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Heart rate and cardiovascular mortality in hypertension: Treatment strategies with heart rate lowering calcium antagonists

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At a recently held satellite symposium during the XVIIIth Congress of the European Society of Cardiology in Birmingham, United Kingdom, Dr. W. B. Kannel reviewed the importance of heart rate on mortality of hypertensive subjects and Dr. L. Hansson updated the findings of an on-going NORDIL study.

Evidence from Framingham study

Dr. Kannel from Boston, US, reviewed the results of the recently published observations from the Framingham study.¹ This analysis was carried out from a 36 year follow-up in subjects with hypertension from the Framingham cohort to address the association of heart rate with mortality from cardiovascular disease. The Framingham study, which began in 1948, has followed up a cohort of 5,209 subjects (2,493 female and 2,037 male) for 36 years who at the time of any of biennial examinations had a blood pressure level exceeding 140 mm Hg systolic or 90 mm Hg diastolic and who

were not taking antihypertensive therapy. Resting heart rate was determined from ECG and blood pressure was measured twice by the examining physician with the average of the two readings being used.

The subjects were free from cardiovascular disease and, on the average, women were slightly older than men (57.3 vs 54.9 years). Figure 1 demonstrates association of heart rate with coronary heart disease mortality (myocardial infarction, coronary insufficiency, angina pectoris), cardiovascular disease mortality (stroke and congestive heart failure), and all cause mortality rate among men and women with hypertension.

Multivariate analysis adjusting for all risk factors (age, systolic blood pressure, serum cholesterol, cigarette smoking, glucose intolerance, left ventricular hypertrophy) demonstrated relationship between heart rate and mortality among subjects with hypertension. For each increment of 40 bpm there was an increase in mortality (Table 1).

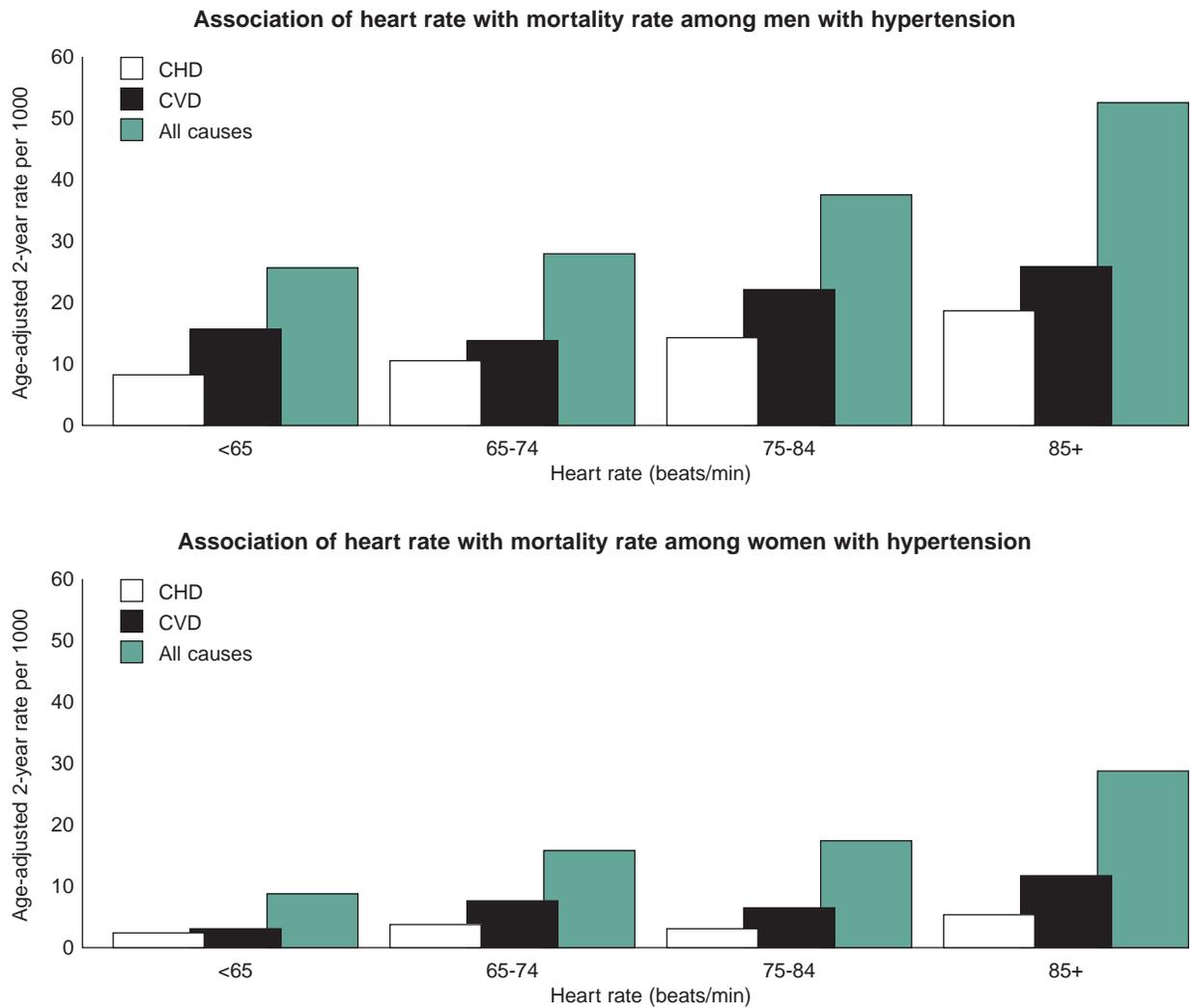
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Figure 1



Incremental increases in heart rate also demonstrated significant relationship with mortality from cancer and other causes of death raising the question of whether the effect is confounded by disease status, i.e. elevated heart rate is merely a marker for serious underlying disease that is likely to be fatal within the next few years. Analysis by 6 year interval, examining events that occurred during the entire 6 years after measurement of risk factors, during only the last 4 years of each interval,

and during only the last 2 years of each interval, demonstrated that the effect of heart rate on cardiovascular death was similar in the three analyses, but that for cancer and other deaths the effect of heart rate diminished as the time between ascertainment of heart rate and death lengthened. Thus, there appears to be a significant relationship between increase in heart rate and mortality in untreated hypertensive subjects which requires further and more intense evaluation.

Table 1

Cause of Death	Adjusted for Age + Systolic BP		Adjusted for All Risk Factors	
	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
All Causes				
Men	2.18	1.68-2.83	1.98	1.52-2.59
Women	2.14	1.59-2.88	1.87	1.37-2.56
Cardiovascular				
Men	1.68	1.19-2.37	1.48	1.05-2.09
Women	1.70	1.08-2.67	1.37	0.85-2.21
Coronary Heart Disease				
Men	1.80	1.20-2.71	1.53	1.01-2.32
Women	1.59	0.85-2.98	1.19	0.62-2.30

NORDIL trial

The Nordic diltiazem study (NORDIL) will evaluate the preventive effects of the heart rate lowering calcium antagonist diltiazem on cardiovascular mortality and morbidity in patients with mild to moderate primary hypertension compared with conventional antihypertensive treatment such as beta blockers and diuretics. In hypertensive patients, the calcium antagonists lower blood pressure by reducing total peripheral resistance at rest and during exercise and, in addition, there may be diuretic activity which may be of value in antihypertensive management.²⁻⁵ When administered as monotherapy, diltiazem lowers blood pressure without causing tachycardia.⁶ Diltiazem's specific cardiovascular profile and its low frequency of side effects has made it one of the most commonly used calcium antagonists in cardiovascular pharmacotherapy.⁶ In addition, antihypertensive therapy with diltiazem may have additional advantages in relation to favourable metabolic profile,⁷⁻¹¹ quality of life,¹² preservation of renal function,¹³ and reversal of left ventricular hypertrophy.^{14,15} Studies during extreme exercise suggest

that diltiazem treatment results in good blood pressure control, prolongation of exercise duration, while maintaining cardiac output and stroke volume.³

NORDIL¹⁶ is a prospective randomized study which will include hypertensive (diastolic blood pressure ≥ 100 mm Hg) patients of both sexes, age between 50-69 years. Both groups will receive active antihypertensive treatment with the aim of reducing the resting diastolic blood pressure to ≤ 90 mm Hg. The aim of NORDIL is to evaluate cardiovascular mortality and morbidity in patients randomized to a diltiazem based treatment strategy compared to patients randomized to a strategy with other currently used compounds, mainly beta blockers or diuretics, although other classes of compounds, for example ACE inhibitors, may also be used. In other words, combination therapy will be allowed based on usual clinical criteria to achieve the goal of blood pressure control.

Approximately 12,000 patients will be enrolled and followed for 5 years to ensure an 80% power in detecting 20% difference in cardiovascular mortality between the two groups ($\alpha = 5\%$, two sided test).

Conclusion

In conclusion, several mechanisms for the effect of heart rate with respect to cardiovascular and coronary heart disease mortality can be postulated, including rheologic and autonomic nervous system influences. Heart rate may be an integrated index of autonomic nervous system influences on the heart which may lead to atherogenesis and arrhythmias. The potential benefit of heart rate control, as well as an independent effect of diltiazem treatment on cardiovascular morbidity and mortality in the hypertensive patients, will be addressed in the NORDIL study.

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