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

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Abstract

Background: First-degree heart block is generally considered a benign condition but emerging evidence suggests that it may be associated with adverse outcomes.

Methods: We searched MEDLINE and EMBASE for comparative studies that evaluated clinical outcomes associated with prolonged and normal PR intervals in general populations or those with cardiovascular risk factors or stable coronary disease. 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 TIA. Sensitivity analyses were performed considering the population type and 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 RR 1.24 95%CI 1.02-1.51. Prolonged PR interval was associated with significant risk of heart failure or left ventricular dysfunction (RR 1.39 95%CI 1.18-1.65) and atrial fibrillation (RR 1.45 95%CI 1.23-1.71) but not cardiovascular mortality, coronary heart disease or myocardial infarction or stroke or TIA. Similar significant increases in mortality, heart failure and atrial fibrillation were observed when limited to studies of first-degree heart block.

Conclusions: Data from observational studies indicates that prolonged PR interval and first-degree heart block is associated with significant increases in atrial fibrillation, heart failure and mortality. Future studies should focus on providing mechanistic insight and define the optimal monitoring strategy for such patients.

Introduction

First-degree atrioventricular block (1°HB), defined as PR interval greater than 200 ms, is frequently encountered in clinical practice and considered a benign process.[1,2] The PR interval measure reflects the propagation of electrical activity from the sinus node to the atrioventricular node. Although the prevalence of PR prolongation is relatively rare amongst the younger population (1% among those age <60) it becomes much more common after the age ≥60 years, with prevalence rising to 6% .[3] However, there is a group within the young population who are trained athletes that having much higher rates of 1°HB due to slow atrioventricular conduction secondary to increase parasympathetic tone and decreased sympathetic tone.[4,5] It has been suggested that enhanced vagal tone is the aetiology of 1°HB in young people while for older subjects organic heart disease is more prevalent and may be linked to myocardial conduction system fibrosis.[6] 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.(http://www.nhs.uk/Conditions/Heart-block/Pages/Introduction.aspx; http://my.clevelandclinic.org/services/heart/disorders/arrhythmia/heart-block http://www.merckmanuals.com/professional/cardiovascular-disorders/arrhythmias-and-conduction-disorders/atrioventricular-block

The European Society of Cardiology 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 >0.3s).[7] The ACC/AHA/HRS 2008 guides suggest that permanent pacemaker is not indicated for asymptomatic 1°HB except for neuromuscular disease such as myotonic dystrophy.[8] However, there is emerging evidence that it may be associated with increased risk of atrial fibrillation, pacemaker insertion and mortality.[9]

However, the current conservative approach to 1°HB may have been developed based on older studies with major methodological limitations.(ref: Erikssen, Rajala) 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 adjustments 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.[9-14] The only previous systematic review evaluated the risk of atrial fibrillation with prolonged PR interval but this review did not look at other outcomes as mortality and cardiovascular diseases.[15] As there are several recent publications, we feel it is very important to re-assess this relationship. The clinical importance is that we do not want to simply dismiss a potential adverse association, and falsely reassure patients that they will not come to any serious harm.

We conducted 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 electrocardiogram. The adverse outcomes of interest were mortality, cardiovascular mortality, heart failure or left ventricular dysfunction, coronary heart disease or myocardial infarction, atrial fibrillation, stroke or transient ischemic attack, progression of heart block or need for pacemaker insertion. While 1°HB was clearly defined as > or ≥ 200 ms, there was no specific choice of cutoff for prolonged PR interval as long as the PR interval was ≥200 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, heart failure) or had received intervention (angiography or cardiac resynchronization 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, 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 were reviewed and the final decision to include or exclude studies were made with two other reviewers (YKL, MAM). Independent double extractions were performed by two reviewers (CSK, MR) and data was 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 were conducted with consideration of ascertainment of PR prolongation, outcome ascertainment, lost to follow up and use of adjustments for medication, cardiovascular disease and other adjustments. We aimed to contact authors to clarify any uncertainties in reported data. Publication bias was considered using asymmetry testing if there were more than 10 studies in the meta-analysis, and if there was statistical heterogeneity <50%.[16]

Data analysis

We used RevMan 5.3.5 (Nordic Cochrane Centre) to conduct random effects meta-analysis using the inverse variance method for pooling risk ratios (RR). Where possible, we shoes to pool adjusted risk estimates from primary studies and when this data was not available raw data was 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 of subjects with cardiovascular disease. We also performed sensitivity analysis by including only studies which evaluated 1°HB (>200ms 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 Figure 1. Out of the 879 studies retrieved from the search, 23 studies were relevant but 9 studies were excluded from the analysis (Appendix 1). A total of 14 studies[6,9-14,17-23] were included: 12 general population studies, 1 coronary heart disease cohorts[17] and 1 hypertensive cohort.[13]

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,[6,9,10,14,17-23] 3 retrospective cohort studies[11-13]). The mean age from 10 studies is 56 years and 62% were male. The studies were undertaken between 1972 and 2011 and they took place in Finland, USA, Norway, Japan, Korea, Australia and Denmark. Prevalence of prolonged PR interval ranged from 2% to 14% across 7 studies and the mean prevalence was 7%.

The evaluation of the quality of studies is shown in Table 2. 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 lost to follow up. Aside for two studies, all the studies used multivariate analysis to adjust for potential confounders (9 adjusted for medications, 7 adjusted for cardiovascular disease and 8 adjusted for heart rate).

Table 3 shows the description of reference group, outcomes evaluated, timing of assessment and results. The definition of PR prolongation varied across the studies from >200 ms to >220 ms and follow up for outcomes amongst studies was between 5 to 24 years. Seven studies used the 200 ms as the cutoff 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 2. 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) suggest a significant increase in mortality with prolonged PR interval (RR 1.24 95% CI 1.02-1.51). The crude event rate for the two unadjusted studies were 547 deaths/2,331 participants (38%) in the PR prolongation arm as compared to ?? in the control arm 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 0.73 (0.55 – 0.99).

The risk of other adverse outcomes with prolonged PR interval is shown in Figure 3. Prolonged PR interval was associated with significant risk of heart failure or left ventricular dysfunction (RR 1.39 95%CI 1.18-1.65, 3 studies, event rate 2,389/17,323, 14%) and atrial fibrillation (RR 1.45 95%CI 1.23-1.71, 8 studies, event rate 15,616/375,526, 4%) but not cardiovascular mortality, coronary heart disease or myocardial infarction or stroke or TIA.

Additional analysis was performed considering the all studies including patients with previous coronary heart disease and hypertension and adjustments for medication and cardiovascular disease (Table 4). 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.

Risk of adverse outcomes with 1°HB heart block

The results for adverse outcomes with 1°HB are shown in Figure 4. Similar to prolonged PR interval there were significant increases in mortality (RR 1.31 95% CI 1.18-1.46), heart failure (RR 1.39 95% CI 1.18-1.65) and atrial fibrillation (RR 1.47 (1.18-1.83) but not cardiovascular mortality, coronary heart disease or stroke.

Discussion

Our results suggest that prolonged PR interval and 1°HB is not a benign condition and is associated with increased mortality, heart failure or left ventricular dysfunction and atrial fibrillation. It is notable that there is a long follow up for many of these studies (up to 24 years) and adjustments for potential confounders is an important consideration. It appears that prolonged PR interval and 1°HB may be clinically relevant when found incidentally but the best management is unclear.

The mechanism of 1°HB and adverse cardiovascular outcomes and mortality is unclear. Cheng et al suggest that chronic PR prolongation could be a precursor to more severe degrees of conduction block.[9] This is supported by their findings that there was a significant increase in need for pacemaker and progression of heart block with 1°HB.[9]. They also suggest that prolongation of PR interval may be a marker of other cardiovascular changes associated with worse prognosis such as advanced physiological age which may manifest as calcification or fibrosis of the cardiac skeleton.[9] The age related changes is supported by electrophysiological studies which suggest that the atrial becomes more refractory and there is increased atrial conduction time.[24,25] Age is known to be associated with increased risk of mortality and cardiovascular disease such as atrial fibrillation and heart failure. We have observed evidence supporting this as the patients in the prolonged PR interval group were older patients in several studies [6, 9,10,14,17] so adjustments for the potential confounder age and age related comorbidity is an important statistical consideration. It is likely that the increase risk of mortality may be related to develop of cardiovascular pathology such as atrial fibrillation, other arrhythmias and heart failure. It is also possible that risk factors (eg. age) for heart block development are also shared risk factors for heart failure, atrial fibrillation and mortality.

We have shown that there is increased risk of both atrial fibrillation and heart failure with prolonged PR interval but whether the two are related is unclear. It is known that 1°HB can manifest from structural heart disease as pathology of the conduction pathway, especially the right atrium. Atrial fibrillation can occur commonly due to heart failure causing stretching of the myocardium and secondary changes to the right atrium. However, prolongation of the PR interval may disrupt the normal cardiac filling pressures which may also exacerbate heart failure.[17] Unfortunately the studies included were unable to determine the sequence of problems that develop after baseline 1°HB as it is not apparent if patients had arrhythmias or heart failure prior to mortality. The study by Aro et al did report observation of a few cases of AF in subjects with long PR interval but higher AV block degree was not noted.[6] More studies are needed to confirm these findings. In addition, prolonged PR interval may unmask existing cardiac pathology such as heart failure.

There are also a few reasons why prolonged PR interval may be associated with heart failure. Crisel et al suggested that 1°HB may be a marker of diffuse ischaemic heart disease.[17] 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 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.[21] They also suggest 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.[21]

Our results support and differ from the findings of existing studies. Cheng et al conducted a meta-analysis of six cohort studies and reported an increased risk of atrial fibrillation with 1°HB. Two additional studies in our review Perez et al[11] and Uhm et al[13] 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. Our findings differ from those of the study Aro et al which suggest no increase in mortality or atrial fibrillation, heart failure or stroke in a middle-aged general population.[6] One possible explanation for the difference in the findings is that for this study there was a much higher event rate compared to the average among the studies (mortality 56% vs 38%, heart failure 16% vs 14%, atrial fibrillation 15% vs 4%). This study made an interesting finding that many patients with 1°HB seem to revert back to normal PR interval.

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. The benign nature of 1°HB is notable because it is not clear 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.

An important question generated from these findings is what should be done 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.[7,8] The options include following up these patients and if so how frequently (probably unrealistic to see them yearly, perhaps every 3 years or 5 years). It is also not clear what should be done for these

patients perhaps some sort of cardiovascular risk assessment with prognostic scores. It may also be a chance to encourage a healthier lifestyle like quitting smoking, eating a healthier diet, lose weight and increase physical activity.

Our studies have a number of strengths and limitations. We included over 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 event follow up the outcome ascertainment is less reliable but for mortality events are easily ascertained. This is a problem for outcomes that may be asymptomatic such as atrial fibrillation especially in studies which use hospitalization 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.

In conclusion, there is growing evidence that prolonged PR interval and 1°HB is not a benign condition and patients with this condition are at increased risk of mortality, heart failure or left ventricular dysfunction and atrial fibrillation. Future studies should focus on providing mechanistic insight and define the optimal monitoring strategy for such patients.

Table 1: Study design and participant characteristics

Study ID	Study design; year; country	No. of participants	Mean age	% Male	Participant inclusion criteria
Aro 2014	Prospective cohort study; 1966 to 2007; Finland.	10,785	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 2009	Prospective cohort study; 1968 to 2007; USA.	7,575	47 years.	46%	Participants were community-based individuals from the Framingham Heart Study.
Crisel 2011	Prospective cohort study; enrolment 2000 to 2002; USA.	938	66 years.	82%	Participants had stable coronary artery disease in the Heart and Soul Study.
Erikssen 1984	Prospective cohort study; enrolment 1972-1975; Norway.	1,635	40-59 years at baseline.	100%	Participants were 'apparently healthy' men aged 40-59 years free of coronary heart disease.
Hisamatsu 2015	Prospective cohort study; 1980 to 2009; Japan.	9,051	50 years.	44%	Participants were community dwellers, aged 30-95 years from 300 randomly selected areas throughout Japan.
Knuiman 2014	Prospective cohort study; 1994 to 2010; Australia.	4,267	52 years.	44%	Participants were community-based adults, age 25-84 years in the Busselton Health Study.
Kobayashi 2014	Prospective cohort study; baseline survey 1989 to 1994; Japan.	5,425	30-83 years.	47%.	Participants were Japanese urban adults age 30-83 years without prior cardiovascular disease who attended a routine examination.
Magnani 2013	Prospective cohort study; 1997 to 2011; USA.	2,722	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 2013	Prospective cohort study; 2001 to 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 2009	Retrospective cohort study; Mar 1987 to Jul 2000; USA.	42,751	56 years.	90%.	Participants had initial ECG between Mar 1987 and Jul 2000. Indications for ECG and background disease – not known, but patients with known AF were excluded from study.
Rajala 1985	Prospective cohort study; Jan 1977 to Dec 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 2009	Retrospective cohort study; 1987 to 1998; USA.	15,429	54.2 years.	45%.	Participants were from 4 US communities aged 45 to 64 years in the Atherosclerosis Risk in Communities study.

Soliman 2014	Prospective cohort study; 1988 to Dec 2006; USA.	7,501	59.3 years.	47%.	Participants were civilian noninstitutionalized US population in the NHANES study.
Uhm 2013	Retrospective cohort study; Unclear; Korea.	3,816	61.0 years.	47.2%.	Participants were age >18 years with hypertension and sinus rhythm on first ECG.

Table 2: Study quality assessment

Study ID	Definition and Ascertainment of PR prolongation	Method of Ascertainment of outcome	Lost to follow up	Adjustment for potential confounders		
				Medications	Cardiovascular disease or risk factors	Other
Aro 2014	12-lead ECG at baseline containing average 7 to 8 beats. PR prolongation was >200 ms. PR interval defined from onset of P-wave to end of PR segment measured from the bipolar limb lead in which the interval was longest.	Mortality data from Causes of Death Register and other outcomes from hospitalization records from the Finnish Hospital Discharge Register.	<2% lost from moving abroad. 95 participants were excluded for missing or unreadable ECG or previous AF or unreadable PR interval.	Chronotropic medications.	Cardiovascular disease.	Age, sex, BMI, heart rate.
Cheng 2009	Baseline 12 lead ECG. A single lead II was used with 2 measurements using digital calipers and PR interval defined by interval from onset of P wave to end of PR segment. PR prolongation defined by >200 ms.	Patients underwent surveillance for death and cardiovascular events and AF and pacemaker implantation was ascertained by a review of medical histories, physical examinations, hospitalization and patient records. A panel of 3 experienced investigators reviewed pertinent medical records for all suspected new events.	146 participants were excluded for inadequate measurement of PR interval and missing covariate data.	Exclusion of nodal-blocking medications.	Stratified by cardiovascular status.	Adjusted for age, heart rate, body mass index, hypertension, smoking, diabetes and total:HDL cholesterol levels. Also adjusted for atrial premature beats, valve disease, ECG left ventricular hypertrophy and QRS interval.
Crisel 2011	12 lead ECG at enrolment. Prolonged PR interval defined by ≥220 ms. Unclear which lead for	Annual telephone interviews or proxies regarding recent emergency room visits, hospitalizations or death. Two independent blinded adjudicator reviewed medical	86 participants were excluded due to lack of ECG or advanced AV block.	Beta-blocker use, digoxin use.	Heart failure.	Age, gender, ethnicity, resting heart rate, QRS duration >100 ms, inducible ischemia, LV ejection fraction, diastolic dysfunction,

	measurement.	records, death certificate and coroner's reports.				arrhythmia or pacemaker.
Erikssen 1984	12 lead ECG. PR taken by mean of 5 consecutive beats in lead with longest PR interval. PR prolongation defined by >210 ms.	Detailed criteria for diagnosis is reported elsewhere Erikssen and Mundal 1982.	182 participants were excluded.	None.	None.	None.
Hisamatsu 2015	Baseline ECG. PR prolongation defined by ≥220 ms. Unclear lead for PR evaluation.	Study participants observed from baseline ECG to death, censor or end of follow up by unclear method.	Unclear number of exclusions.	Antihypertensive medications.	None.	Age, sex, body mass index, systolic blood pressure, total cholesterol, diabetes mellitus, smoking status, drinking status, heart rate, LVH on ECG, suspected CHD on ECG.
Knuiman 2014	12-lead ECG. Unclear definition for long PR and unclear lead for PR evaluation.	AF from hospital admission with primary or other diagnosis of atrial fibrillation/flutter and no prosthetic heart valve or coronary artery bypass procedure or ECG codes.	Unclear.	Hypertension treatment.	None.	Sex, age, height, body mass index.
Kobayashi 2014	Baseline 12-lead ECG. PR prolongation defined by ≥220 ms. Unclear lead for PR evaluation.	Unclear.	Unclear.	None.	None.	Age, sex, body mass index, hypertension, hypercholesterolemia, diabetes, current smoking, current alcohol drinking and estimated glomerular filtration rate.
Magnani 2013	Baseline ECG. PR interval defined by lead II using average measure of 3 consecutive beats	Follow up with annual examinations and 12 month telephone contact and records from hospitalizations were reviewed. Incident AF from linking ICD codes and	81 had missing ECG data or PR interval.	Amiodarone, cardiac glycosides, calcium channel blockers, beta-blockers.	Prevalent cardiovascular disease.	Age, sex, site, body mass index, heart rate, systolic and diastolic blood pressure, past/current smoking, ratio of Total/HDL cholesterol,

	or 2 at slower heart rates. PR prolongation defined by >200 ms.	mortality from participant proxy or other participant representative, hospital records, obituary or search of National Death Index.				electrocardiographic LVH.
Nielsen 2013	ECG digitally recorded and stored electronically. PR interval from median beat using information from all 12 leads. PR prolongation ≥196 ms for women and ≥204 ms for men.	Follow up data from Danish registry with hospital, ambulatory or emergency room discharge diagnosis of atrial fibrillation or flutter.	17,708 ECG not consistent with measured PR interval.	AV nodal-blocking medications (beta-blockers or calcium antagonist).	Heart failure, myocardial infarction, valvular heart disease.	Gender, hypertension, diabetes, hyperthyroidism, heart rate, QT interval, left ventricular hypertrophy.
Perez 2009	ECG with computer measurements of PR interval. Unclear lead for evaluation and PR prolongation defined by >200 ms.	Follow up ECG and death from Veterans Affairs Health Care System electronic medical records.	Unclear.	None.	None.	Age, sex, premature atrial contraction, abnormal P axis, P_{max} >120 ms, P_{index} >35 ms, left atrial enlargement, premature ventricular complex, left bundle branch block, left ventricular hypertrophy.
Rajala 1985	12-lead ECG. First degree heart block with ≥220 ms in any leads I, II, III, aVL or aVF.	Follow up for survival but unclear how.	Unclear.	None.	None.	None.
Soliman 2009	ECG at baseline with PR duration defined by mean P wave duration plus the mean PR segment duration in 12-lead ECG. PR prolongation	Annual phone contact, hospital cardiovascular disease discharges and diagnoses were adjudicated.	363 with poor quality baseline ECG recording, baseline ECG condition affecting quality of P wave measurement or ethnicity other than black or white were	None.	None.	Age, sex, ethnicity, hypertension, systolic blood pressure, diabetes, blood lipids, smoking status, body mass index.

	defined by upper 5th centile and 1 increase in standard deviation.		excluded.			
Soliman 2014	12-lead ECG at baseline with PR interval defined in lead II. PR prolongation defined by >200 ms.	Follow up mortality by probabilistic matching with National Death Index.	Unclear.	Use of antiarrhythmic or AV nodal blocking drugs.	Prior cardiovascular disease.	Age, sex, race/ethnicity, heart rate, smoking status, systolic blood pressure, diabetes, total/HDL cholesterol ratio and BMI.
Uhm 2013	Medical records of all ECG. PR prolongation defined by >200 ms. Unclear lead for PR evaluation.	Review of medical records and ECG.	Unclear.	Use of nondihydropyridine calcium channel blockers.	History of myocardial infarction.	Age, sex, heart rate, QRS duration, left ventricular hypertrophy on ECG.

Table 3: Outcomes evaluated and results

Study ID	Description of reference group (e.g. PR interval less than 200 ms or PR interval in normal range 120-200 ms, 80-200 ms, other)	Outcomes evaluated and timing of assessment	Results
Aro 2014	≤200 ms	Follow up for 30 years.	Multivariate adjusted HR: All-cause mortality: 140/222 vs 5,933/10,563, HR 1.05 (0.89-1.24). Cardiovascular mortality: 44/222 vs 1,904/10,563, HR 0.94 (0.70-1.27). Heart failure: 42/222 vs 1,673/10,563, HR 1.22 (0.90-1.65). Coronary artery disease: 74/222 vs 3,465/10,563, HR 0.97 (0.77-1.22). Atrial fibrillation: 35/222 vs 1,591/10,563, HR 1.03 (0.74-1.45). TIA or stroke: 50/222 vs 1,877/10,563, HR 1.23 (0.92-1.62).
Cheng 2009	≤200 ms	Up to 35 years.	Atrial fibrillation: 25/124 vs 456/7,451, multivariate HR 2.36 (1.53-3.64). Pacemaker insertion: 26/124 vs 98/7,451, multivariate HR 4.32 (2.46-7.59). All-cause mortality: 62/124 vs 1,677/7,451, multivariate HR 1.48 (1.10-1.99).
Crisel 2011	<220 ms	Up to 5 years.	Heart failure: 26/87 vs 97/851, adjusted for medications HR 2.33 (1.49-3.65). Cardiovascular mortality: 15/87 vs 52/851, adjusted for medications HR 2.33 (1.28-4.22). All-cause mortality: 42/87 vs 243/851, adjusted for medications HR 1.58 (1.13-2.20). Heart failure or cardiovascular mortality: 34/87 vs 122/851, adjusted for medications HR 2.43 (1.64-3.61). Heart failure: 26/87 vs 97/851, adjusted for heart failure HR 2.02 (1.24-3.31). Cardiovascular mortality: 15/87 vs 52/851, adjusted for heart failure HR 2.29 (1.18-4.45). All-cause mortality: 42/87 vs 243/851, adjusted for heart failure HR 1.49 (1.04-2.14). Heart failure or cardiovascular mortality: 34/87 vs 122/851, adjusted for heart failure HR 2.09 (1.36-3.23).

Erikssen 1984	≤210 ms	Myocardial infarction, angina pectoris, pathological exercise ECG, death from CHD, total CHD events.	Myocardial infarction: 6/98 vs 54/1,537. Angina pectoris: 3/98 vs 76/1,537. Pathological exercise ECG: 7/98 vs 205/1,537. Death from CHD: 1/98 vs 36/1,537. Total deaths: 3/98 vs 71/1,537.
Hisamatsu 2015	<220 ms	All cause mortality, cardiovascular disease mortality, coronary heart disease mortality, stroke mortality with mean follow up of 24.3 years.	All cause mortality: total events 3,269/9,051, multivariate HR 1.06 (0.85-1.31). Cardiovascular disease mortality: total events 1,101/9,051, multivariate HR 0.94 (0.65-1.37). Coronary heart disease mortality: total events 227/9,051, multivariate HR 1.49 (0.76-2.92). Stroke mortality: total events 491/9,051, multivariate HR 0.70 (0.37-1.31).
Knuiman 2014	Unclear, not long PR interval.	Incident atrial fibrillation at follow up of 15 years.	Incident atrial fibrillation: total events 343/4,267, multivariate HR 1.29 (0.68-2.44).
Kobayashi 2014	<220 ms	Cardiovascular disease, coronary heart disease and stroke at 13.1 years follow up.	All cardiovascular disease: total events 421/5,425, multivariate HR 2.98 (1.22-7.31). Coronary heart disease: total events 180/5,425, multivariate HR 1.57 (0.22-11.42). Stroke: total events 241/5,425, multivariate HR 3.90 (1.42-10.72). Cerebral infarction: total events 144/5,425, multivariate HR 2.98 (1.22-7.31).
Magnani 2013	≤200 ms	Incident heart failure, atrial fibrillation and all-cause mortality.	Incident heart failure: total events 369/2,722, multivariate HR 1.46 (1.11-1.93) Incident atrial fibrillation: total events 537/2,722, multivariate HR 1.26 (0.99-1.61) All-cause mortality: total events 832/2,722, multivariate HR 1.14 (0.94-1.39).
Nielsen 2013	<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 (1.17-1.35) (reference group PR interval 150-161 ms). Men multivariate HR 1.18 (1.06-1.30) and women multivariate HR 1.30 (1.17-1.44).
Perez 2009	≤200 ms	Incident atrial fibrillation at 5.3 years.	Risk of AF with PR >200 ms: total events 1,050/42,751, multivariate HR 1.3 (1.1-1.6).
Rajala 1985	<220 ms	Mortality at 5 years follow up.	Crude 5 year mortality: first degree heart block 20/39 vs normal 453/657.

Soliman 2009	1SD change and upper 5th centile vs 95th centile of PR duration.	Incident atrial fibrillation and ischemic stroke with follow up of 6.97 years.	Total AF events 117/15,429. Total ischemic stroke events 599/15,429. Risk of ischemic stroke with 1 SD change in PR duration: multivariate HR 1.00 (0.92-1.08). Risk of AF with 1 SD change in PR duration: multivariate HR 1.41 (1.20-1.65). Risk of AF with upper 5th centile vs 95th centile of PR duration: multivariate HR 1.59 (0.77-3.30).
Soliman 2014	≤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 2,216/6,847. High-P duration prolong PR interval and mortality: multivariate HR 2.00 (1.34-2.99). Low-P duration prolong PR interval and mortality: multivariate HR 0.99 (0.86-1.14).
Uhm 2013	≤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 26/3,272, HR 2.77 (1.38-5.59). Sick sinus syndrome: 8/544 vs 277/3,272, HR 1.32 (0.61-2.84). Atrial fibrillation: 98/544 vs 277/3,272, HR 2.33 (1.84-2.94). LV dysfunction: 59/544 vs 245/3,272, HR 1.49 (1.11-2.00).

Table 4: Summary of meta-analysis results

A) General population studies

Adverse outcome	General population studies		
	No. of studies	Events/Total	Risk ratio (95% CI)
All mortality			
Adjusted only	5	14,454/37,634	1.24 (1.02-1.51)
Unadjusted only	2	15,001/39,965	0.73 (0.55-0.99)
Cardiovascular mortality	3	3,086/21,471	0.93 (0.74-1.17)
Heart failure or LV dysfunction	3	2,389/17,323	1.39 (1.18-1.65)
CHD or MI	4	4,006/26,896	1.08 (0.85-1.36)
Atrial fibrillation	8	15,616/37,526	1.45 (1.23-1.71)
Stroke or TIA	4		1.13 (0.82-1.56)

B) All studies (including studies of patients with CAD)

Adverse outcome	All studies (including studies of patients with CAD)		
	No. of studies	Events/Total	Risk ratio (95% CI)
All mortality			
Adjusted only	7	14,739/38,572	1.23 (1.01-1.49)
Unadjusted only	2	547/2,331	0.73 (0.55-0.99)
Cardiovascular mortality	4	3,153/22,409	1.14 (0.73-1.76)
Heart failure or LV dysfunction	4	2,512/18,261	1.51 (1.22-1.88)
CHD or MI	4	4,006/26,896	1.08 (0.85-1.36)
Atrial fibrillation	8	15,616/375,526	1.45 (1.23-1.71)
Stroke or TIA	4	3,258/40,690	1.13 (0.82-1.56)

C) Only inclusion of studies that adjusted for medications

Adverse outcome	Only inclusion of studies that adjusted for medications		
	No. of studies	Events/Total	Risk ratio (95% CI)
All mortality			
Adjusted only	7	14,739/48,209	1.23 (1.01-1.49)
Cardiovascular mortality	3	3,116/20,774	1.19 (0.75-1.88)
Heart failure or LV dysfunction	4	2,512/18,261	1.51 (1.22-1.88)
CHD or MI	1	3,539/10,785	0.97 (0.77-1.22)
Atrial fibrillation	6	14,449/317,346	1.50 (1.15-1.96)
Stroke or TIA	2	2,418/19,836	1.00 (0.59-1.70)

D) Only inclusion of studies that adjusted for CVD

Adverse outcome	Only inclusion of studies that adjusted for CVD		
	No. of studies	Events/Total	Risk ratio (95% CI)
All mortality			
Adjusted only	6	11,470/39,158	1.26 (1.02-1.56)
Cardiovascular mortality	2	2,015/11,723	1.42 (0.59-3.46)
Heart failure or LV dysfunction	4	2,512/18,261	1.51 (1.22-1.88)
CHD or MI	1	3,539/10,785	0.97 (0.77-1.22)
Atrial fibrillation	5	14,106/313,079	1.53 (1.14-2.04)
Stroke or TIA	1	1,927/10,785	1.23 (0.93-1.63)

CAD=coronary artery disease, CVD=cardiovascular disease, CHD=coronary heart disease, MI=myocardial infarction, TIA=transient ischemic attack

Figure 1: Process of study selection

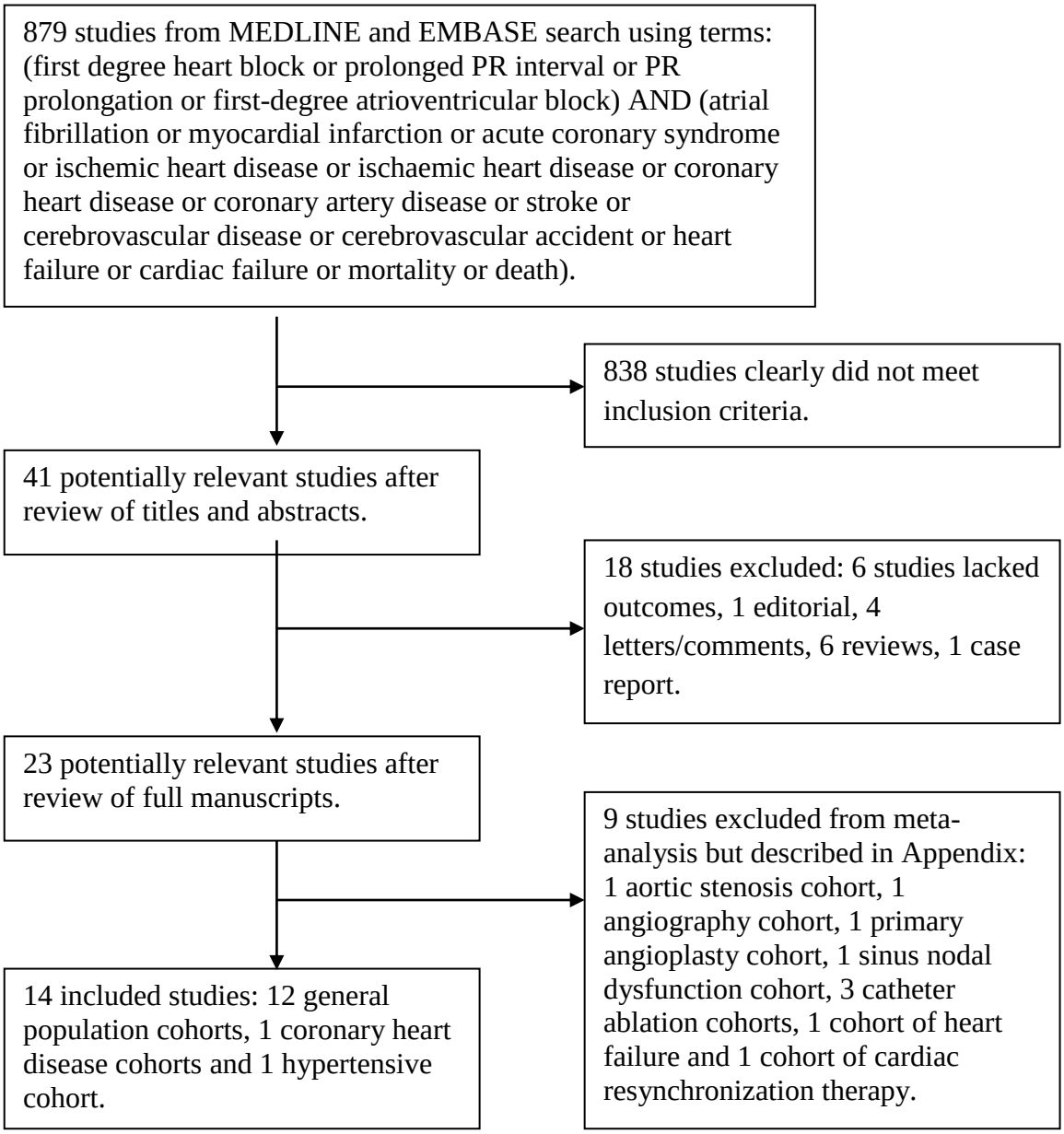


Figure 2: Risk of mortality with prolonged PR interval

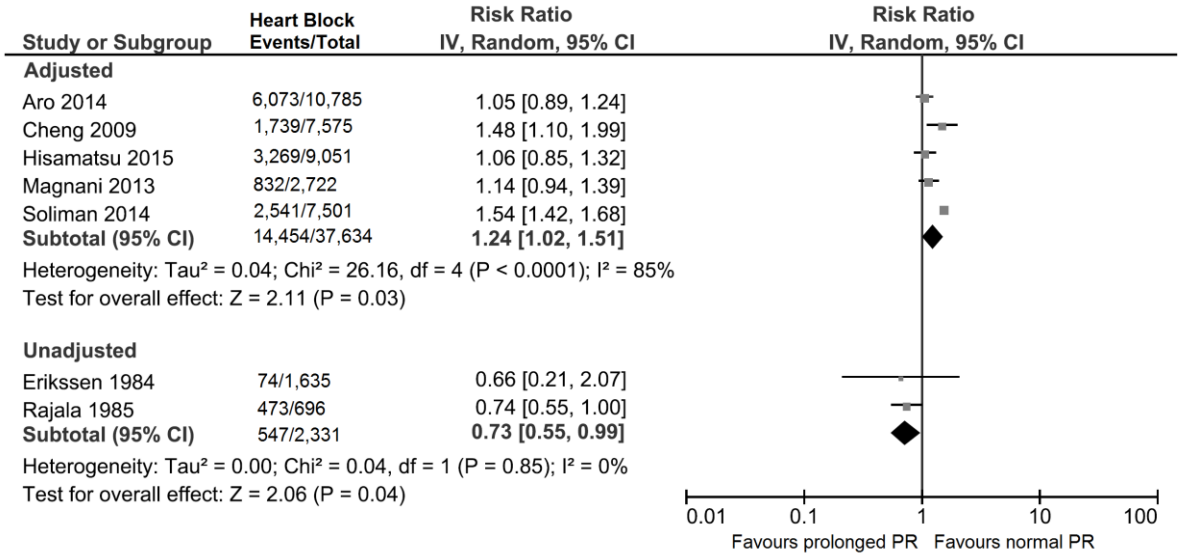


Figure 3: Risk of adverse outcomes with prolonged PR interval

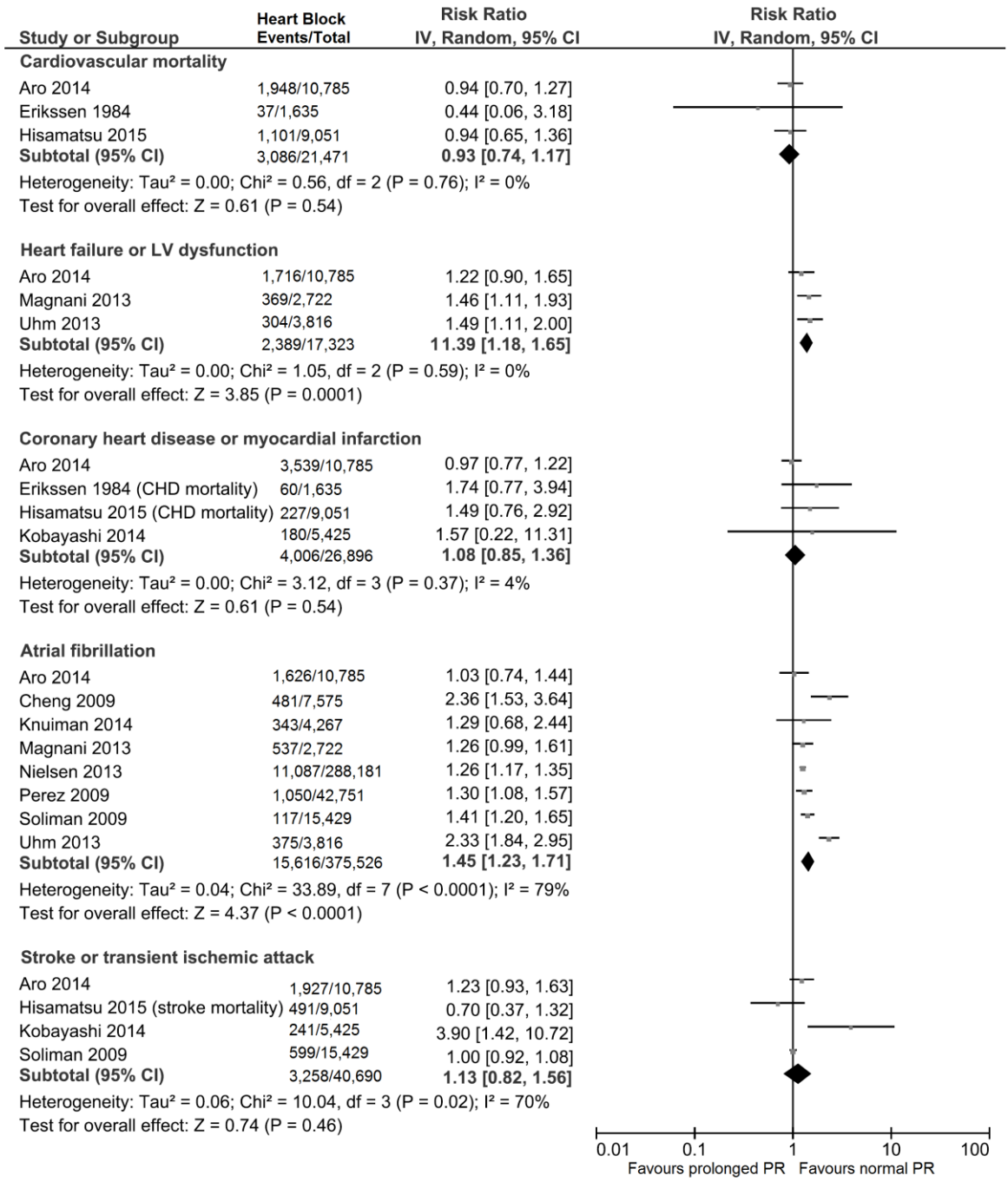
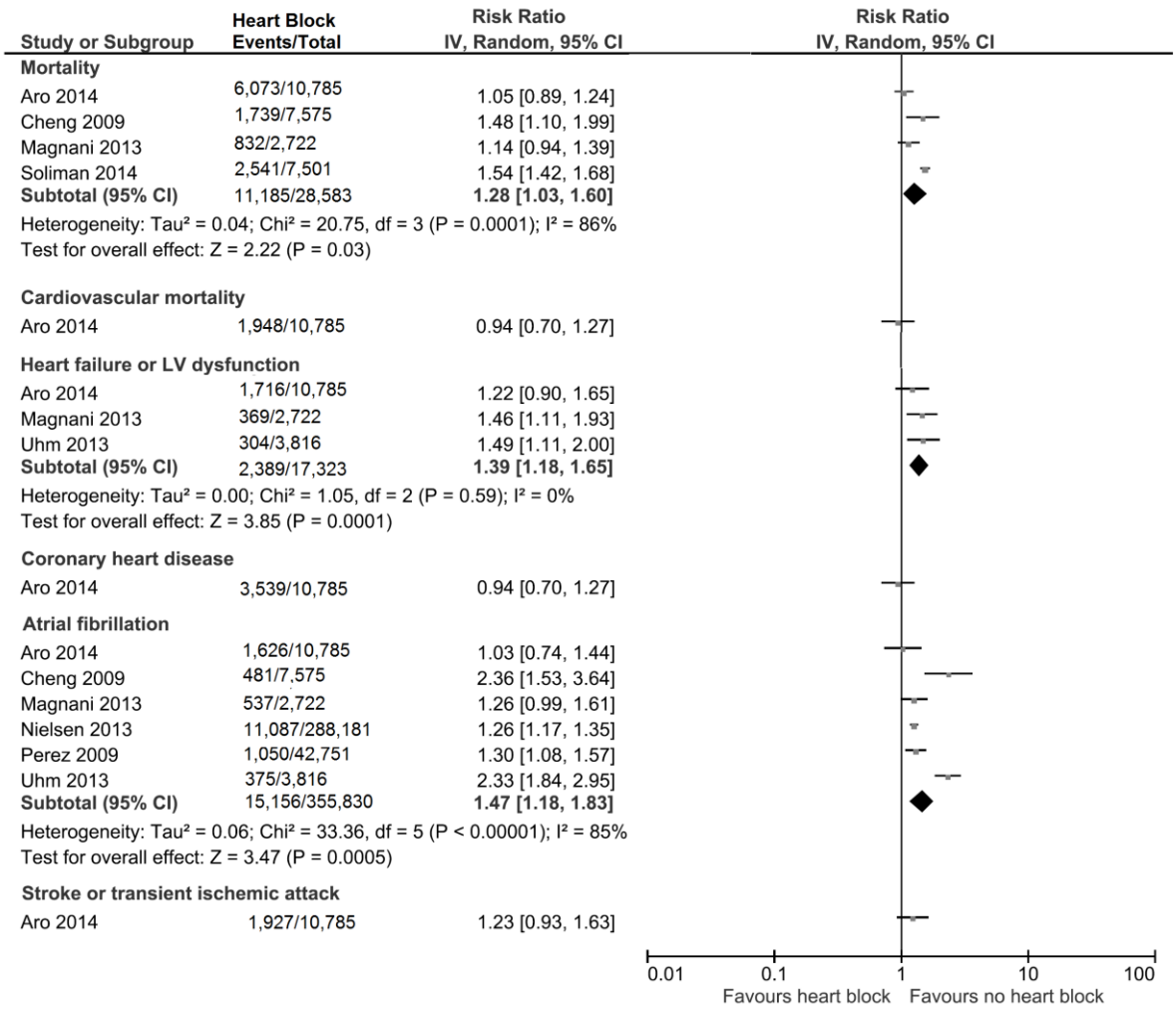


Figure 4: Risk of adverse outcomes with first-degree heart block



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Appendix 1: Excluded studies

Study ID	No. of Participants	Population	Outcomes evaluated
Bang 2014	1,421	Mild-moderate aortic stenosis	Atrial fibrillation, heart failure, aortic valve replacement
Gomez-Talavera 2014	913	Primary angioplasty cohort	Death, re-infarction, death/recurrent infarction
Holmqvist 2014a	9,637	Coronary angiography cohort	Death, sudden cardiac death, death or stroke, CV death or hospitalization.
Holmqvist 2014b	2,010	Sinus nodal dysfunction	Death/stroke, death/stroke/heart failure, heart failure, death, cardiovascular death, atrial fibrillation
Lee 2012	351	Cardiac resynchronization therapy	Mortality
Ozcan 2014	1,573	Patients with SVT with catheter ablation	Atrial fibrillation
Park 2014a	576	Patients with catheter ablation	Atrial fibrillation
Park 2014b	1,986	Heart failure	Death
Wu 2014	224	Atrial fibrillation with catheter ablation	Atrial fibrillation recurrence

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