RR values than in post-AMI patients. The HF cohorts analyzed included a mixed population of patients with ischemic heart disease and nonischemic dilated cardiomyopathy. The sole cohort that included exclusively nonischemic dilated cardiomyopathy patients did not show a statistically significant predictive power for AE.[29] It is likely that autonomic tone assessment is less useful in patients with dilated nonischemic cardiomyopathy, as reported in previous studies.[46] The component of patients with this cause may partially explain the lower predictive value of HRT in HF patients compared with post-AMI patients.

Polyparametric Analysis

In post-AMI patients, the combination of HRT with another marker of autonomic tone (SAF index) slightly increased the predictive value for the TM end point. On the other hand, the additional information provided by a marker of the electric substrate, such as TWA, markedly increased the predictive power for both CD and AE. HRT and TWA are easily assessable by a 24-hour Holter recording, and their combination had a high predictive power especially in post-AMI patients with the EF >30% (4/5 studies, Table 4). In addition, TWA has been shown to be strongly associated with SCD, whereas HRT is more related to death from cardiac failure.[26,47] The REFINE-ICD trial (Risk Estimation After Infarction Noninvasive Evaluation–Implantable Cardioverter-Defibrillator; Unique identifier: NCT00673842) is currently ongoing to assess the prognostic value of HRT in combination with TWA. The trial randomizes post-AMI patients with an EF between 36% and 50%, a positive TWA test and an impaired HRT, to receive ICD or optimal medical therapy. However, the completion date of the trial has been postponed to December 2021. The results of this systematic review provide preliminary indications to the issues posed by the REFINE-ICD study, showing a consistent increase of the predictive power, when the HRT and TWA markers are combined.

Limitations

Meta-analyses are inherently limited by the presence of heterogeneity among studies and small size effects. Specific tests[15,16] were performed to evaluate the presence of these factors in our study, which showed their limited effects in the performed meta-analyses. The results of this systematic review and meta-analysis were mostly based on male patients with an average age ranging between 48 and 71 years, and so they can be hardly extended to female and elderly populations. Data pertained mainly to cohorts with EF >30%, especially in post-AMI patients. Follow-up was variable among studies. Nevertheless, the studies with larger populations (>500 patients), which included >70% of the overall population, had all average follow-ups longer than 21 months. The majority of cohorts had only 1 or 2 end points available for the quantitative analysis, so that few studies were available in some of the meta-analyses. The exact definition of the type of death has limitations in clinical trials.[48] Our analysis showed that, similarly to other markers of autonomic tone, HRT was predictive not only for SCD, but also for CD. The performance of HRT as a marker for SCD stratification may be improved by combining it with markers specific for SCD, such as TWA.[26,47] Although a meta-analysis of the studies integrating HRT and TWA analyses could not be performed in our study, the combined use of HRT and TWA markers represents a promising objective of future research, which needs to be deepened in further clinical studies.

Conclusions

The results of this systematic review and meta-analysis show the usefulness of autonomic tone evaluation by HRT in CD and AE risk stratification in post-AMI and HF patients. In particular, in post-AMI patients with EF >30%, the detection of an abnormal HRT could provide indications to improve the therapy. The polyparametric evaluation further increases the prognostic value of HRT, where the combination of abnormal HRT with abnormal TWA markedly improved the predictive power for CD and AE. This marker combination, assessable by the same Holter recording technique, may identify a subset of post-AMI patients, where the indication for ICD implantation could be discussed despite an EF >30%.

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Disclosures

None.

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