Meta-Analysis of Ventricular Premature Complexes and Their Relation to Cardiac Mortality in General Populations

Feven Ataklte, MPhil[a,*], Sebhat Erqou, MD, PhD[b], Jari Laukkanen, MD, PhD[c], and Stephen Kaptoge, PhD[c]

Although previous studies have shown that frequent ventricular premature complexes (VPCs) in patients with established heart disease are associated with increased risk of cardiac mortality, the significance of VPCs in general populations is unclear. The aim of this study was to assess the association between VPCs and risk of sudden cardiac death or total cardiac death in general populations by conducting a meta-analysis of published research. The electronic databases MEDLINE and Embase were searched for relevant studies. Data were abstracted using standardized forms. Study-specific relative risk estimates were pooled using a random-effects meta-analysis model. Eleven studies comprising a total of 106,195 participants sampled from general populations were included. Studies generally defined frequent VPCs as occurring ≥1 time during a standard electrocardiographic recording or ≥30 times over a 1-hour recording. The prevalence of frequent VPCs in the studies ranged from 1.2% to 10.7%. The overall adjusted relative risk for sudden cardiac death comparing participants with frequent VPCs versus those without frequent VPCs was 2.64 (95% confidence interval 1.93 to 3.63). The corresponding value for total cardiac death was 2.07 (95% confidence interval 1.71 to 2.50). Although most studies made attempts to exclude high-risk subjects, such as those with histories of cardiovascular disease, they did not test participants for underlying structural heart disease. In conclusion, findings from observational studies in general populations indicate that frequent VPCs are associated with a substantial increase in the risk for sudden cardiac death and total cardiac death. Further study is needed to determine the role of confounding and underlying structural heart disease in the observed association and its utility in cardiovascular risk prediction. **(Am J Cardiol 2013;■:■−■)**

Ventricular premature complexes (VPCs) are common findings on electrocardiography in healthy subjects.[1] Observational studies have documented VPCs in about 6% of the general population.[1,2] The significance of VPCs in subjects with existing coronary heart disease is relatively well understood; for instance, it has been shown that the presence of recurrent VPCs in survivors of myocardial infarction is an indicator of poor prognosis.[3] VPCs may trigger fatal cardiac arrhythmias in patients with underlying heart disease.[4] However, the role of VPCs in generally healthy subjects remains controversial.[1] Whether frequent VPCs are associated with sudden cardiac death (SCD) or total cardiac death (TCD) in subjects without underlying heart disease is not clear, although VPCs are commonly believed to be less harmful in this setting.[4,5] The objective of the present study was to provide a systematic review and meta-analysis of the available evidence on the association between VPCs and the risk for SCD or TCD in general populations.

Methods

Two investigators (FA, SE) conducted the primary search in PubMed through October 2012, using free-text or Medical Subject Headings terms related to the exposure (i.e., "ventricular premature complexes," "premature ventricular contractions," and "premature ventricular complexes") and those related to the outcome (i.e., "sudden cardiac death," "sudden death," "death," and "mortality") without restriction to publication date. Supplementary searches were also conducted in the Web of Knowledge and Embase using the same search terms. We supplemented the electronic searches by manually scanning the reference lists of relevant reports.

The PubMed search retrieved 928 citations, from which 95 potentially relevant reports were selected for further review on the basis of the titles and abstracts. After reviewing the full-text reports, 9 studies that met the prespecified inclusion criteria were identified. In addition, 2 distinct eligible studies were identified from the Web of Knowledge and Embase search and scanning of reference lists of the retrieved reports, yielding a total of 11 studies[1,6−15] included in the present review (Figure 1).

Prospective cohort, nested case-control, and retrospective cohort studies based in general populations that assessed the association of VPCs with TCD or SCD outcomes were eligible for this review. We excluded case-control and cross-sectional studies to minimize bias. Other exclusions were studies (1) that selected participants on the basis of specific

[a]Department of Medicine, King's College London, London, United Kingdom; [b]Department of Medicine, Weil Cornell Medical College, New York, New York; and [c]Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom. Manuscript received April 21, 2013; revised manuscript received and accepted May 20, 2013.

See page 8 for disclosure information.

*Corresponding author: Tel: +44-646-581-2072.
E-mail address: feven.ataklte@kcl.uk (F. Ataklte).

0002-9149/13/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2013.05.065

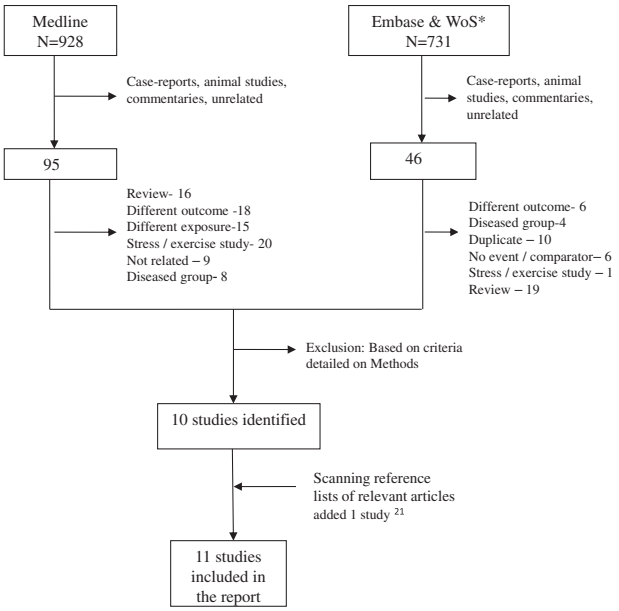

Figure 1. Study flow diagram. *Web of Science.

characteristics (e.g., those with coronary heart disease at baseline) or were conducted in hospitalized patients, (2) that assessed outcomes other than SCD or TCD, and (3) that measured stress or exercise-induced VPCs.

SCD is untimely cardiac-related death that occurs in an otherwise asymptomatic subject without warning symptoms. The exact definition of "sudden" or "untimely" has been variable across studies, with the major difference being the length of time window between the onset of cardiac symptoms and death, which could span anywhere from <1 to 24 hours.[16–18] TCD is death in which cardiac disease is confirmed as the primary cause. Coronary heart disease contributes to most cardiac mortality and a substantial proportion is sudden in nature.[1]

Studies generally defined frequent VPCs as occurring ≥1 time during a 10-second or 2-minute electrocardiographic (ECG) recording or ≥30 times over a 1-hour recording.[19] If a study used multiple criteria to define frequent VPCs,[7–9] we considered the definition that was most consistent with the rest of the studies. For example, Abdalla et al[7] defined frequent VPCs on a 2-minute ECG recording as "at least one VPC" and also as "more than one VPC," and we used the former definition for the meta-analysis.

Two investigators (FA, SE) extracted the relevant information using a standardized abstraction form. The abstracted information included general characteristics of the studies (Table 1); definition of exposure, outcome, and relevant methodologic details (Table 2); and estimate of association between frequent VPCs and either SCD or TCD (along with their 95% confidence intervals [CIs] and p values) and the covariates adjusted for in regression models (Table 3).

The reported measures of association included risk ratios, odds ratios, hazard ratios, and mortality ratios, which, assuming a rare disease, were considered to be equivalent measures of association and are herein collectively referred to as relative risk (RR). When the association measure or corresponding 95% CI was lacking, crude RRs and CIs were calculated on the basis of the reported number of subjects with or without the outcome according to VPC status. For studies that only provided RR estimate and z statistics, the standard error was calculated assuming a normal approximation (i.e., standard error = $\log_e$[RR]/z) and used to calculate the 95% CI. For studies that provided p values instead of z statistics, the normal distribution was used to determine the z statistic corresponding to the p value, and the preceding calculation was then applied. When studies reported RRs with various degrees of adjustment for covariates, the RRs from the model with the greatest degree of covariate adjustment were chosen. For comparison, RRs from models with the least degree of covariate adjustment were also extracted (Table 3). The quality of the evidence from the studies was assessed using the Newcastle-Ottawa Scale[20] (see Supplementary Table 1 for details of the scoring system).

Because this systematic review combined estimates from studies of potentially considerable clinical and methodologic diversity (e.g., differences in the ages of study participants and methods of VPC measurement), between-study heterogeneity was expected a priori.[21] We therefore combined the study-specific $\log_e$ RRs using a random-effects meta-analysis model, which assumed that studies may have estimated different underlying population parameters and included uncertainty due to between-study heterogeneity in the calculation of the pooled estimate.[22] Two studies reported RR estimates for men and women separately,[11,15] in which the case estimates were first combined using a fixed-effect meta-analysis to obtain a single estimate within each study, before pooling with the rest of the studies using the random-effects model meta-analysis. Between-study heterogeneity was quantified using Cochran's Q statistic and the I^2 statistic. The I^2 statistic measures the percentage of variation in the study-specific estimates that is due to true between-study differences rather than chance.[23] In general, I^2 values >60% are considered to indicate substantial heterogeneity.[21] Cochran's Q-statistic is a chi-square-distributed statistic that measures the statistical significance of heterogeneity.[22] Publication bias was assessed by checking for funnel plot asymmetry and formal testing of small-study effects.[24] All analyses were conducted using Stata version 11 (StataCorp LP, College Station, Texas).

Results

This review included 9 prospective cohort studies,[1,6–9,11,12,14,15] 1 retrospective cohort study,[10] and 1 nested case-control study,[13] involving a total of 106,195 participants. The study characteristics are summarized in Table 1. Seven of the studies were conducted in the United States, and the remaining 4 were conducted in Australia, Canada, Denmark, and Japan. The proportion of male participants ranged from 39% to 100%, with 3 studies[7,10,12] including only male participants. The average age of participants ranged from 31 to 65 years. The prevalence of VPCs in the studies ranged from 1.2% to 10.7%. The incidence of SCD or TCD ranged from 2.6 to 97 per 1,000 subjects over a mean follow-up period of 5 to 30 years (Table 1).

Table 1
Baseline characteristics of 11 studies included in the present meta-analyses

Study	Study Name	Location	Study Design	Total n	Mean Age (or Range) (yrs)	Male Patients	VPC Prevalence	Average Follow-Up (yrs)	SCD (n)	TCD (n)	NOS Quality Score
Abdalla et al (1987)[7]	MRFIT (ancillary*)	United States	PC	15,637	35−57	100%	4.4%	7.5	41	131	8
Sajadieh et al (2006)[6]	Copenhagen Holter study	Denmark	PC	678	65	59%	8%	5	NA	66	8
Engel et al (2007)[8]	NA	United States	PC	43,671	56	90%	3.8%	5.5	NA	3,768	6
Fisher and Tyroler (1973)[10]	NA	United States	RC	1,214	35−69	100%	6.7%	11	59	NA	6
Cheriyath et al (2011)[1]	ARIC	United States	PC	14,574	53	43%	4.8%	14	130	288	9
Hirose et al (2010)[11]	JMS cohort study	Japan	PC	11,158	59	39%	1.2%	11.9	NA	92	8
Cullen et al (1982)[9]	Busselton study	Australia	PC	2,119	40−79	50%	4.1%	13	NA	15	8
Rabkin (1984)[12]	Manitoba study	Canada	PC	3,983	31	100%	10.7%	30	70	NA	7
Stein et al (2010)[13]	CHS	United States	NCC	1,814	>65	43%	5.3%	13	49	NA	6
Chiang et al (1969)[14]	TCHS	United States	PC	5,129	>16	NR	3.6%	6	45	NA	7
Bikkina et al (1992)[15]	FHS	United States	PC	6,218	54	45%	7%	6	NA	163	9

ARIC = Atherosclerosis Risk in Communities; CHS = Cardiovascular Heart Study; FHS = Framingham Heart Study; JMS = Jichi Medical School; MRFIT = Multiple Risk Factor Intervention Trial; NA = not applicable; NCC = nested case-control; NOS = Newcastle-Ottawa Scale; NR = not reported; PC = prospective cohort; RC = retrospective cohort; TCHS = Tecumseh Community Health Study.

* Ancillary project to MRFIT.

All except 3 studies[10,14,15] attempted to exclude participants with histories of cardiovascular disease (CVD) at baseline (Table 2). The exposure definition differed among studies largely because of the duration of ECG measurement. In the studies that used short-period electrocardiography, VPC exposure was defined as the presence of ≥1 VPC on the 10-second or 2-minute ECG recording. In the studies that used ambulatory electrocardiography,[6,13,15] VPCs were defined as the presence of ≥30 ectopic ventricular beats/hour (Table 2). Bikkina et al,[15] who recorded 1-hour ambulatory electrocardiograms, additionally included complex VPCs that were <30 beats/hour in the exposure definition. Complex VPCs were defined as multiform VPCs, ventricular couplets, ventricular tachycardia, or R-on-T VPCs.[15]

With regard to study outcomes, 4 studies[10,12−14] focused on SCD, 5 studies[6,8,9,11,15] assessed TCD, and 2 studies[1,7] investigated both cardiac outcomes. Outcomes were ascertained using death certificates, record linkage, patient or hospital registries, death registers, or cardiologists' record review. The studies attempted to account for ≥1 potential confounder, but the degree of adjustment was variable (Table 2).

Among the 6 prospective studies of VPCs and SCD[1,7,12−14] involving a total of 42,351 participants and 394 incident SCD cases, the random-effects meta-analysis combined maximally adjusted RR for SCD comparing participants with frequent VPCs versus participants without frequent VPCs was 2.64 (95% CI 1.93 to 3.63; Figure 2) There was no significant heterogeneity across the 6 studies ($I^2 = 0\%$, 95% CI 0% to 75%, p = 0.47). The corresponding estimate in a fixed-effect meta-analysis model was 2.64 (95% CI 1.93 to 3.60), virtually the same as the random-effects model estimate. For the 3 studies[7,12,14] reporting RRs with >1 level of adjustment for confounders, the combined minimally adjusted RR for SCD was 3.23 (95% CI 2.12 to 4.94), and the maximally adjusted RR was 2.52 (95% CI 1.75 to 3.61) (Table 3).

Among 7 prospective studies of VPCs and TCD[1,6−9,11,15] involving a total of 95,146 participants and 4,523 TCD cases, the random-effects meta-analysis combined maximally adjusted RR for TCD comparing participants with frequent VPCs versus those without frequent VPCs was 2.07 (95% CI 1.71 to 2.50; Figure 3). There was no significant heterogeneity across the 7 studies ($I^2 = 0\%$, 95% CI 0 to 71, p = 0.644). The corresponding RR estimate in a fixed-effect model meta-analysis was 2.07 (95% CI 1.71 to 2.50). For the 5 studies[1,7,8,11,15] reporting RRs with >1 level of adjustment for confounders, the combined minimally adjusted RR for TCD was 2.19 (95% CI 1.68 to 2.86), and the maximally adjusted RR was 1.95 (95% CI 1.58 to 2.4) (Table 3).

The pooled adjusted RR for SCD comparing subjects with frequent VPCs versus those without frequent VPCs among 5 studies that used short-period ECG recording was 2.42 (95% CI 1.74 to 3.38). The corresponding RR was 4.61 (95% CI 1.96 to 10.84) (p = 0.17 for the difference) for subjects with ≥30 VPCs per hour compared with those with <30 VPCs in the 1 study that used ambulatory ECG recording (Figure 4). The corresponding pooled RR for TCD in the 5 studies that used short-period ECG recording was 2.12 (95% CI 1.70 to 2.66), compared with RR of 2.31 (95% CI 1.08 to 4.94) for 2 studies that were based on ambulatory electrocardiography (p = 0.70 for the difference; Figure 4).

Two studies[7,8] assessed the association of complex VPCs with SCD or TCD. Abdalla et al[7] reported a substantial increase in the risk for SCD and TCD in participants with complex VPCs compared with those without VPCs (RR 5.3, 95% CI 2.1 to 13.7, and RR 3.0, 95% CI 1.6 to 5.8, respectively). Similarly Engel et al[8] found a significant increase in the risk for TCD in patients with complex VPCs compared with those without VPCs (RR 2.1, 95% CI 1.6 to 2.8). There was no significant funnel plot asymmetry, and the test of small-study effects was not statistically significant (p = 0.24 for SCD, p = 0.13 for TCD; Figure 5).

Table 2
Population selection and exposure and outcome measurement methods in 11 studies included in the present meta-analysis

Study	Population/ Sampling Method	Participant Exclusion Criteria	Exposure Definition	Exposure Measurement Method	Outcome Definition	Outcome Ascertainment	Variables Included in Maximally Adjusted Model
Abdalla et al (1987)[7]	Ancillary project of first screening examination for MRFIT	Hx of MI, DM, other abnormalities on ECG	Presence of any VPC on 2-minute ECG	2-minute ECG	SCD[‖]	Social Security data, NOK interview, hospital record review	Age, BP, total cholesterol, smoking status
Sajadieh et al (2006)[6]	Copenhagen Holter study, apparently healthy middle and elderly patients, random[*]	Hx of heart disease and stroke	>30 VPCs/h	48-hour ambulatory ECG (Holter)	Total CVD death	National Central Patient Registry	BP, DM, physical exercise
Engel et al (2007)[8]	Veterans at Palo Alto VA Medical Center who underwent ECG for any reason	ECG of AF and paced rhythms	Presence of any VPCs on 12-lead ECG	10-second ECG	Total CVD death and AMI	Social Security Death Index, California Health Department Service and VA database	Age, BMI, findings on ECG
Fisher and Tyroler (1973)[10]	White male factory workers in Canton, North Carolina	None	Presence of any VPCs on 12-lead ECG	10-second ECG	SCD,[¶,#] total CHD death	Death certificate	Age
Cheriyath et al (2011)[1]	ARIC, population-based sample, complete	Hx of CHD or stroke	Presence of any VPCs on 2-minute ECG	2-minute ECG	SCD[¶] total CHD death	Hospital record, death certificate, questionnaire and interview of NOK	Age, race, gender, education, smoking status, BMI, serum K, Mg, LDL-C/HDL-C, DM, HTN, HR, anti-HTN, antiarrhythmic
Hirose et al (2010)[11]	JMS cohort study, study districts in rural Japan, complete	Hx of MI or stroke	Presence of any VPCs on 12-lead ECG	10-second ECG	TCD	Death certificate from local public centers	BMI, SBP, TC, HDL-C, blood glucose
Cullen et al (1982)[9]	Busselton study, unselected subjects	Separate analysis by angina status	Presence of any VPCs on 12-lead ECG	10-second ECG	TCD[††]	Registrar of death	Age and gender
Rabkin (1984)[12]	Manitoba study, men who were either pilots or pilots in training in the Royal Canadian Air Force in World War II, complete[†]	Previous MI, angina	Presence of any VPCs on 12-lead ECG	10-second ECG	SCD[#]	Annual letters, medical records	Age
Stein et al (2010)[13]	CHS, population based, random,[‡] patients who experienced SCD during follow-up and controls[§]	Hospitalized or nursing home patients	>30 VPCs/h	24-hour ambulatory ECG (Holter)	SCD[**]	Cardiologists' record review	Age, gender, MI history, DM medication, β blocker
Chiang et al (1969)[14]	TCHS, complete, community of Tecumseh	None	Presence of any VPCs on 12-lead ECG	10-second ECG	SCD[¶]	Death certificate	Age

Table 2
(*continued*)

Study	Population/ Sampling Method	Participant Exclusion Criteria	Exposure Definition	Exposure Measurement Method	Outcome Definition	Outcome Ascertainment	Variables Included in Maximally Adjusted Model
Bikkina et al (1992)[15]	FHS, surviving patients and offspring of the original cohort members	Separate analysis by CHD status	>30 VPCs h or complex VPCs	48-hour ambulatory ECG (Holter)	Total CHD death and AMI	Medical record review, hospital record and pathology report	Age, TC, HDL-C, BMI, HTN, smoking, SBP, DM, CHF, anti-HTN, β blocker, antiarrhythmic

AF = atrial fibrillation; AMI = acute myocardial infarction; BMI = body mass index; BP = blood pressure; CHD = coronary heart disease; CHF = congestive heart failure; DM = diabetes mellitus; ECG = electrocardiography; HDL-C = high-density lipoprotein cholesterol; HR = heart rate; HTN = hypertension; Hx = history; K = potassium; LDL-C = low-density lipoprotein cholesterol; Mg = magnesium; MI = myocardial infarction; NOK = next of kin; SBP = systolic blood pressure; TC = total cholesterol; VA = US Department of Veterans Affairs. Other abbreviations as in Table 1.

* Random sample of 60% subjects with no or 1 self-reported CVD risk factor.

† Pilots who at the time had electrocardiographic records in addition to general medical tests. Eligibility: electrocardiographic abnormality and no evidence of ischemic or valvular heart disease (clinical or on ECG).

‡ Randomly selected government-sponsored health insurance (Medicare) cohort members free of prevalent or incident CVD and free of MRI-detectable infarcts who did not have illness expected to lead to early death.

§ Controls were participants alive at the time of death of the patient who had not died at follow-up; each patient was matched on age within 5 years, gender, β-blocker use, history of MI, and use of oral hypoglycemic medications with 2 controls.

|| Witnessed death occurring <1 hour after onset of acute symptoms.

¶ Death occurring <1 hour after onset of acute signs and symptoms.

SCD from CHD defined as death occurring <24 hours after onset of acute signs and symptoms.

** SCD defined as a sudden pulseless condition (presumably, but not definitely, ventricular fibrillation) due to cardiac cause in an otherwise stable patient. Patients who had their events at emergency departments or out of the hospital were included, whereas those already hospitalized or at nursing homes with multiple co-morbidities were excluded.

†† Definition from International Classification of Disease, Eighth Revision, codes 390 to 458, 746, and 747.

Table 3
Study-specific relative risk estimates for the association between ventricular premature complexes and sudden cardiac death or total cardiac mortality

Study	SCD RR (95% CI)			TCD RR (95% CI)		
	n	Minimally Adjusted	Maximally Adjusted	n	Minimally Adjusted	Maximally Adjusted
Abdalla et al (1987)[7]	41	4.0 (1.3−4.67)	3.00 (1.3−7.3)	131	2.00 (1.10−3.80)	1.60 (0.80−2.90)
Sajadieh et al (2006)[6]	NA	—	—	66	—	3.78 (1.61−8.89)
Engel et al (2007)[8]	NA	—	—	3,768	1.81 (1.62−2.01)	2.00 (1.10−2.80)
Fisher and Tyroler (1973)[10]	59	—	1.30 (0.39−3.35)	NA	—	—
Cheriyath et al (2011)[1]	130	2.8 (1.68−4.67)	2.09 (1.22−3.96)	288	3.01 (2.16−4.21)	2.18 (1.53−3.12)
Hirose et al (2010)[11]	NA	—	—	92	4.20 (1.54−11.5)	2.75 (0.99−7.60)
Cullen et al (1982)[9]	NA	—	—	15	—	2.40 (1.46−3.96)
Rabkin (1984)[12]	70	—	3.96 (1.01−15.67)	NA	—	—
Stein et al (2010)[13]	49	—	4.61 (1.96−10.84)	NA	—	—
Chiang et al (1969)[14]	45	6.1 (1.32−27.98)	2.91 (2.17−7.16)	NA	—	—
Bikkina et al (1992)[15]	NA	—	—	163	1.88 (1.30−2.69)	1.70 (1.15−2.51)

NA = not applicable.

Discussion

Synthesis of currently available evidence from prospective studies involving >106,000 participants in general populations showed a substantial increase in the risk for SCD and TCD in those with frequent VPCs, with no significant heterogeneity across the studies. Two previously published reviews[4,5] looked at the prognostic significance of VPCs in largely diseased populations. They found that certain VPC types are associated with lethal arrhythmias in patients with cardiac disease and concluded that the significance of VPCs is well defined when patient co-morbidities (e.g., underlying cardiac disease) are known.[4,5] The present review importantly extends current knowledge by investigating the significance of VPCs in general populations.

A number of biologic mechanisms have been proposed to explain the observed association between VPC and cardiac death. One hypothesis proposes that VPCs may act as triggers for fatal cardiac arrhythmias. Retrospective analysis of ambulatory ECG recordings of 21 patients who experienced cardiac arrest showed that most had increased heart rates and VPC activity before the onset of terminal ventricular fibrillation.[25] The transition from VPC to fatal arrhythmia can be mediated by various transient factors,

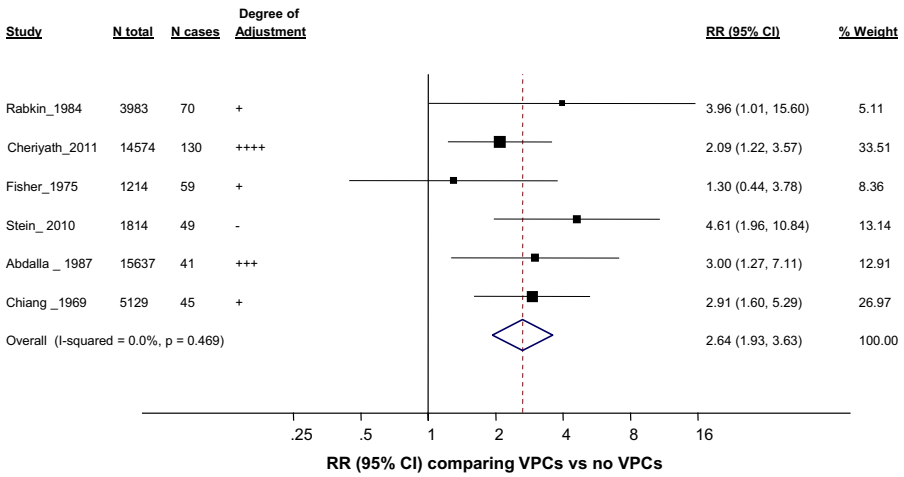

Figure 2. Association of VPCs with risk for SCD. Degree of adjustment: - = no adjustment; + = adjusted for age and/or gender; ++ = adjusted for age, gender, and 1 conventional CVD risk factor; +++ = adjusted for age, gender, and >2 conventional CVD risk factors; ++++ = adjusted for age, gender, >2 conventional CVD risk factors, and ECG abnormality and/or antiarrhythmic or other medications and/or serum level of potassium or magnesium.

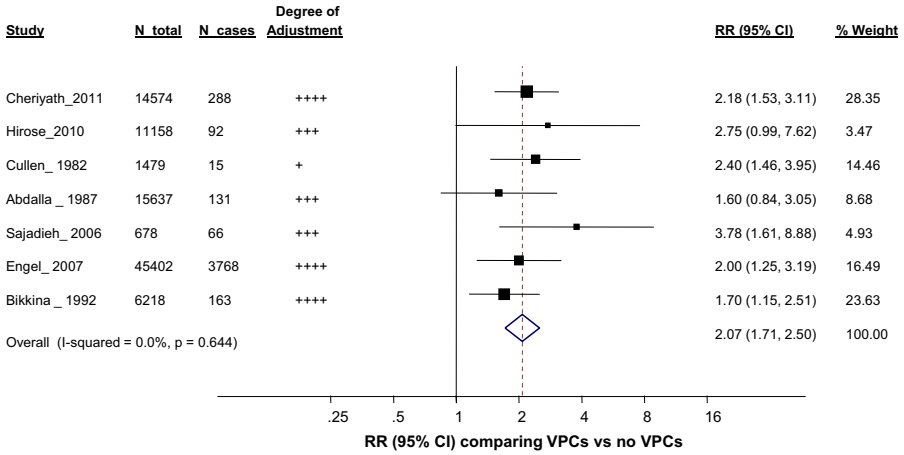

Figure 3. Association of VPCs with risk for TCD. Degree of adjustment: - = no adjustment; + = adjusted for age and/or gender; ++ = adjusted for age, gender, and 1 conventional CVD risk factor; +++ = adjusted for age, gender, and >2 conventional CVD risk factors; ++++ = adjusted for age, gender, >2 conventional CVD risk factors, and ECG abnormality and/or antiarrhythmic or other medications and/or serum level of potassium or magnesium.

such as increased sympathetic tone or altered hemodynamic status, that may destabilize the myocardium.[4]

An alternative explanation for the observed association between VPCs and the risk for cardiac mortality is reverse causation; that is, presence of frequent VPCs may just be a marker of an underlying cardiac disease such as coronary heart disease or cardiomyopathy and not a cause of SCD or TCD. Most studies in the present review attempted to avoid reverse causation bias by excluding participants with histories of coronary heart disease, stroke, and even diabetes in some studies. However, it would not be possible to rule out asymptomatic or silent heart disease without invasive investigations (e.g., coronary angiography).[26,27] Nonetheless, VPCs may still be important as markers of covert CVD, thereby helping identify subjects who may require additional testing. Further studies are needed to determine if the detection of frequent VPCs can predict the risk of future coronary heart disease outcomes after accounting for conventional CVD risk factors.

Most studies in this review attempted to control for confounders, including age, gender, and conventional CVD risk factors. However, adjustment was not consistent across the studies, and 4 studies adjusted only for age and gender. In the studies reporting RRs with >1 level of confounder adjustment, the maximally adjusted RRs were 10% to 20% weaker than the minimally adjusted RRs, suggesting presence of some confounding. However, the pooled adjusted RRs were still indicative of a substantial two-fold greater risk for SCD or TCD with frequent VPCs, suggesting that any residual confounding would have to be large to fully explain the observed associations.

Most studies in this review used spot ECG recording for exposure measurement. The sensitivity and specificity of this method, compared with Holter monitoring, have been found to be 74% and 94%, respectively.[28] Ideally, ambulatory electrocardiography would be preferred for detecting significant VPCs, since a spot ECG recording is not long enough to detect all participants with frequent VPCs,

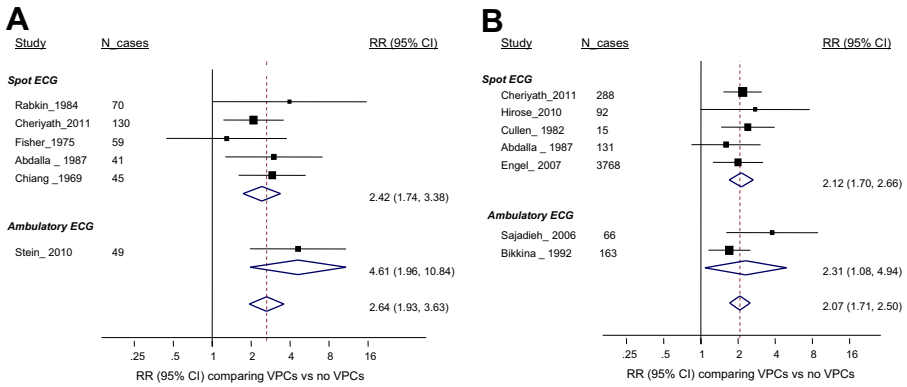

Figure 4. Association of VPCs with risk for *(A)* SCD and *(B)* TCD. The p values for heterogeneity, calculated by random-effects model meta-regression, were 0.17 for SCD and 0.70 for TCD. ECG = electrocardiography.

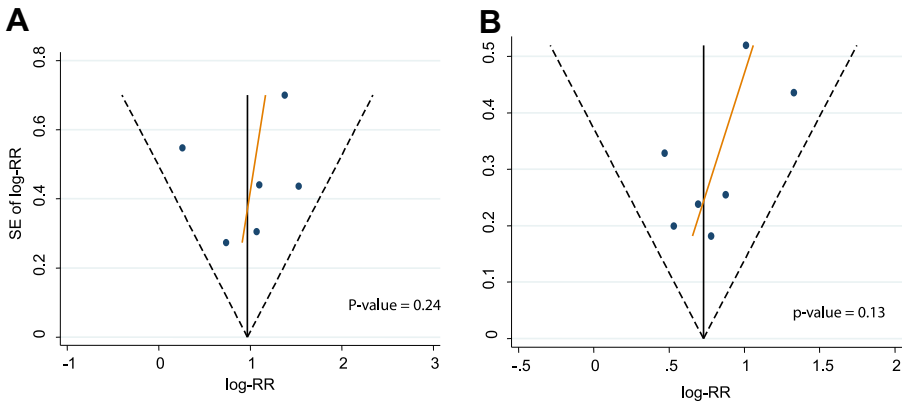

Figure 5. Funnel plots for studies of *(A)* SCD and *(B)* TCD. The p values for publication bias were calculated using Egger's test.

potentially leading to underestimation of the true prevalence. However, the resulting misclassification is likely to be nondifferential.

The definition of SCD varied among studies, mainly because of differences in criteria for the time window between the onset of symptoms and death required to qualify as sudden death. Studies that defined sudden death to be within 1 hour of symptoms may have underestimated the number of SCDs, whereas studies that included all deaths beyond 24 hours may have been more likely to include deaths that were not SCDs. However, despite such potential difference, there was no significant heterogeneity among the studies.

In addition to within-study biases, bias in meta-analysis can arise from study selection or the publication process. Publication bias arises when studies with statistically significant results tend to be preferentially published.[29] We did not find evidence of significant publication bias in this meta-analysis.

The strengths and limitations of the present study merit some consideration. First, we conducted a comprehensive review on the association of frequent VPCs with TCD and SCD by searching 2 complementary electronic databases and the reference lists of relevant publications. Second, the studies in this review were prospective in design, which makes them less prone to selection bias compared with retrospective case-control studies and thereby more useful for establishing temporal exposure-risk associations. Moreover, most of the studies were population based, increasing their external validity. Third, there was no significant heterogeneity across the studies, indicating their comparability, and statistical tests and funnel plot analysis showed no significant evidence for publication bias. However, we acknowledge that statistical power to detect heterogeneity or publication bias may be limited when the number of studies is relatively small.

Regarding limitations, first, the available results were based on observational studies; hence, the study cannot prove causality. Frequent VPCs may simply be markers of undiagnosed cardiac disease in asymptomatic subjects. Although most studies included in the meta-analysis made attempts to exclude high-risk subjects, such as those with histories of CVD, they did not test participants for underlying structural heart disease. However, VPCs may still have a significant role as risk markers, which may be equally important.

Second, the analyses were based on summary estimates, not individual participant data; hence, we could not assess the effect of confounding in a consistent manner across studies or determine whether the association varies among clinically relevant subgroups of individual characteristics, such as age.

Finally, we were not able to investigate factors such as the type of VPC and other associated ECG changes that may influence the significance of VPCs, besides underlying heart disease and the frequency of VPCs.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary Data

Supplementary data related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2013.05.065.

1. Cheriyath P, He F, Peters I, Li X, Alagona P Jr, Wu C, Pu M, Cascio WE, Liao D. Relation of atrial and/or ventricular premature complexes on a two-minute rhythm strip to the risk of sudden cardiac death (the Atherosclerosis Risk in Communities [ARIC] study). *Am J Cardiol* 2011;107:151−155.
2. Simpson RJ Jr, Cascio WE, Schreiner PJ, Crow RS, Rautaharju PM, Heiss G. Prevalence of premature ventricular contractions in a population of African American and white men and women: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J* 2002;143:535−540.
3. Kostis JB, Byington R, Fredman LM, Goldstein S, Furberg C. Prognostic significance of ventricular ectopic activity in survivors of acute myocardial infarctio. *J Am Coll Cardiol* 1987;10:231−242.
4. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death: epidemiology, transient risk, and intervention assessment. *Ann Intern Med* 1993;119:1187−1197.
5. Moss AJ, Akiyama T. Prognostic significance of ventricular premature beats. *Cardiovasc Clin* 1974;6:273−298.
6. Sajadieh A, Nielsen OW, Rasmussen V, Hein HO, Frederiksen BS, Davanlou M, Hansen JF. Ventricular arrhythmias and risk of death and acute myocardial infarction in apparently healthy subjects of age >or=55 years. *Am J Cardiol* 2006;97:1351−1357.
7. Abdalla IS, Prineas RJ, Neaton JD, Jacobs DR Jr, Crow RS. Relation between ventricular premature complexes and sudden cardiac death in apparently healthy men. *Am J Cardiol* 1987;60:1036−1042.
8. Engel G, Cho S, Ghayoumi A, Yamazaki T, Chun S, Fearon WF, Froelicher VF. Prognostic significance of PVCs and resting heart rate. *Ann Noninvasive Electrocardiol* 2007;12:121−129.
9. Cullen K, Stenhouse NS, Wearne KL, Cumpston GN. Electrocardiograms and 13 year cardiovascular mortality in Busselton study. *Br Heart J* 1982;47:209−212.
10. Fisher FD, Tyroler HA. Relationship between ventricular premature contractions on routine electrocardiography and subsequent sudden death from coronary heart disease. *Circulation* 1973;47:712−719.
11. Hirose H, Ishikawa S, Gotoh T, Kabutoya T, Kayaba K, Kajii E. Cardiac mortality of premature ventricular complexes in healthy people in Japan. *J Cardiol* 2010;56:23−26.
12. Rabkin SW. Electrocardiographic abnormalities in apparently healthy men and the risk of sudden death. *Drugs* 1984;28(suppl):28−45.
13. Stein PK, Sanghavi D, Sotoodehnia N, Siscovick DS, Gottdiener J. Association of Holter-based measures including T-wave alternans with risk of sudden cardiac death in the community-dwelling elderly: the Cardiovascular Health Study. *J Electrocardiol* 2010;43:251−259.
14. Chiang BN, Perlman LV, Ostrander LD, Epstein FH. Relationship of premature systoles to coronary heart disease and sudden death in the Tecumseh Epidemiologic Study. *Ann Intern Med* 1969;70:1159−1166.
15. Bikkina M, Larson MG, Levy D. Prognostic implications of asymptomatic arrhythmias: the Framingham heart study. *Ann Intern Med* 1992;117:990−996.
16. Zipes DP, Wellens HJ. Sudden cardiac death. *Circulation* 1998;98:2334−2351.
17. Paul O, Schatz M. On sudden death. *Circulation* 1971;43:7−10.
18. Chugh SS, Kelly KL, Titus JL. Sudden cardiac death with apparently normal heart. *Circulation* 2000;102:649−654.
19. Erdogan O. Holter monitoring in the prognosis of sudden cardiac death. *Anadolu Kardiyol Derg* 2007;7(suppl):64−67.
20. Wells GA, Shea B, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: *http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp*. Accessed July 17, 2013.
21. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557−560.
22. Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Stat Med* 1999;18:2693−2708.
23. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539−1558.
24. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med* 2006;25:3443−3457.
25. Nikolic G, Bishop RL, Singh JB. Sudden death recorded during Holter monitoring. *Circulation* 1982;66:218−225.
26. Kennedy HL, Pescarmona JE, Bouchard RJ, Goldberg RJ. Coronary artery status of apparently healthy subjects with frequent and complex ventricular ectopy. *Ann Intern Med* 1980;92:179−185.
27. Kennedy HL, Whitlock JA, Sprague MK, Kennedy LJ, Buckingham TA, Goldberg RJ. Long-term follow-up of asymptomatic healthy subjects with frequent and complex ventricular ectopy. *N Engl J Med* 1985;312:193−197.
28. DeBacker G, Jacobs DR Jr, Prineas RJ, Crow RS, Kennedy H, Vilandre J, Blackburn H. Ventricular premature beats: screening and induction tests in normal men. *Cardiology* 1980;65:23−41.
29. Egger M, Smith GD. Bias in location and selection of studies. *BMJ* 1998;316:61−66.