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ORIGINAL ARTICLE

Prolonged PR interval, first-degree heart block and adverse cardiovascular outcomes: a systematic review and meta-analysis

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ABSTRACT

Objective First-degree atrioventricular block is frequently encountered in clinical practice and is generally considered a benign process. However, there is emerging evidence that prolonged PR interval may be associated with adverse outcomes. This study aims to determine if prolonged PR interval is associated with adverse cardiovascular outcomes and mortality.

Methods We searched MEDLINE and EMBASE for studies that evaluated clinical outcomes associated with prolonged and normal PR intervals. Relevant studies were pooled using random effects meta-analysis for risk of mortality, cardiovascular mortality, heart failure, coronary heart disease, atrial fibrillation and stroke or transient ischaemic attack (TIA). Sensitivity analyses were performed considering the population type and the use of adjustments.

Results Our search yielded 14 studies that were undertaken between 1972 and 2011 with 400 750 participants. Among the studies that adjusted for potential confounders, the pooled results suggest an increased risk of mortality with prolonged PR interval risk ratio (RR) 1.24 95% CI 1.02 to 1.51, five studies. Prolonged PR interval was associated with significant risk of heart failure or left ventricular dysfunction (RR 1.39 95% CI 1.18 to 1.65, three studies) and atrial fibrillation (RR 1.45 95% CI 1.23 to 1.71, eight studies) but not cardiovascular mortality, coronary heart disease or myocardial infarction or stroke or TIA. Similar observations were recorded when limited to studies of first-degree heart block.

Conclusions Data from observational studies suggests a possible association between prolonged PR interval and significant increases in atrial fibrillation, heart failure and mortality. Future prospective studies are needed to confirm the relationships reported, consider possible mechanisms and define the optimal monitoring strategy for such patients.

INTRODUCTION

First-degree atrioventricular block (1°HB), defined as PR interval >200 ms, is frequently encountered in clinical practice and considered a benign process.[1 2] The PR interval reflects the propagation of electrical impulses from the onset of atrial depolarisation to the beginning of ventricular depolarisation. Although the prevalence of PR prolongation is relatively rare among the younger population (1% among those age <60 years) it becomes much more common after the age of ≥60 years, with prevalence rising to 6%.[3] While it has been suggested that enhanced vagal tone underlies the aetiology of 1°HB in young people, organic heart disease is more prevalent in older subjects and may be linked to myocardial conduction system fibrosis and conduction abnormalities in these groups of patients.[4] In patients who are incidentally found to have 1°HB, current expert advice suggests that 1°HB poses little risk, is not associated with significant symptoms and no specific treatment is required.[5–7]

The ACC/AHA/HRS 2008 guidelines suggest that permanent pacemaker is not indicated for asymptomatic 1°HB except for neuromuscular disease such as myotonic dystrophy[8] while the European Society of Cardiology (ESC) recommends with class IIa and level C evidence that permanent pacemaker should be considered for patients with persistent symptoms similar to those of pacemaker syndrome and attributable to 1°HB (PR >0.3 s).[9]

However, the current conservative approach to 1°HB may have been based on older studies with major methodological limitations.[10 11] Judgements regarding the benign nature of 1°HB and prolonged PR interval may be erroneous because of small sample sizes, inadequate follow-up to capture sufficient events, confounding, lack of adjustment for baseline characteristics or poor outcome ascertainment. Several more recent studies have drawn association between prolonged PR interval and cardiovascular outcomes but there are clearly conflicting viewpoints in the existing literature.[12–17] The only previous systematic review evaluated the risk of atrial fibrillation with prolonged PR interval but this review did not look at other outcomes such as mortality and cardiovascular diseases.[18] As there are several recent publications that have studied the association between prolonged PR interval/1°HB, we have reassessed the relationship between prolonged PR interval/1°HB and CV outcomes. We conduct a systematic review and meta-analysis to evaluate the association between prolonged PR interval or 1°HB and mortality, atrial fibrillation, heart failure, coronary heart disease and stroke.

METHODS

Eligibility criteria

We selected studies that evaluated adverse outcomes in patients with and without 1°HB or

prolonged PR interval on ECG. The adverse outcomes of interest were mortality, cardiovascular mortality, heart failure or left ventricular (LV) dysfunction, coronary heart disease or myocardial infarction, atrial fibrillation, stroke or transient ischaemic attack (TIA), progression of heart block or need for pacemaker insertion. While 1°HB is clearly defined as ≥200 ms, we chose to also include studies that focused on 'prolonged PR interval', in which this was variably defined by individual authors as anywhere between >196 and >220 ms. Included studies had to have two groups (one with longer PR interval), which would allow risk estimates to be calculated. There was no restriction based on study design, cohort type or language of study report. However, we excluded studies of patients with specific cardiac pathologies that were uncommon (such as aortic stenosis, sinus nodal dysfunction and heart failure) or had received intervention (angiography or cardiac resynchronisation therapy) from the main analysis.

Search strategy

We searched MEDLINE and EMBASE using OVID SP with no date or language restriction in May 2015. The exact search terms were: (first degree atrioventricular heart block or prolonged PR interval or PR prolongation or first-degree atrioventricular block) AND (atrial fibrillation or myocardial infarction or acute coronary syndrome or ischemic heart disease or ischaemic heart disease or coronary heart disease or coronary artery disease or stroke or cerebrovascular disease or cerebrovascular accident or heart failure or cardiac failure or mortality or death). We checked the bibliography of relevant studies and reviews for additional studies that met the inclusion criteria.

Study selection and data extraction

Two reviewers (CSK and MR) screened all titles and abstracts retrieved from the search for studies that met the inclusion criteria. The full manuscript of studies that potentially met the inclusion criteria was reviewed and the final decision to include or exclude studies was made with two other reviewers (YKL and MAM). Independent double extractions were performed by two reviewers (CSK and MR) and data were collected on study design, year, country, number of participants, mean age, % male, participant inclusion criteria, definition of prolonged PR interval, outcomes evaluated, timing of assessment and results.

Risk of bias assessment

Quality assessment of the studies was conducted with consideration of ascertainment of PR prolongation, outcome ascertainment, loss to follow-up and the use of adjustments for medication, cardiovascular disease and other adjustments.

Data analysis

We used RevMan V.5.3.5 (Nordic Cochrane Centre) to conduct random effects meta-analysis using the inverse variance method for pooling log risk ratios (RRs). We used random effects because the studies were conducted in a wide range of settings in different populations, hence the need to take heterogeneity into account for the pooled effect estimate. Where possible, we chose to pool adjusted risk estimates from primary studies and when these data were not available, raw data were used to calculate unadjusted risk estimates. The primary outcome was all-cause mortality, and analysis was performed considering adjusted and unadjusted group separately. Subgroup analysis was performed considering whether the population evaluated was a general population or subjects with cardiovascular disease. We also performed sensitivity analysis by including only studies which evaluated 1°HB (>200 or ≥200 ms) excluding studies which did not adjust for (a) medications and (b) cardiovascular disease.

RESULTS

Description of studies included in analysis

The progress of study selection is shown in online supplementary figure S1. Out of the 879 studies retrieved from the search, 26 studies were relevant but 12 studies were excluded from the analysis (see online supplementary table S1). A total of 14 studies[4 10–17 19–23] were included: 12 general population studies, 1 cohort with coronary heart disease[19] and 1 cohort with hypertension.[16]

Table 1 shows the baseline characteristics of the participants. There were a total of 400 750 participants among the 14 studies (11 prospective cohort studies,[4 10–13 17 19–23] 3 retrospective cohort studies[14–16]). The mean age from the 10 studies was 56 years and the percentage of participants that were male ranged from 18% to 100%. The studies were undertaken between 1972 and 2011 and were undertaken in Finland, USA, Norway, Japan, Korea, Australia and Denmark. Prevalence of prolonged PR interval ranged from 2% to 14% across seven studies and the mean prevalence was 7%.

Risk of bias in studies

The evaluation of the quality of studies is shown in online supplementary table S2. All studies used ECG to ascertain PR prolongation but only eight studies reported the leads used to measure PR interval. A variety of methods were used to ascertain outcomes including data from registries, telephone contact and medical records. Seven studies reported some degree of loss to follow-up which ranged from 1% to 9%. Aside from two studies, all the studies used multivariate analysis to adjust for potential confounders (nine adjusted for medications, seven adjusted for cardiovascular disease and eight adjusted for heart rate). Two studies with unadjusted data were considered to be at high risk of bias.[10 11]

Description of included studies

Table 2 shows the description of reference group, outcomes evaluated, timing of assessment and results. The definition of PR prolongation varied across the studies from >196 to >220 ms and follow-up for outcomes among studies was between 5 and 24 years. Seven studies used the 200 ms as the cut-off and were included in the 1°HB analysis.

Risk of adverse outcomes with prolonged PR interval

The risk of mortality with prolonged PR interval is shown in figure 1A. There were a total of seven studies in the analysis and five of which adjusted for potential confounders. The pooled estimate of adjusted studies (based on a total of 14 454 deaths/37 634 participants) suggests a significant increase in mortality with prolonged PR interval (RR 1.24 95% CI 1.02 to 1.51). The crude event rate for the two unadjusted studies was 547 deaths/2331 participants (38%). The pooled estimate from unadjusted analyses (that are at high risk of bias) showed that prolonged PR interval was associated with reduced overall mortality (RR 0.72 95% CI 0.55 to 0.99).

The risk of other adverse outcomes with prolonged PR interval is shown in figure 1B. Prolonged PR interval was associated with significant risk of heart failure or LV dysfunction (RR 1.39 95% CI 1.18 to 1.65, three studies, event rate 2389/17 323, 14%) and atrial fibrillation (RR 1.45 95% CI 1.23 to 1.71, eight studies, event rate 15 616/375 526, 4%) but not

Table 1 Study design and participant characteristics

Study ID	Study design; year; country	Participants (n)	Mean age, median age or age range	Male (%)	Participant inclusion criteria
Aro *et al*[4]	Prospective cohort study; 1966–2007; Finland	10 785	Mean 44 years	52	Participants were 'apparently healthy' community population, aged 30–59 years between 1966 and 1972 in the Finnish Social Insurance Institution's Coronary Heart Disease Study
Cheng *et al*[12]	Prospective cohort study; 1968–2007; USA	7575	Mean 47 years	46	Participants were community-based individuals from the Framingham Heart Study
Crisel *et al*[19]	Prospective cohort study; enrolment 2000–2002; USA	938	Mean 66 years	82	Participants had stable coronary artery disease in the Heart and Soul Study
Erikssen and Otterstad[10]	Prospective cohort study; enrolment 1972–1975; Norway	1635	40–59 years at baseline	100	Participants were apparently healthy men aged 40–59 years free of coronary heart disease
Hisamatsu *et al*[17]	Prospective cohort study; 1980–2009; Japan	9051	Mean 50 years	44	Participants were community dwellers, aged 30–95 years from 300 randomly selected areas throughout Japan
Knuiman *et al*[20]	Prospective cohort study; 1994–2010; Australia	4267	Mean 52 years	44	Participants were community-based adults, aged 25–84 years in the Busselton Health Study
Kobayashi *et al*[21]	Prospective cohort study; baseline survey 1989–1994; Japan	5425	30–83 years	47	Participants were Japanese urban adults aged 30–83 years without prior cardiovascular disease who attended a routine examination
Magnani *et al*[22]	Prospective cohort study; 1997–2011; USA	2722	Mean 74 years	48	Participants were a random sampling of community-dwelling older patients (age 70–79 years) free of disability or functional limitation from the Health, Aging and Body Composition Study
Nielsen *et al*[13]	Prospective cohort study; 2001–2010; Denmark	288 181	Median 54 years	45	Participants were from primary care who had ≥1 ECG recorded at the Copenhagen General Practitioners' Laboratory
Perez *et al*[14]	Retrospective cohort study; March 1987 to July 2000; USA	42 751	Mean 56 years	90	Participants had initial ECG between March 1987 and July 2000. Indications for ECG and background disease—not known, but patients with known atrial fibrillation were excluded from study
Rajala *et al*[11]	Prospective cohort study; January 1977 to December 1982; Finland	674	Age >85 years	18	Participants were 85 years or older community-based sample living in the city of Tampere in 1977
Soliman *et al*[15]	Retrospective cohort study; 1987–1998; USA	15 429	Mean 54.2 years	45	Participants were from four US communities aged 45–64 years in the Atherosclerosis Risk in Communities Study
Soliman *et al*[23]	Prospective cohort study; 1988 to December 2006; USA	7501	Mean 59.3 years	47	Participants were civilian non-institutionalised US population in the NHANES Study
Uhm *et al*[16]	Retrospective cohort study; unclear; Korea	3816	Mean 61.0 years	47.2	Participants were aged >18 years with hypertension and sinus rhythm on first ECG

cardiovascular mortality, coronary heart disease or myocardial infarction or stroke or TIA.

Additional analysis was performed considering all studies including patients with previous coronary heart disease and hypertension and adjustments for medication and cardiovascular disease (table 3). We observed similar significant increases in adjusted mortality, heart failure or LV dysfunction and atrial fibrillation in these additional analyses.

In addition, Cheng *et al* was the only study to report two important outcomes associated with 1°HB which were need for pacemaker insertion and progression of heart block.

The results for adverse outcomes with prolonged PR interval using the cut-offs for 1°HB are shown in figure 2. Similar to prolonged PR interval there were significant increases in mortality (RR 1.31 95% CI 1.18 to 1.46), heart failure (RR 1.39 95% CI 1.18 to 1.65) and atrial fibrillation (RR 1.47 (1.18 to 1.83)) but not cardiovascular mortality, coronary heart disease or stroke.

DISCUSSION

Our results suggest that prolonged PR interval and 1°HB are not benign conditions and are associated with increased mortality, heart failure and atrial fibrillation. Physicians should not, therefore, consider 1°HB as a benign condition. Contrary to current expert advice, our results suggest that closer monitoring may be warranted for future events, although effective risk reduction strategies still need to be developed.

The mechanism that underlies the association between 1°HB and adverse cardiovascular outcomes and mortality is unclear. Cheng *et al*[12] suggests that chronic PR prolongation could be a precursor to more severe degrees of conduction block. This is supported by their findings that there was a significant increase in need for pacemaker and progression of heart block with 1° HB.[12] Further evidence supporting the progression of heart block is provided by a study of 446 participants with acute myocardial infarction which found that one-third of those who developed first-degree heart block progressed to third-degree heart block.[24] Progression of heart block may relate to underlying causes of atrioventricular block and progression of these pathologies which include primary or idiopathic (generally considered as fibrosis in origin), and secondary to conditions such as coronary heart disease, calcification, inflammation, infiltrative diseases and neuromuscular disorders.[25] Myocardial fibrosis is known to slow conduction and increase vulnerability to arrhythmia.[26] Fibrosis of the conduction tissue is a dynamic process which can accumulate with repeated insults secondary to these pathological processes. These accumulated changes over time may explain the initial manifestation of first-degree heart and progression to higher degree of heart block and mortality.

Cheng *et al*[12] also suggest that prolongation of PR interval may be a marker of other cardiovascular changes associated with worse prognosis such as advanced physiological age. Electrophysiological studies which have demonstrated that atrial conduction velocity in both atria declines and the atria becomes more refractory with increasing age; this may explain age-related increase in prevalence of atrial fibrillation.[27 28] Ageing can also manifest as calcification or fibrosis of the cardiac skeleton.[12] In

Table 2 Outcomes evaluated and results

Study ID	Description of reference group	Outcomes evaluated and timing of assessment	Results
Aro *et al*[4]	≤200 ms	Follow-up for 30 years	Multivariate adjusted HR: ▶ All-cause mortality: 140/222 vs 5933/10 563, HR 1.05 (0.89 to 1.24) ▶ Cardiovascular mortality: 44/222 vs 1904/10 563, HR 0.94 (0.70 to 1.27) ▶ Heart failure: 42/222 vs 1673/10 563, HR 1.22 (0.90 to 1.65) ▶ CAD: 74/222 vs 3465/10 563, HR 0.97 (0.77 to 1.22) ▶ Atrial fibrillation: 35/222 vs 1591/10 563, HR 1.03 (0.74 to 1.45) ▶ TIA or stroke: 50/222 vs 1877/10 563, HR 1.23 (0.92 to 1.62)
Cheng *et al*[12]	≤200 ms	Up to 35 years	Atrial fibrillation: 25/124 vs 456/7451, multivariate HR 2.36 (1.53 to 3.64) Pacemaker insertion: 26/124 vs 98/7451, multivariate HR 4.32 (2.46 to 7.59) All-cause mortality: 62/124 vs 1677/7451, multivariate HR 1.48 (1.10 to 1.99)
Crisel *et al*[19]	<220 ms	Up to 5 years	Heart failure: 26/87 vs 97/851, adjusted for medications HR 2.33 (1.49 to 3.65) Cardiovascular mortality: 15/87 vs 52/851, adjusted for medications HR 2.33 (1.28 to 4.22) All-cause mortality: 42/87 vs 243/851, adjusted for medications HR 1.58 (1.13 to 2.20) Heart failure or cardiovascular mortality: 34/87 vs 122/851, adjusted for medications HR 2.43 (1.64 to 3.61) Heart failure: 26/87 vs 97/851, adjusted for heart failure HR 2.02 (1.24 to 3.31) Cardiovascular mortality: 15/87 vs 52/851, adjusted for heart failure HR 2.29 (1.18 to 4.45) All-cause mortality: 42/87 vs 243/851, adjusted for heart failure HR 1.49 (1.04 to 2.14) Heart failure or cardiovascular mortality: 34/87 vs 122/851, adjusted for heart failure HR 2.09 (1.36 to 3.23)
Erikssen and Otterstad[10]	≤210 ms	MI, angina pectoris, pathological exercise ECG, death from CHD, total CHD events	MI: 6/98 vs 54/1537 Angina pectoris: 3/98 vs 76/1537 Pathological exercise ECG: 7/98 vs 205/1537 Death from CHD: 1/98 vs 36/1537 Total deaths: 3/98 vs 71/1537
Hisamatsu *et al*[17]	<220 ms	All-cause mortality, cardiovascular disease mortality, CHD mortality, stroke mortality with mean follow-up of 24.3 years	All-cause mortality: total events 3269/9051, multivariate HR 1.06 (0.85 to 1.31) Cardiovascular disease mortality: total events 1101/9051, multivariate HR 0.94 (0.65 to 1.37) CHD mortality: total events 227/9051, multivariate HR 1.49 (0.76 to 2.92) Stroke mortality: total events 491/9051, multivariate HR 0.70 (0.37 to 1.31)
Knuiman *et al*[20]	Unclear, not long PR interval	Incident atrial fibrillation at follow-up of 15 years	Incident atrial fibrillation: total events 343/4267, multivariate HR 1.29 (0.68 to 2.44)
Kobayashi *et al*[21]	<220 ms	Cardiovascular disease, CHD and stroke at 13.1 years follow-up	All cardiovascular disease: total events 421/5425, multivariate HR 2.98 (1.22 to 7.31) CHD: total events 180/5425, multivariate HR 1.57 (0.22 to 11.42) Stroke: total events 241/5425, multivariate HR 3.90 (1.42 to 10.72) Cerebral infarction: total events 144/5425, multivariate HR 2.98 (1.22 to 7.31)
Magnani *et al*[22]	≤200 ms	Incident heart failure, atrial fibrillation and all-cause mortality	Incident heart failure: total events 369/2722, multivariate HR 1.46 (1.11 to 1.93) Incident atrial fibrillation: total events 537/2722, multivariate HR 1.26 (0.99 to 1.61) All-cause mortality: total events 832/2722, multivariate HR 1.14 (0.94 to 1.39)
Nielsen *et al*[13]	<200 ms	Atrial fibrillation at median follow-up of 5.7 years	Incident atrial fibrillation: total events 11 087/288 181, multivariate HR 1.26 (1.17 to 1.35) (reference group PR interval 150–161 ms) Men multivariate HR 1.18 (1.06 to 1.30) and women multivariate HR 1.30 (1.17 to 1.44)
Perez *et al*[14]	≤200 ms	Incident atrial fibrillation at 5.3 years	Risk of atrial fibrillation with PR >200 ms: total events 1050/42 751, multivariate HR 1.3 (1.1 to 1.6)
Rajala *et al*[11]	<220 ms	Mortality at 5 years follow-up	Crude 5 years mortality: first-degree heart block 20/39 vs normal 453/657
Soliman *et al*[15]	1 SD change and upper 5th centile vs 95th centile of PR duration	Incident atrial fibrillation and ischaemic stroke with follow-up of 6.97 years	Total atrial fibrillation events 117/15 429. Total ischaemic stroke events 599/15 429 Risk of ischaemic stroke with 1 SD change in PR duration: multivariate HR 1.00 (0.92 to 1.08) Risk of atrial fibrillation with 1 SD change in PR duration: multivariate HR 1.41 (1.20 to 1.65) Risk of atrial fibrillation with upper 5th centile vs 95th centile of PR duration: multivariate HR 1.59 (0.77 to 3.30)
Soliman *et al*[23]	≤200 ms for crude analysis but adjusted analysis 120–200 ms	Mortality at median follow-up of 13.8 years	Prolonged PR interval and mortality: 325/654 vs 2216/6847 High-P duration prolong PR interval and mortality: multivariate HR 2.00 (1.34 to 2.99) Low-P duration prolong PR interval and mortality: multivariate HR 0.99 (0.86 to 1.14)
Uhm *et al*[16]	≤200 ms	Advanced AV block, sick sinus syndrome, atrial fibrillation, LV dysfunctions follow-up period of 9.4 years	First-degree heart block and multivariate outcomes: ▶ Advanced AV block: 12/544 vs 26/3272, HR 2.77 (1.38 to 5.59) ▶ Sick sinus syndrome: 8/544 vs 277/3272, HR 1.32 (0.61 to 2.84) ▶ Atrial fibrillation: 98/544 vs 277/3272, HR 2.33 (1.84 to 2.94) ▶ LV dysfunction: 59/544 vs 245/3272, HR 1.49 (1.11 to 2.00)

CAD, coronary artery disease; CHD, coronary heart disease; LV, left ventricular; MI, myocardial infarction; TIA, transient ischaemic attack.

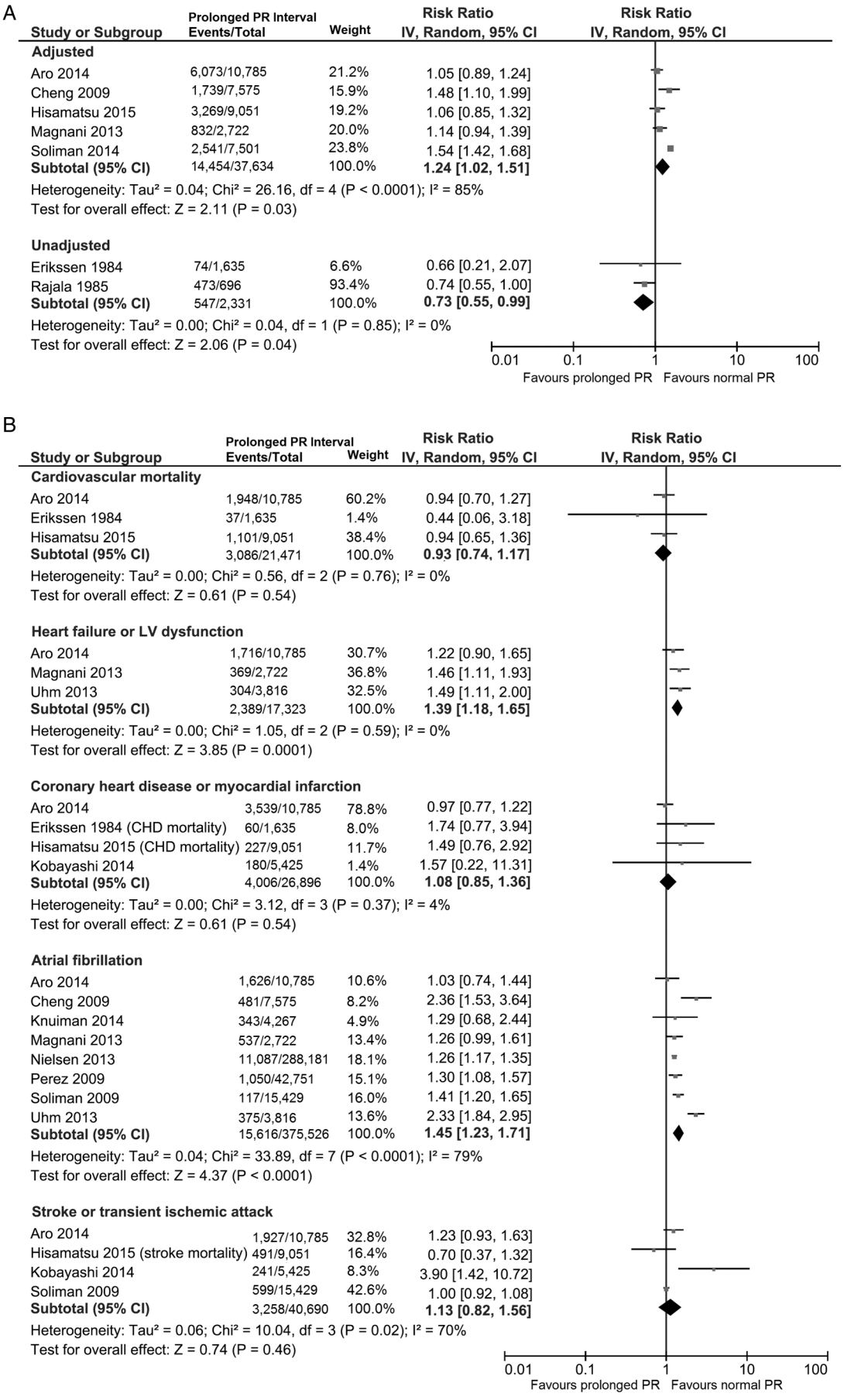

Figure 1 Risk of (A) mortality and (B) adverse outcomes with prolonged PR interval. CHD, coronary heart disease; LV, left ventricular.

Table 3 Summary of meta-analysis results

Panel A: general population studies			
	General population studies		
Adverse outcome	Studies (n)	Events/total	RR (95% CI)
All mortality			
Adjusted only	5	14 454/37 634	1.24 (1.02 to 1.51)
Unadjusted only	2	15 001/39 965	0.73 (0.55 to 0.99)
Cardiovascular mortality	3	3086/21 471	0.93 (0.74 to 1.17)
Heart failure or LV dysfunction	3	2389/17 323	1.39 (1.18 to 1.65)
CHD or MI	4	4006/26 896	1.08 (0.85 to 1.36)
Atrial fibrillation	8	15 616/37 526	1.45 (1.23 to 1.71)
Stroke or TIA	4		1.13 (0.82 to 1.56)
Panel B: all studies (including studies of patients with CAD)			
	All studies (including studies of patients with CAD)		
Adverse outcome	Studies (n)	Events/total	RR (95% CI)
All mortality			
Adjusted only	7	14 739/38 572	1.23 (1.01 to 1.49)
Unadjusted only	2	547/2331	0.73 (0.55 to 0.99)
Cardiovascular mortality	4	3153/22 409	1.14 (0.73 to 1.76)
Heart failure or LV dysfunction	4	2512/18 261	1.51 (1.22 to 1.88)
CHD or MI	4	4006/26 896	1.08 (0.85 to 1.36)
Atrial fibrillation	8	15 616/375 526	1.45 (1.23 to 1.71)
Stroke or TIA	4	3258/40 690	1.13 (0.82 to 1.56)
Panel C: only inclusion of studies that adjusted for medications			
	Only inclusion of studies that adjusted for medications		
Adverse outcome	Studies (n)	Events/total	RR (95% CI)
All mortality			
Adjusted only	7	14 739/48 209	1.23 (1.01 to 1.49)
Cardiovascular mortality	3	3116/20 774	1.19 (0.75 to 1.88)
Heart failure or LV dysfunction	4	2512/18 261	1.51 (1.22 to 1.88)
CHD or MI	1	3539/10 785	0.97 (0.77 to 1.22)
Atrial fibrillation	6	14 449/317 346	1.50 (1.15 to 1.96)
Stroke or TIA	2	2418/19 836	1.00 (0.59 to 1.70)
Panel D: only inclusion of studies that adjusted for CVD			
	Only inclusion of studies that adjusted for CVD		
Adverse outcome	Studies (n)	Events/total	RR (95% CI)
All mortality			
Adjusted only	6	11 470/39 158	1.26 (1.02 to 1.56)
Cardiovascular mortality	2	2015/11 723	1.42 (0.59 to 3.46)
Heart failure or LV dysfunction	4	2512/18 261	1.51 (1.22 to 1.88)
CHD or MI	1	3539/10 785	0.97 (0.77 to 1.22)
Atrial fibrillation	5	14 106/313 079	1.53 (1.14 to 2.04)
Stroke or TIA	1	1927/10 785	1.23 (0.93 to 1.63)

CAD, coronary artery disease; CHD, coronary heart disease; CVD, cardiovascular disease; LV, left ventricular; MI, myocardial infarction; RR, risk ratio; TIA, transient ischaemic attack.

addition, age is known to be associated with increased risk of mortality and cardiovascular disease such as ischaemic heart disease and heart failure. We observed a greater mean age in patients in the prolonged PR interval group compared with normal PR interval group in several studies.[4 12 13 17 19] However, the majority of the included studies adjusted for age which suggests that the increased risk of cardiovascular events with 1°HB cannot be explained by ageing alone.

Crisel *et al*[19] suggest that 1°HB may be a marker of diffuse ischaemic heart disease. However, our findings do not support this as prolonged PR interval does not increase coronary heart disease, stroke and cardiovascular mortality which are related to atherosclerosis and vascular pathology. Magnani *et al*[22] suggest that prolongation of PR has been associated with obesity, waist circumference and components of metabolic syndrome which are also associated with incident heart failure. They also suggest

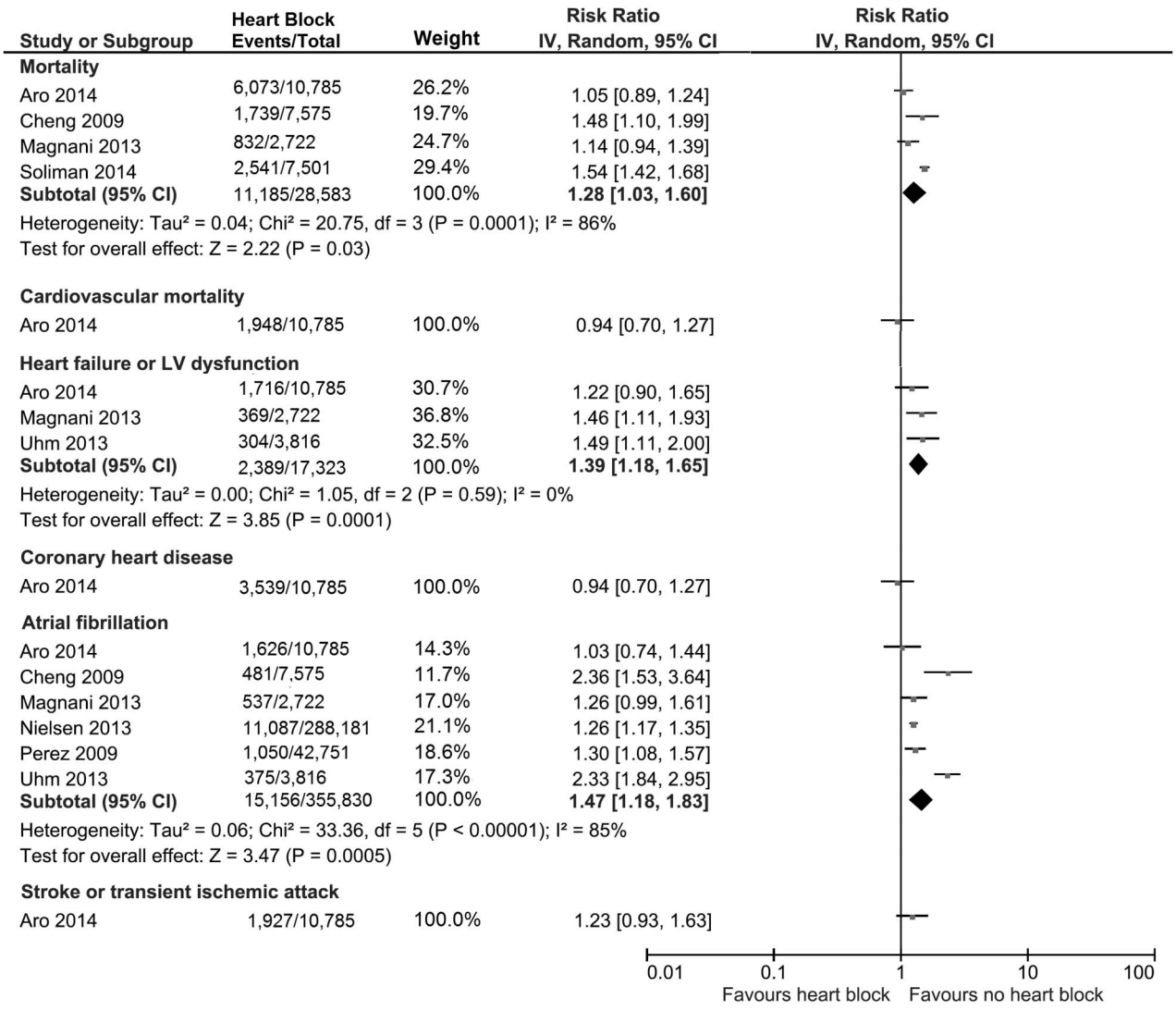

Figure 2 Risk of adverse outcomes with first-degree heart block.

that hypertension may be a confounder that causes heart failure with both preserved and compromised systolic function and cause elevated intracardiac pressures and secondary altered atrial electrical function.[22] In addition, prolonged PR interval may unmask existing cardiac pathology such as heart failure.

Our results support the findings of existing studies. Cheng *et al*[18] conducted a meta-analysis of six cohort studies and reported an increased risk of atrial fibrillation with 1°HB. There are two additional studies in our review, Perez *et al*[14] and Uhm *et al*[16] and both of these studies suggest an increased risk of atrial fibrillation with 1°HB. We build upon this review by including the other outcomes mortality, cardiovascular mortality, heart failure, coronary heart disease and stroke.

We identified three older studies suggesting no increase in mortality with AV block or first-degree heart block but these studies did not provide specific statistical analyses and results that met our criteria for inclusion in the meta-analysis. The study by Kitchin and Milne,[29] evaluated mortality rates of 487 random adults with and without AV block. Mortality was lower in the AV block group compared with control group (21% vs 24%) but the study did not report specifically on first-degree heart block. The study by Rose *et al*,[30] evaluated coronary heart disease death at 5 years with different ECG abnormalities. However, CIs for the adjusted rates were not reported. The Copenhagen City Heart Study of 19 662 adults stated that there was no difference between the normal ECG group and those with AV conduction defects but did not quantify outcome data.[31] We believe that there is insufficient granularity in data from these older studies for us to make any robust interpretation on cardiovascular or mortality risk. Moreover, the population and management of cardiovascular disease have changed substantially since these older studies, so it is unclear if these results are generalisable to current practice.

The long follow-up in many of these studies is an important consideration in the interpretation of the findings. This may suggest that event rates may be very low so a long follow-up time is need to capture enough events to show a difference. Because 1°HB can be asymptomatic it is unclear exactly how long patients have had heart block for prior to inclusion in the study. This represents a problem because all of the studies are observational in nature. However, the long follow-up time between heart block and adverse events may provide a window for which patients can be identified and management can be implemented to reduce risk of cardiovascular pathology.

While first-degree heart block is generally considered to be PR interval >200 ms the upper limit of the 'normal' PR interval is necessarily arbitrary.[3] In the current study, prolonged PR interval ranged from 196 to 220 ms.

An important question generated from these findings is the management strategy that should be undertaken if 1°HB is incidentally found. Guidelines recommend against pacemaker insertion unless patients are symptomatic and according to ESC guidelines the PR interval is >300 ms.[7 9] The options include following up these patients and if so how frequently (probably unrealistic to see them yearly, perhaps every 3 or 5 years). Furthermore, it is unclear whether formal cardiovascular risk assessment should be undertaken as recommended for high-risk groups at risk of future cardiovascular events such as those with established cardiovascular disease, diabetes mellitus and renal disease.[32]

While we were able to show significant associations between prolonged PR interval and certain adverse outcomes (eg, mortality, atrial fibrillation and heart failure) the pooled effect sizes are small and there are only a limited number of studies for each outcome. Consequently, the findings may be affected by the possibility of residual confounding. Therefore, findings of this current systematic review should be interpreted as evidence to raise the hypothesis that prolonged PR interval may be a risk factor for several adverse cardiac outcomes. These results do support further studies to assess the association of prolonged PR interval and adverse cardiovascular outcome but at present we cannot definitely conclude that the association is causal.

We observed differences in study results and this may be attributed to dissimilarity among the include studies in terms of geographic locations, baseline cardiovascular risk and underlying aetiology of prolonged PR interval. Equally, the effects of potential confounding factors may vary across the studies because of these differences. Collectively, these factors are likely to contribute to clinical heterogeneity in effect sizes. In addition, we note that the participants in the currently pooled studies are of different design with different inclusion criteria. This form of methodological heterogeneity among the studies may account for different results in each study. Therefore, it is possible that for some populations, prolonged PR interval may be a benign finding. Our study has a number of strengths and limitations. We included >400 000 subjects from 12 studies. We were able to consider the effects of adjustments including the impact of adjustments for medications and cardiovascular disease. Furthermore, we evaluated a variety of clinically relevant cardiovascular outcomes. All of the included studies are all observational in nature. For some cardiovascular events follow-up, the outcome ascertainment is less reliable but mortality events are easily ascertained. This is a problem for outcomes that may be asymptomatic such as atrial fibrillation especially in studies that use hospitalisation data. We also observed either a lack of description of the leads use for evaluation of PR interval or inconsistencies in choice of leads for evaluation for heart block among the included studies. We were also unable to determine if prolongation of PR interval was persistent among the studies. Additional limitations include the lack of trending data with regards to the degree of PR interval and risk of adverse outcomes. Furthermore, an important consideration is the use of pharmacological agents which could impact PR prolongation. We found that eight studies adjusted for medications as potential confounders and one study excluded patients on nodal-blocking medications while six studies did not consider the effects of medications. There are also limitations because end points have been defined and measured in different ways and at different time points among the studies.

CONCLUSIONS

In a relatively, unselected population of patients in this meta-analysis, PR interval prolongation might be associated with adverse cardiovascular events and mortality but further studies are needed. Future studies should also focus on providing mechanistic insight and define the optimal monitoring strategy for such patients.

Key messages

What is already known on this subject?

- First-degree atrioventricular block, defined as PR interval >200 ms, is frequently encountered in clinical practice.
- In patients who are incidentally found to have first-degree heart block, current expert advice suggests that this poses little risk and is not associated with significant symptoms and no specific treatment is required.

What might this study add?

- Our review of 14 studies with >400 000 participants suggests that prolonged PR interval was associated with increased risk of mortality, heart failure and atrial fibrillation.
- Similar significant increases in mortality, heart failure and atrial fibrillation were observed when limited to studies of first-degree heart block.

How might this impact on clinical practice?

- Physicians should not automatically dismiss first-degree heart block as a benign condition.
- Contrary to current expert advice, our results suggest that closer monitoring may be warranted for future events, although effective risk reduction strategies still need to be developed.

Contributors CSK conceptualised and designed the review. CSK and YKL performed the literature search. CSK and MR screened and collected data for the systematic review which was checked by YKL and MAM. CSK and YKL conducted the meta-analysis. CSK wrote the draft for the paper and all authors contributed to the writing of the paper.

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REFERENCES

1 Bexton RS, Camm AJ. First degree atrioventricular block. *Eur Heart J* 1984;5(Suppl A):107–9.
2 Mymin D, Mathewson FA, Tate RB, *et al*. The natural history of primary first-degree atrioventricular heart block. *N Engl J Med* 1986;315:1183–7.
3 Perlman LV, Ostrander LD, Keller JB, *et al*. An epidemiologic study of first degree atrioventricular block in Tecumseh, Michigan. *Chest* 1971;59:40–6.
4 Aro AL, Anttonen O, Kerola T, *et al*. Prognostic significance of prolonged PR interval in the general population. *Eur Heart J* 2014;35:123–9.
5 Heart Block. http://www.nhs.uk/Conditions/Heart-block/Pages/Introduction.aspx (accessed 31 Oct 2015).
6 Heart Block. http://my.clevelandclinic.org/services/heart/disorders/arrhythmia/heart-block (accessed 31 Oct 2015).
7 Atrioventricular block. http://www.merckmanuals.com/professional/cardiovascular-disorders/arrhythmias-and-conduction-disorders/atrioventricular-block (accessed 31 Oct 2015).
8 Epstein AE, DiMarco JP, Ellebogen KA, *et al*. ACC/AHA/HRS 2008 guidelines for device-based therapy for cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *Circulation* 2008;117:e350–408.
9 Brignole M, Auricchio A, Baron-Esquivias G, *et al*. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and

resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J* 2013;34:2281–329.
10 Erikssen J, Otterstad JE. Natural course of a prolonged PR interval and the relation between PR and incidence of coronary heart disease. A 7-year follow-up study of 1832 apparently health men age 40–59 years. *Clin Cardiol* 1984;7:6–13.
11 Rajala S, Haavisto M, Kaltiala K, *et al*. ECG findings and survival in very old people. *Eur Heart J* 1985;6:247–52.
12 Cheng S, Keyes MJ, Larson MG, *et al*. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. *JAMA* 2009;301:2571–7.
13 Nielsen JB, Pietersen A, Graff C, *et al*. Risk of atrial fibrillation as a function of electrocardiographic PR interval: results from the Copenhagen ECG study. *Heart Rhythm* 2013;10:1249–56.
14 Perez MV, Dewey FE, Marcus R, *et al*. Electrocardiographic predictors of atrial fibrillation. *Am Heart J* 2009;158:622–8.
15 Soliman EZ, Prineas RJ, Case LD, *et al*. Ethnic distribution of ECG predictors of atrial fibrillation and its impact of understanding the ethnic distribution of ischemic stroke in the Atherosclerosis Risk in Communities (ARIC) Study. *Stroke* 2009;40:1204–11.
16 Uhm JS, Shim J, Wi J, *et al*. First-degree atrioventricular block is associated with advanced atrioventricular block, atrial fibrillation and left ventricular dysfunction in patients with hypertension. *J Hypertension* 2014;32:1115–20.
17 Hisamatsu T, Miura K, Fujiyoshi A, *et al*. Long-term outcomes associated with prolonged PR interval in the general Japanese population. *Int J Cardiol* 2015;184:291–3.
18 Cheng M, Lu X, Huang J, *et al*. Electrocardiographic PR prolongation and atrial fibrillation risk: a meta-analysis of prospective cohort studies. *J Cardiovasc Electrophysiol* 2015;26:36–41.
19 Crisel RK, Farzaneh-Far R, Na B, *et al*. First-degree atrioventricular block is associated with heart failure and death in persons with stables coronary artery disease: data from the Heart and Soul Study. *Eur Heart J* 2011;32:1875–80.
20 Knuiman M, Briffa T, Divitini M, *et al*. A cohort study examination of established and emerging risk factors for atrial fibrillation: the Busselton Health Study. *Eur J Epidemiol* 2014;29:181–90.
21 Kobayashi T, Watanabe M, Kokubo Y, *et al*. Prolonged PR interval is significantly associated with increased risk of cardiovascular diseases and stroke in a population-based cohort study. *Circulation* 2014;130:A13451.
22 Magnani JW, Wang N, Nelson KP, *et al*. Electrographic PR interval and adverse outcomes in older adults: the Health, Aging, and Body Composition study. *Circ Arrhythm Electrophysiol* 2013;6:84–90.
23 Soliman EZ, Cammarata M, Li Y. Explaining the inconsistent associations of PR interval with mortality: the role of P-duration contribution to the length of PR interval. *Heart Rhythm* 2014;11:93–8.
24 Brown RW, Hunt D, Sloman JG. The natural history of atrioventricular conduction defects in acute myocardial infarction. *Am Heart J* 1969;78:460–6.
25 Waller BF, Gering LE, Branyas NA, *et al*. Anatomy, histology and pathology of the cardiac conduction system-Part V. *Clin Cardiol* 1993;16:565–9.
26 de Jong S, van Veen TAB, van Rijen HVM, *et al*. Fibrosis and cardiac arrhythmias. *J Cardiovasc Pharmacol* 2011;57:630–8.
27 Kistler PM, Sanders P, Fynn SP, *et al*. Electrophysiologic and electroanatomic changes in the human atrium associated with age. *J Am Coll Cardiol* 2004;44:109–16.
28 Kojodjojo P, Kanagaratnam P, Markides V, *et al*. Age-related changes in human left and right atrial conduction. *J Cardiovasc Electrophyiol* 2006;17:120–7.
29 Kitchin AH, Milne JS. Longitudinal survey of ischaemic heart disease in randomly selected sample of older population. *Br Heart J* 1997;39:889–93.
30 Rose G, Baxter PJ, Reid DD, *et al*. Prevalence and prognosis of electrocardiographic findings in middle-aged men. *Br Heart J* 1978;40:636–43.
31 Ostor E, Schnohr P, Jensen G, *et al*. Electrocardiographic findings and their association with mortality in the Copenhagen City Heart Study. *Eur Heart J*. 1981;2:317–28.
32 Perk J, De Backer G, Gohlke H, *et al*. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012;33:1635–701.

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