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Heart Rate Variability and Risk of All-Cause Death and Cardiovascular Events in Patients With Cardiovascular Disease: A Meta-Analysis of Cohort Studies

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Abstract

Lower heart rate variability (HRV) is associated with a higher risk of cardiovascular events and mortality, although the extent of the association is uncertain. We performed a meta-analysis of cohort studies to elucidate the association between HRV and the risk of all-cause death or cardiovascular events in patients with cardiovascular disease (CVD) during a follow-up of at least 1 year. We searched four databases (PubMed, MEDLINE, Embase, and Cochrane Central Register of Controlled Trials) and extracted the adjusted hazard ratio (HR) from eligible studies. We included 28 cohort studies involving 3,094 participants in the meta-analysis. Results revealed that lower HRV was associated with a higher risk of all-cause death and cardiovascular events; the pooled HRs were 2.12 (95% confidence interval [CI] = [1.64, 2.75]) and 1.46 (95% CI [1.19, 1.77]), respectively. In subgroup analyses, the pooled HR of all-cause death was significant for patients with acute myocardial infarction (AMI) but not for those with heart failure. The pooled HR for cardiovascular events was significant for the subgroup of patients with AMI and acute coronary syndrome but not for those with coronary artery disease and heart failure. Additionally, both time and frequency domains of HRV were significantly associated with risk of all-cause death and cardiovascular events in patients with CVD.

Keywords

heart rate variability, risk factor, cardiovascular events, mortality, meta-analysis

Cardiovascular disease (CVD) is a major health problem worldwide and a leading cause of morbidity and mortality in developed countries (Deaton et al., 2011; Lozano et al., 2012). According to the World Health Organization (WHO), in 2015, approximately one third of deaths worldwide were caused by CVD (WHO, 2015). Cardiac autonomic dysfunction is a risk factor for CVD (Thayer, Yamamoto, & Brosschot, 2010).

Autonomic dysfunction is associated with various pathological conditions (Thayer et al., 2010), including hyperglycemia, high blood pressure, high triglycerides, low high-density lipoprotein cholesterol, high body mass index, incident diabetes, CVD, and high mortality (Dekker et al., 2000; Stein et al., 2008; Wulsin, Horn, Perry, Massaro, & D'Agostino, 2015). Heart rate variability (HRV) is a noninvasive measure of autonomic function (Acharya, Joseph, Kannathal, Lim, & Suri, 2006). A large population-based cohort study revealed that lower HRV at baseline is associated with a higher risk of heart disease and mortality (Lopez et al., 2015). At the time of the writing of the present article, the most recent meta-analysis to explore HRV was published in 2009 and comprised only five studies (Buccelletti et al., 2009). Findings revealed that patients with postmyocardial infarction (MI) syndrome with a lower (< 70 ms) standard deviation of all normal-to-normal HRV intervals (SDNN), as assessed using 24-hr electrocardiogram recordings, were almost 4 times more likely to die during the subsequent 3 years compared to those with a higher standard deviation. However, that study only assessed mortality in patients with MI, and researchers did not adjust for covariates or perform an assessment of the risk of bias.

We therefore performed a systematic review and up-to-date search of the literature and a meta-analysis of cohort studies to assess HRV as a marker for predicting all-cause death and cardiovascular events in patients with CVD. Findings from this study can provide quantitative evidence to elucidate the

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associations between HRV and the risk of all-cause death or cardiovascular events in patients with CVD.

Materials and Methods

Literature Search Strategy

We developed a search strategy to identify studies that investigated the association between HRV and the risk of all-cause death or cardiovascular events in patients with CVD over a follow-up of at least 1 year. We used the electronic databases PubMed, MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials to search for eligible studies published in English in peer-reviewed journals from their inception to April 2019. We searched for the following terms in the key words, title, abstract, or medical subject headings: "HRV" OR "heart rate variability" and "cardiovascular" OR "mortality" OR "death." We hand-searched conference abstracts, reference lists of relevant papers, and previous review articles for unpublished research and other relevant studies. Only full-length articles were considered.

Inclusion and Exclusion Criteria

The inclusion criteria for the studies were (1) a prospective or retrospective cohort study design, (2) the reporting of hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) or p values for evaluating the association of cardiovascular events or mortality with HRV parameters, (3) a follow-up period of $\geq$12 months, and (4) participants with CVD who were aged 18 years or older. The exclusion criteria for the studies were (1) a case–control design, (2) the inclusion of pregnant women, and (3) HRV recorded in patients implanted with a cardioverter defibrillator or during the HRV stressor or head-up tilt test. We restricted studies for inclusion to those had a follow-up period of at least 12 months because we aimed to examine the predictor role of HRV as a marker of mortality and cardiovascular events. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the literature search and selection processes.

Data Extraction and Analysis

Two investigators (S.-C. F. and Y.-L. W.) independently extracted data. We resolved discrepancies through discussion with a third investigator (P.-S. T.). Relevant data comprised the first author's name, year of publication, country of origin of the study centers, population characteristics, mean follow-up duration, HRV measurement methods, covariates adjusted for in the statistical analysis, and the HRV cutoff value for predicting end points (Supplementary Table 1). When a study presented several HR estimates (e.g., unadjusted and adjusted HRs), we extracted the most completely adjusted HR to reduce the effects confounders might have on the estimate.

We conducted two separate meta-analyses, one for all-cause deaths and one for cardiovascular events in relation to HRV. We defined all-cause deaths and cardiovascular events according to a previous meta-analysis (Kodama et al., 2009). In order to avoid competing risks, when an individual study provided data on both all-cause death and cause-specific death, we gave priority for data extraction to all-cause death because all-cause death is more comprehensive (Ablonskyte-Dudoniene et al., 2012; Bošković, Belada, & Knežević, 2014; Cygankiewicz et al., 2015; Lanza et al., 1998). Cardiovascular events comprised cardiac-related death, cardiac events, and sudden cardiac death. When an individual study provided composite data on cardiac death or cause-specific cardiac death, we gave priority for data extraction to cardiac death (Al-Zaiti, Fallavollita, Canty, & Carey, 2014; Batchvarov, Hnatkova, Poloniecki, Camm, & Malik, 2004; La Rovere et al., 2003; P. Y. Liu et al., 2003). When an individual study provided data on cardiac events or noncardiac events, we gave priority for data extraction to cardiac events (Lucreziotti et al., 2000). Similarly, if a study provided data on both events and deaths, we gave priority to deaths (Carpeggiani et al., 2005; Harris, Stein, Fung, & Drew, 2014; Krüger et al., 2002).

Assessment of the Risk of Bias

Two authors (S.-C. F. and Y.-L. W.) independently assessed the risk of bias. They evaluated the quality of all included articles using the Newcastle–Ottawa Scale items designed for cohort studies (Stang, 2010). This scale uses a star system to assess the quality of a study in three domains: selection, comparability, and outcome/exposure. For the present meta-analysis, our assessment of the risk of bias focused on the design elements that could bias the assessment of HRV measurement and outcomes. Specifically, we used five items: (1) selection: representativeness of the exposed cohort, (2) selection: ascertainment that the outcome of interest was not present at baseline, (3) comparability: effect estimates were adjusted for confounders, (4) outcome: adequacy of end point verification, and (5) outcome: adequacy of follow-up (an attrition rate of <20% was considered adequate). Therefore, five stars indicate a higher quality study.

Statistical Analyses

Adjusted HR estimates were used to elucidate the relationship between HRV and the risk of all-cause death or cardiovascular events in patients with CVD during a follow-up of at least 1 year. To pool HRs, we employed a random-effect model weighted using the inverse variance method (DerSimonian & Laird, 1986). We assessed heterogeneity across studies by using the I^2 statistic as a measure of the proportion of total variation in estimates due to heterogeneity. I^2 values of 25%, 50%, and 75% correspond to cutoff points for low, moderate, and high degrees of heterogeneity, respectively (Higgins & Thompson, 2002). Sensitivity and subgroup analyses were performed when a high degree of heterogeneity was identified (Higgins, Thompson, Deeks, & Altman, 2003).

Subgroup analyses were conducted to examine the differences in HRs among different strata according to diagnoses

(acute myocardial infarction [AMI], acute coronary syndrome [ACS], coronary artery disease [CAD], or heart failure), domains of HRV measurements (time domain vs. frequency domain), diabetes status (yes vs. no), duration of HRV recordings (<18 hr vs. ≥18 hr), and duration of follow-up (12–59 months vs. ≥60 months). In one study, researchers included patients with CAD based on the criteria that the patients had AMI or unstable angina events (Janszky et al., 2004). Therefore, we classified participants of that study as part of the AMI subgroup. To assess between-stratum differences, we performed these subgroup analyses using the random-effect model to pool the estimates and Cochran's Q statistic. We conducted a subgroup analysis for the end points represented by at least three studies. To evaluate publication bias, we used the funnel plot, fail-safe *N*, and trim-and-fill test (Egger, Smith, & Phillips, 1997).

Results

Study Selection and Characteristics

We retrieved 4,331 potentially relevant studies from the four databases and excluded 1,890 duplicated studies. Of the remaining 2,441 studies, we deemed 2,408 ineligible for inclusion after reviewing the titles and abstracts. Of the excluded studies, 9 were abstracts in conference proceedings, 106 were review articles, 1,943 did not use a cohort study design (i.e., they were cross-sectional or intervention studies), 178 included participants who did not meet our inclusion criteria (i.e., age ≤ 18 years, pregnant women, participants with implantable cardioverter defibrillator, and patients without CVD), 109 had a follow-up duration of less than 1 year, 27 did not include death or cardiovascular events as end points, 23 did not report HR data, and 13 did not use appropriate HRV measurements. In addition, three studies were substudies of the Cardiac Arrhythmias and Risk Stratification After Myocardial Infarction (CARISMA) study (Gang et al., 2011; Jørgensen et al., 2015; Jons et al., 2010). To avoid multiple inclusions of the same study sample, we included only the paper with the largest sample size in our meta-analysis (Gang et al., 2011). After these exclusions, 31 studies remained in the present systematic review. Of these studies, three did not report the adjusted HR data (Ho et al., 1997; Kiyono, Hayano, Watanabe, Struzik, & Yamamoto, 2008; Uznańska-Loch et al., 2018); therefore, we finally included 28 eligible studies in the meta-analysis (Ablonskyte-Dudoniene et al., 2012; Al-Zaiti et al., 2014; Anastasiou-Nana et al., 2005; Aronson, Mittleman, & Burger, 2004; Batchvarov et al., 2004; Bonaduce et al., 1999; Bošković et al., 2014; Carpeggiani et al., 2005; Cebula et al., 2012; Cygankiewicz et al., 2015; Erdogan et al., 2008; Gang et al., 2011; Guzzetti et al., 2005; Harris et al., 2014; Hayano et al., 2001; Janszky et al., 2004; Kiviniemi et al., 2007; Krüger et al., 2002; La Rovere et al., 2003; Lanza et al., 1998; Y. Liu et al., 2014; P. Y. Liu et al., 2003; Lucreziotti et al., 2000; Moore et al., 2007; Nolan et al., 1998; Perkiomaki, Jokinen, Tapanainen, Airaksinen, & Huikuri, 2008; Sosnowski et al., 2002; Zuanetti et al., 1996). We provide the PRISMA diagram of our selection procedure in Figure 1.

The main characteristics of the included studies are summarized in the Supplemental table. Of the 31 studies included in the systematic review, 20 were performed in Europe, 9 in the United States, and 2 in Asia. The studies were published between 1996 and 2018, and the mean follow-up duration ranged from 12 to 108 months. The size of the study population ranged from 28 to 1,082 participants (total size: 3,135), and the mean age of participants ranged from 50.5 to 71.8 years. All-cause death was the end point for 8 studies, cardiovascular events for 15 studies, and a composite end point (all-cause death and cardiovascular events) for the remaining 8 studies. Regarding the HRV outcome measures, 16 studies used both time- and frequency-domain methods, 12 used the time domain only, and 3 used the frequency domain only. Moreover, 24 studies used long-term HRV measurements (more than 18 hr), and 7 used short-term measurements (from 5 min to 4 hr). The most commonly used HRV parameters in the time domain were SDNN ($n = 28$), the root mean square successive difference (rMSSD; $n = 14$), the standard deviation of 5-min mean R-R intervals (SDANN; $n = 13$), and the percentage of R-R intervals that differed from each other by more than 50 ms (pNN50; $n = 9$). Among the 19 studies that used the frequency domain, 15 defined frequency bands as follows, according to guidelines from the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (Camm et al., 1996): high-frequency band (HF: 0.15–0.4 Hz), low-frequency band (LF: 0.04–0.15 Hz), very low–frequency band (VLF: 0.04–0.003 Hz), and ultra low–frequency band (ULF: ≤0.003 Hz). In only 13 studies, did researchers report how they handled ectopic beats. The most commonly used frequency domains were LF ($n = 18$), HF ($n = 18$), the LF/HF ratio ($n = 13$), VLF ($n = 11$), and total power (TP; $n = 11$). The studies categorized the HRV groups according to the percentiles (median, tertiles, quartiles, and quintiles) of the HRV distribution of the study samples, reported cutoff value, or author-defined cutoff (e.g., receiver operating characteristic). The SDNN cutoff value ranged from 30 to 100.24 ms, and the SDANN cutoff value ranged from 37 to 87 ms. Researchers in all of the studies used the groups with the highest value in an HRV category as the reference group.

Quality Assessment and Risk of Bias

The reporting quality of the included studies was globally acceptable. We awarded six of the studies three stars because they provided an unclear description of the ascertainment of the end point, their attrition rate was >20%, or they did not provide any description of patients lost to follow-up. To ascertain the vital status of patients, studies used active follow-up ($n = 8$), medical records ($n = 6$), and death registries ($n = 1$), while 15 studies did not report the method of end point ascertainment. Adjustment for potential confounders was not consistent across the studies: 30 studies adjusted for multiple cardiovascular

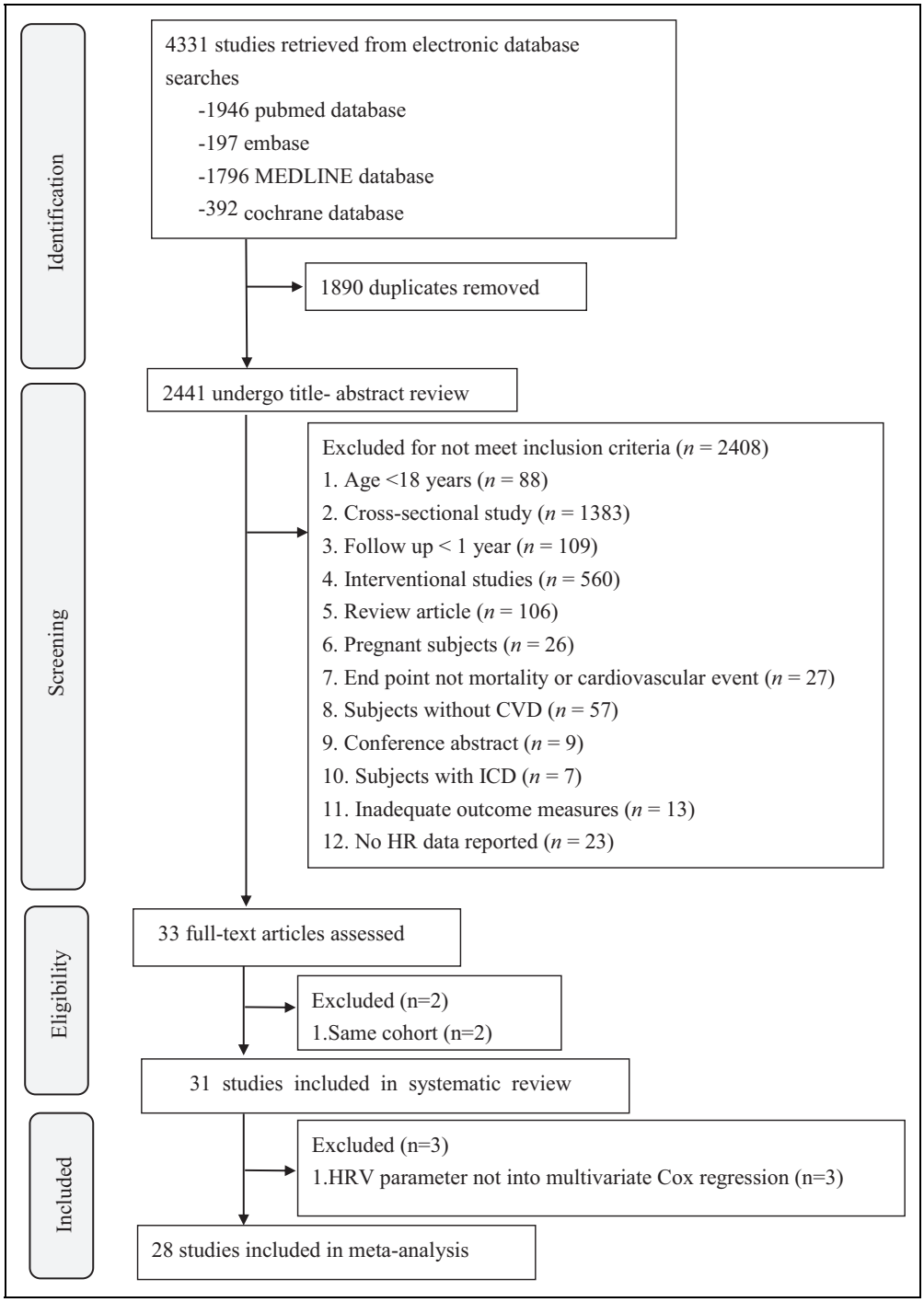

Figure 1. Flow diagram of search strategy and study selection. CVD = cardiovascular disease; HR = hazard ratio; ICD = implantable cardioverter defibrillator.

conditions, 23 adjusted for age, 14 adjusted for sex, and 11 adjusted for diabetes.

Meta-Analysis

In this meta-analysis, we extracted 55 risk estimates from 28 studies. We present the pooled estimates for the association between lower HRV and risk of all-cause death and cardiovascular events in Figures 2 and 3. Lower HRV was significantly associated with a higher risk of all-cause death and cardiovascular events, with pooled HRs for these end points of 2.12 (95% CI [1.64, 2.75]) and 1.46 (95% CI [1.19, 1.77]), respectively.

Significant heterogeneity existed across studies (I^2 = 85.6%; I^2 = 89.50%; $p < .01$ for all-cause death; $p < .01$ for cardiovascular events); therefore, we conducted a

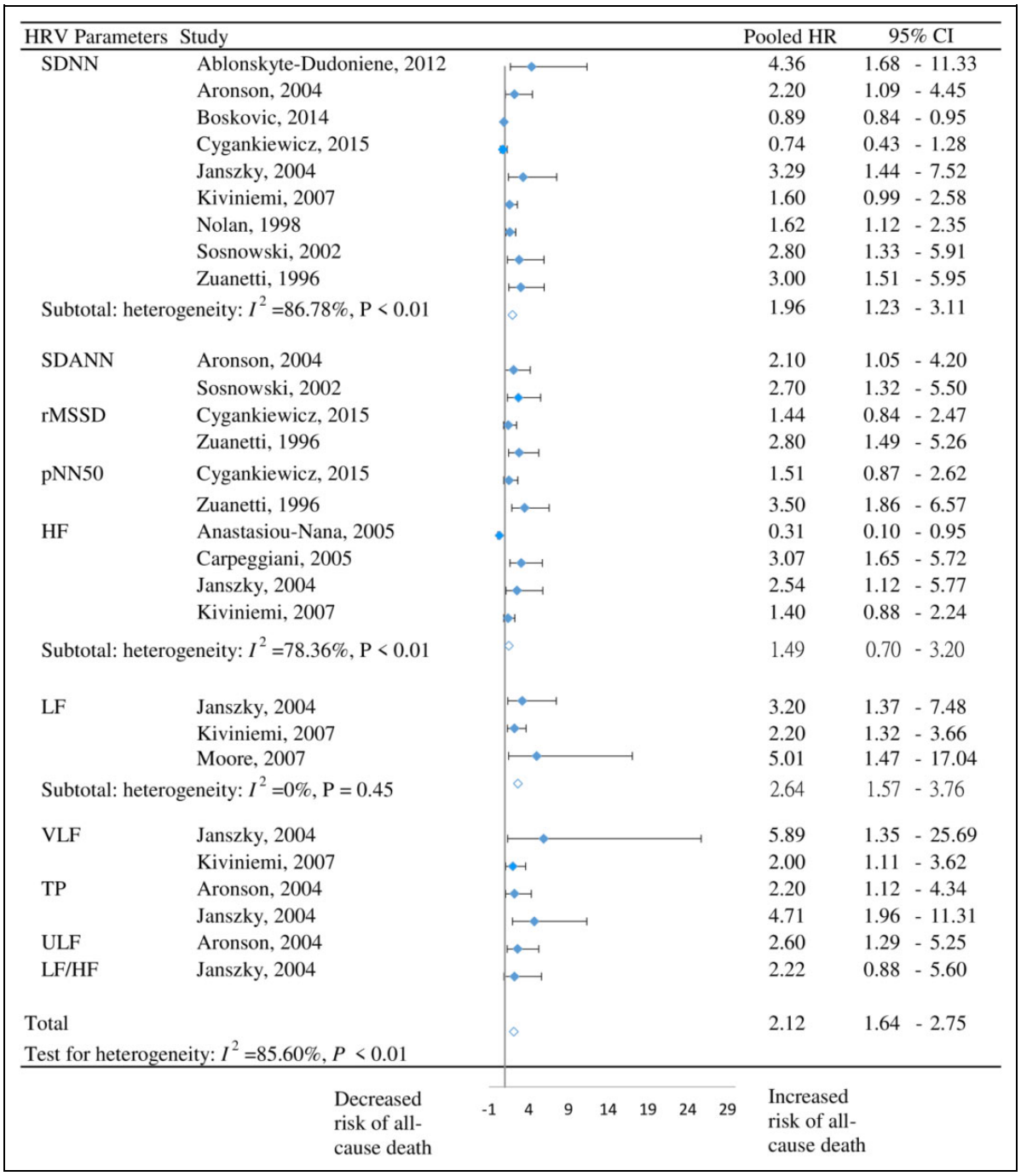

Figure 2. Meta-analysis of pooled hazard ratios (HRs) and 95% confidence intervals (CIs) for heart rate variability (HRV) and all-cause death. We drew 28 estimates from 13 studies. Some studies assessed more than one HRV parameter. ASDNN = average standard deviation of NN intervals; HF = high frequency; LF = low frequency; pNN50 = the percentage of R-R intervals that differ from each other by more than 50 ms; rMSSD = the square root of the average of the squares of the differences between consecutive R-R intervals; SDANN = standard deviation of sequential 5-min R-R interval means; SDNN = standard deviation of all normal-to-normal intervals; TI = triangular index; TP = total power; ULF = ultra low frequency; VLF = very low frequency.

sensitivity analysis by omitting one study in each turn. The pooled results did not change significantly. We then conducted the planned subgroup analyses to investigate the sources of heterogeneity for all-cause death and cardiovascular events.

For all-cause death, heterogeneity was explained by the type of diagnosis ($p = .04$) and duration of follow-up ($p < .01$). Lower HRV was significantly associated with a higher risk of all-cause death in the AMI subgroup but not in the subgroup of patients with heart failure. Additionally, it appeared that

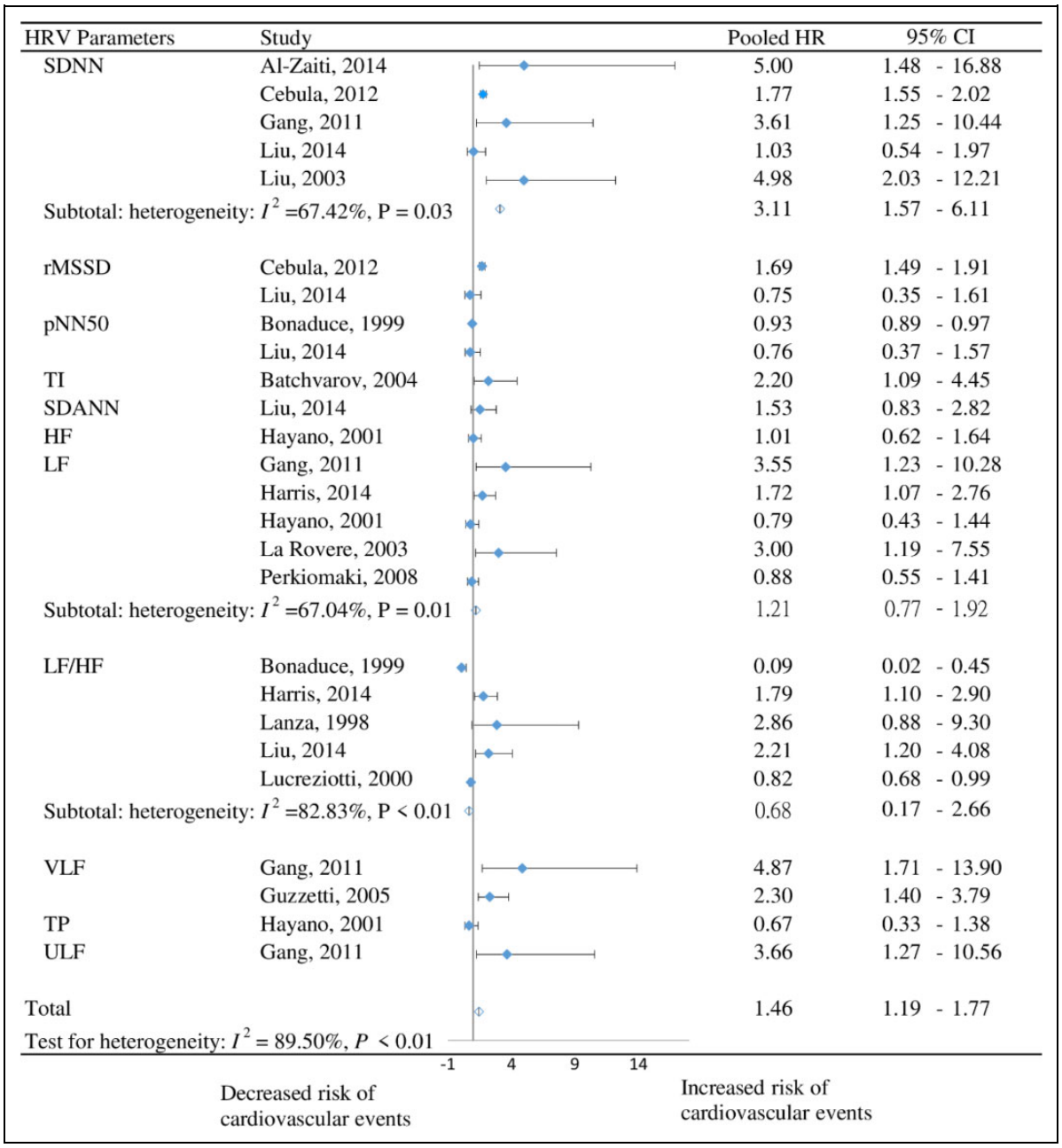

Figure 3. Meta-analysis of pooled hazard ratios (HRs) and 95% confidence intervals (CIs) for heart rate variability (HRV) and cardiovascular events. We drew 27 estimates from 15 studies. Some studies assessed more than one HRV parameter. ASDNN = average standard deviation of NN intervals; HF = high frequency; LF = low frequency; pNN50 = the percentage of R-R intervals that differ from each other by more than 50 ms; rMSSD = the square root of the average of the squares of the differences between consecutive R-R intervals; SDANN = standard deviation of sequential 5-min R-R interval means; SDNN = standard deviation of all normal to normal intervals; TI = triangular index; TP = total power; ULF = ultra low frequency; VLF = very low frequency.

participants in studies with a follow-up of 60 months or longer had a significantly higher risk of all-cause death compared with those in studies with a follow-up of less than 60 months ($p < .01$). The heterogeneity was not explained by the use of different domains of HRV measurements (time domain vs. frequency domain; $p = .94$; Figure 4A).

For cardiovascular events, the heterogeneity was explained by the type of diagnosis ($p < .01$). Lower HRV was significantly associated with a higher risk of cardiovascular events in the AMI and ACS subgroups but not in the subgroups of patients with CAD and heart failure. A posthoc test showed that pooled HR was significantly higher in patients with AMI than in those with heart failure (pooled HR = 1.99 vs. 1.10, $p < .01$) and CAD (pooled HR = 1.99 vs. 0.98, $p < .01$). This heterogeneity was not explained by the domains of HRV measurements or the duration of follow-up (Figure 4B).

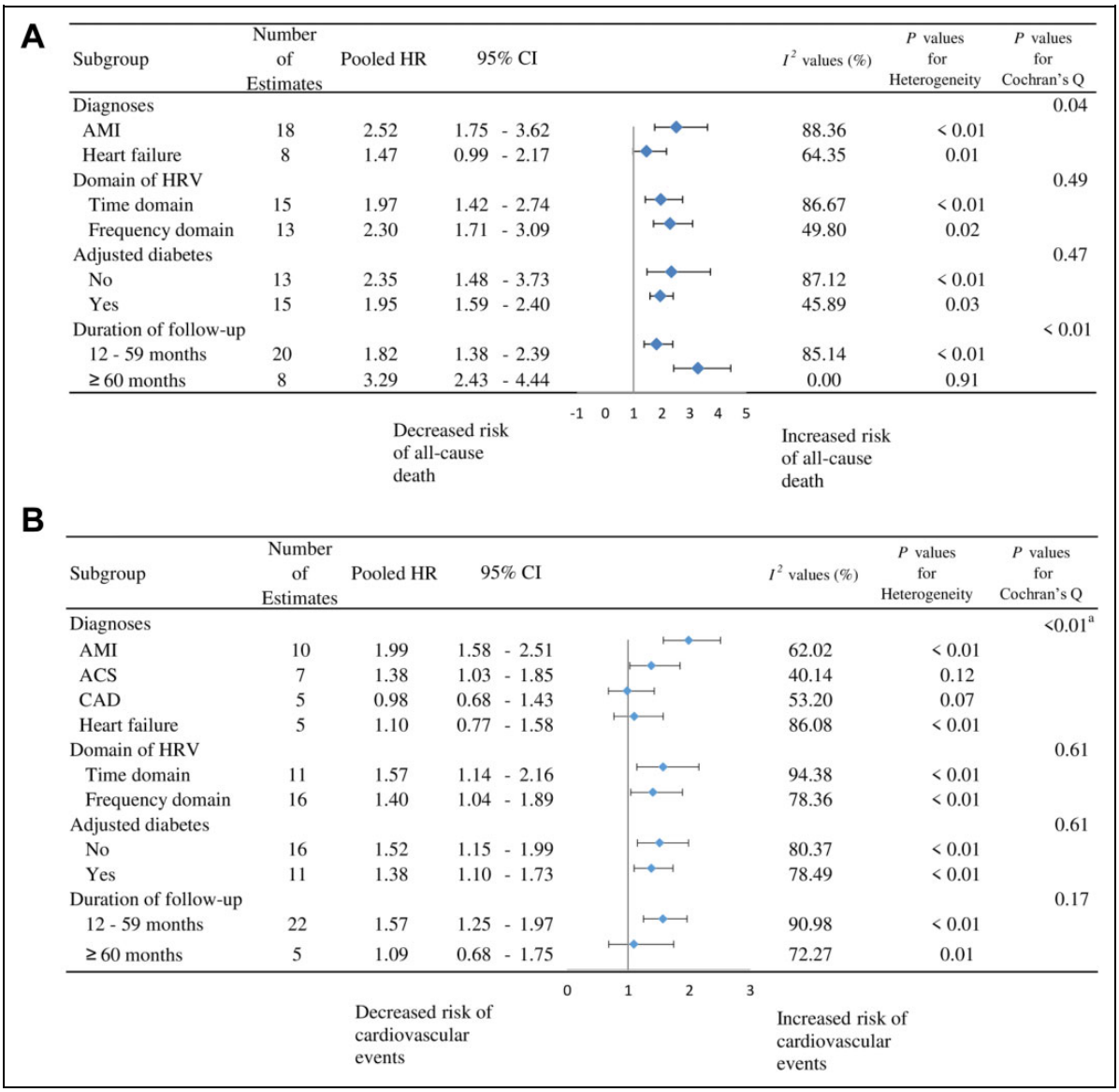

Figure 4. Subgroup analysis of pooled hazard ratios (HRs) and 95% confidence intervals (CIs) for heart rate variability (HRV) and all-cause death and cardiovascular events. (A) For HRV and all-cause death, we drew 28 estimates from 13 studies. Some studies assessed more than one HRV parameter. (B) For HRV and cardiovascular events, we drew 27 estimates from 15 studies. Some studies assessed more than one HRV parameter. Posthoc tests for diagnostic subgroups: AMI versus ACS, $p = .06$; AMI versus CAD, $p < .01$; AMI versus heart failure, $p < .01$; ACS versus CAD, $p = .16$; ACS versus heart failure, $p = .34$; CAD versus heart failure, $p = .68$. AMI = acute myocardial infarction; ACS = acute coronary syndrome; CAD = coronary artery disease.

HRV Measures as Predictors of All-Cause Death

For the analysis of HRV measures as predictors of all-cause death, we extracted 28 risk estimates from 13 studies. In a random-effect meta-analysis, long-term HRV measurements and time- and frequency-domain HRV were associated with risk of all-cause death, with a pooled HR of 1.69 (95% CI [1.32, 2.16]), 1.97 (95% CI [1.42, 2.74]), and 2.30 (95% CI [1.71, 3.09]), respectively. Additionally, a lower SDNN and LF HRV were significantly associated with a higher risk of all-cause death compared with a higher SDNN and LF in patients with CVD, with a pooled HR of 1.96 (95% CI [1.27, 3.11]) and 2.64 (95% CI [1.75, 3.98]), respectively. Conversely, HF HRV and short-term HRV measurements were not significantly associated with risk of all-cause death.

HRV Measures as Predictors of Cardiovascular Events

For the analysis of HRV measures as predictors of cardiovascular events, we extracted 27 risk estimates from 15 studies. In a random-effect meta-analysis, long-term HRV measurements and time- and frequency-domain HRV were associated with a higher risk of cardiovascular events, with a pooled HR of 2.30

(95% CI [1.68, 3.15]), 1.57 (95% CI [1.14, 2.16]), and 1.40 (95% CI [1.04, 1.89]), respectively. Additionally, a lower SDNN was significantly associated with a higher risk of cardiovascular events compared with a higher SDNN in patients with CVD. Conversely, HF HRV, the LF/HF ratio, and short-term HRV measurements were not significantly associated with the risk of cardiovascular events in patients with CVD.

Publication Bias

We constructed a funnel plot to evaluate publication bias in the studied literature. The fail-safe *N* for our pooled analysis was 3,864, which was reassuring because it is unlikely that more than 390 unpublished or undiscovered studies existed that could have reversed our findings. We used the trim-and-fill method to impute the missing studies and recalculate our pooled risk estimate. The imputed HR was 1.61 (95% CI [1.41, 1.83]), which is similar to our original risk estimate (HR = 1.90, 95% CI [1.65, 2.20]), suggesting that the apparent publication bias in this area is insufficient to meaningfully affect our results or interpretations.

Discussion

To our knowledge, this was the first meta-analysis that collected and analyzed longitudinal follow-up data to examine the associations between HRV and the risk of cardiovascular events or death in patients with CVD during a follow-up of at least 1 year. Our results revealed that, compared with patients with a higher HRV, those with a lower HRV had a 112% and 46% higher risk of all-cause death and cardiovascular events, respectively. Sensitivity analyses supported the robustness of this finding. In the subgroup analysis, the pooled HRs consistently demonstrated positive associations between low HRV and the risk of cardiovascular events or death across all subgroups. The finding is similar to that of a previous meta-analysis, in which low SDNN was associated with higher mortality in patients with MI (Buccelletti et al., 2009). An important strength of our meta-analysis is that we extracted the most adjusted HR estimates from multivariate Cox regression models. Therefore, our study confirms the role of HRV in predicting cardiovascular events and mortality in patients with CVD.

The pathophysiological mechanisms through which low HRV increases the risk of cardiovascular events or death remain unclear. HRV is the result of changes in heart rate caused by fluctuations of the sympathetic and parasympathetic divisions of the autonomic nervous system (Acharya et al., 2006). Lower HRV, which indicates fewer compensatory changes, is likely to be attributable to sympathetic dominance probably secondary to reduced parasympathetic activity (Florea & Cohn, 2014) because evidence has shown that poor parasympathetic fiber function precedes sympathetic involvement with cardiovascular manifestations of dysfunction (Metelka, 2014). Patients with ischemic heart disease exhibit heterogeneous responses to sympathetic nervous stimulation and reduced protection from vagal-activity denervation, which contribute to the formation of ventricular arrhythmias (Vaseghi & Shivkumar, 2008). Therefore, autonomic dysfunction (Thayer & Lane, 2007) and the resultant increased risk of fatal arrhythmias may explain the finding that low HRV increased the risk of cardiovascular events or death in patients with CVD compared with those with high HRV.

Subgroup analyses results revealed that lower HRV was associated with a higher risk of all-cause death in patients with AMI but not in patients with heart failure. Similarly, lower HRV was associated with a higher risk of subsequent cardiovascular events in patients with AMI and ACS but not in patients with CAD and heart failure. We also demonstrated that the pooled HRs of both all-cause death and cardiovascular events were significantly higher in patients with AMI compared with patients with heart failure. Heart failure, a complex condition characterized by hemodynamic abnormalities, is a common clinical syndrome following severe myocardial infarction (Florea & Cohn, 2014; Hill & Singal, 1996). Applying time- and frequency-domain methods to measure HRV in patients with heart failure may not be sufficient to determine the characteristics of these complex dynamics, leading to inaccurate estimations (de Godoy, 2016; Joshi & Bairagi, 2016; Lo, Tsai, Lin, Lin, & Hsin, 2009). Mäkikallio et al. (1999) revealed that the predictive ability of HRV indices, such as SDNN, for mortality in patients after AMI diminished after controlling for heart failure severity and other prognostic factors. This observation may explain why lower HRV was associated with a lower risk of subsequent all-cause death or cardiovascular events in patients with heart failure than in those with AMI and ACS in the present study. We also did not find that lower HRV was associated with a higher risk of cardiovascular events in patients with CAD. The etiology underlying the association of HRV with increased cardiovascular events in patients with CAD remains unclear (Huikuri, 1995). Research has shown that patients with CAD have blunted vagal responses compared with age-matched healthy participants (Qtsuka, Cornélissen, & Halberg, 1997). This finding may explain why lower HRV was not associated with an increased risk of cardiovascular events in the CAD subgroup.

Meta-analytic (Buccelletti et al., 2009) and systemic review (Sandercock & Brodie, 2006) studies have revealed that SDNN, SDANN, LF, VLF, and ULF HRV measures independently predict all-cause mortality in patients with CVD. In the present meta-analysis, we demonstrated that lower SDNN and LF HRV were significantly associated with a higher risk of all-cause death in patients with CVD. Notably, SDNN HRV is influenced by circadian rhythms (Vandewalle et al., 2007; Zhao et al., 2015); however, the included studies had controlled for the effects of sleep and circadian rhythms. HF HRV, meanwhile, was not associated with an increased risk of all-cause death in patients with CVD in the present review. HF HRV is influenced by the respiratory pattern (Aysin & Aysin, 2006). Only four of the studies in the present meta-analysis controlled breathing rhythm during measurement of HF HRV measurement. This methodological issue may explain why we did not find an association between HF HRV and an increased risk of

all-cause death in patients with CVD in our analysis. TP HRV was also not associated with an increased risk of all-cause death or cardiovascular events in patients in our study because only a few HR estimates were available for the meta-analyses.

Clinical Implications

HRV is a useful predictor of cardiovascular events or death in patients with CVD and is a potential indicator for monitoring the progression of autonomic dysfunction and treatment effects. In related studies, HRV alone or in combination with risk factors positively predicted malignant arrhythmias and sudden death (Bigger, Fleiss, Rolnitzky, & Steinman, 1993; Huikuri et al., 2009). Moreover, a randomized crossover study revealed that high-intensity interval exercise increased HF and LF HRV and significantly reduced premature ventricular contractions in patients with heart failure (Guiraud et al., 2013). Therefore, HRV determination can be incorporated into evaluating the progression of autonomic dysfunction in patients with CVD.

Limitations

Our study has several limitations. First, the definition of HRV varied across the studies, and significant heterogeneity existed across the studies. Although the random-effect model could account for the between-study heterogeneity to a certain extent, the results should be interpreted with caution. Second, our interpretation of between-study subgroup analyses may be less valid than within-group subgroup analyses, and the multiple testing conducted in our analyses entails a risk of Type I errors. Third, some of the included studies only reported the risk estimates of HRV parameters that were significantly associated with the end points. Nevertheless, funnel plots and fail-safe *N* did not reveal publication bias. Fourth, in this study, competing risk events such as noncardiovascular death may have altered the probability of the outcome of cardiovascular events and impeded the consideration of many subsequent events, thus limiting sufficiently powerful analyses (Bonofiglio, Beyersmann, Schumacher, Koller, & Schwarzer, 2016; Latouche, Allignol, Beyersmann, Labopin, & Fine, 2013). Fifth, a possible misclassification bias might have affected our results, as the scaling and cutoff values of HRV varied among the studies. Sixth, investigators collected the cardiovascular conditions and diabetes covariates at baseline upon enrollment in the included studies; therefore, it was not possible to correct the estimates for dynamics in cardiovascular conditions and diabetes status over time. Seventh, HRV measurements were obtained when a patient was enrolled in an individual study. Different timescales and, hence, different measures of effects might have been included in the meta-analysis to estimate the association between HRV and outcomes of interest. Nevertheless, we only extracted the most completely adjusted HR estimates to assess the association between HRV and all-cause death and cardiovascular events. The adjusted HR model adjusted baseline confounders and considered observed time differences. Therefore, the effects of time and prognostic confounders on outcomes were minimized. Eighth, among the 19 studies, only 13 reported how they handled ectopic beats. Potential influences of these undetected ectopic beats on the frequency domain of HRV cannot be ruled out. Finally, due to the limited amount of data, we did not perform a subgroup analysis according to disease severity. In addition, because of the small number of studies in some subgroups (e.g., triangular index, ultra low frequency), caution should be taken when interpreting the results.

Conclusion

Our meta-analysis showed that, compared with patients with CVD with a high HRV, those with a low HRV had a 121% and 46% increased risk of all-cause death and cardiovascular events, respectively, during a follow-up of at least 1 year. Our findings support the hypothesis that cardiac autonomic dysfunction is associated with the occurrence of cardiovascular events or death.

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Authors' Contribution

Su-Chen Fang and Pei-Shan Tsai conceived and designed the experiments. Su-Chen Fang and Yu-Lin Wu performed the literature search and data extraction. Pei-Shan Tsai contributed to the conception and design of the critically revised article. Su-Chen Fang contributed to the acquisition, analysis, and interpretation of the drafted article. Yu-Lin Wu contributed to the interpretation of the critically revised article. All authors have read and approved the final version of the article and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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Ethical approval

This article describes a meta-analysis of studies with human participants and thus does not require ethical approval.

Supplemental Material

Supplemental material for this article is available online.

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