Title: Does Silent Myocardial Ischemia based on Resting Electrocardiogram Criteria Predict Cardiovascular Mortality in Older Adults with and without diabetes: A 23 Year Prospective Study

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Abstract:

Background: Heart disease remains the leading cause of mortality in the United States and many experience no symptoms prior to a cardiovascular disease (CVD) death. We asked if Silent Myocardial Ischemia (Silent MI) predicts CVD mortality among community-dwelling older adults and if diabetes status impacts this association.

Methods and Results: We analyzed 1882 participants from the 1984-1987 Rancho Bernardo Study clinic visit who were ≥50 years old with no history of coronary heart disease (defined by prior revascularization, myocardial infarction, or angina). We detected Silent MI using ischemic resting changes on 12-lead electrocardiogram (one or more: major or small Q or QS wave, complete left bundle-branch block, ST depression, or T wave items). We determined diabetes status by oral glucose tolerance test and CVD death (*ICD-9* codes 390.0-459.0) through 2007 by death certificate. Kaplan-Meier analysis showed reduced mean survival times in participants with Silent MI (16.4 versus 19.4 years, $p<0.001$) or diabetes (17.4 versus 19.1 years, $p=0.008$). In Cox proportional hazards models, Silent MI was independently associated with CVD death (HR 1.58, 95% CI 1.29-1.95) after adjusting for age, waist hip ratio, systolic blood pressure, exercise, sex, and diabetes. For participants with diabetes, Silent MI did not predict CVD death (HR 1.34, 95% CI 0.826-2.17).

Conclusions: Silent MI is independently associated with CVD death in older adults, and not significantly associated for those with diabetes. Therefore, Silent MI identified by resting ECG remains an important predictor of CVD mortality regardless of other risk factors in those without diabetes.

Key Words: ischemia, electrocardiography, diabetes mellitus

Text

Introduction:

Heart disease remains the leading cause of mortality for both men and women in the United States.[1] While some patients with cardiovascular disease (CVD) will experience typical cardiac symptoms such as chest pain upon exertion, others may have no symptoms preceding a cardiovascular death. Studies utilizing the recent American Heart Association guidelines concerning cardiovascular health confirm the importance of key metrics (nonsmoking, body mass index (BMI)<25 kg/m^2, physical activity, ideal diet, untreated total cholesterol <200 mg/dL, untreated blood pressure <120/80 mm Hg, and fasting blood glucose <100 mg/dL) in predicting cardiac death[2] and future cardiac health[3]. However, when caring for asymptomatic older adults, interpreting cardiac tests beyond these cardiovascular health metrics can remain challenging. While resting ECGs remain an important tool in detecting heart disease, the prognostic significance of silent myocardial ischemia remains uncertain. Some ECG abnormalities have been shown to predict future cardiovascular mortality,[3;4] but studies have shown mixed results for the predictive value of minor ECG abnormalities. A 30 year follow-up of a random sampling of Charleston County residents at least 35 years of age found that minor ECG abnormalities (T wave inversions, low QRS amplitude, high amplitude R waves and left-axis deviation) did not significantly predict the risk of all-cause mortality.[5] A recent analysis of ECG findings from the Women's Health Initiative found that major ST-T and minor ST-T abnormalities were associated with significantly increased risk of CVD mortality (HR 3.11 (2.06-4.70) and HR 1.65 (1.25-2.16) respectively) after 8 years of follow-up when adjusted for CVD risk factors.[6]

Additionally, the increasing prevalence of diabetes over the past thirty years[7] demands a deeper understanding of the effect of diabetes on predicting cardiovascular mortality risk. Presently according to NHANES 2011 data, 11.3% of the U.S. population over the age of 20 years has diabetes, and 26.9% of the population over 65 years of age has diabetes.[8] When oral glucose tolerance testing is used 31.6% of those 65 years old and over have diabetes.[9] Patients with diabetes mellitus suffer from higher rates of cardiovascular disease. Mortality is also known to be higher for patients with both diabetes and cardiovascular disease, especially women.[10;11;12;13;14] Also concerning is the finding that patients with diabetes have higher rates of asymptomatic cardiovascular disease than those without diabetes. In a

cross-sectional analysis from the Rancho Bernardo Study asymptomatic ischemic heart disease was significantly more prevalent in participants with diabetes (34.7%) than those with without (22.3%).[15] The reported prevalence of Silent MI in those with diabetes ranges from 41.9%[16] in one study to 16% in another where patients had normal ECGs and underwent stress testing.[17]

The absence of consensus among previous studies merits further investigation into the prognostic significance of an abnormal resting ECG in asymptomatic populations with and without diabetes. This is of particular relevance to older adults, who are less likely to experience typical chest pain with advancing age[18] and more likely to have a fatal MI. The purpose of this study was to determine if Silent MI predicts CVD mortality among a population of white, community-dwelling older adults, and to determine the role of diabetes status on any observed excess CVD mortality in those with Silent MI. The present analysis assesses mortality rates for cardiovascular disease, 23 years after the initial evaluation for diabetes and ischemic heart disease in community-dwelling older adults from the Rancho Bernardo cohort. The analysis compares participants with Silent MI documented by resting 12 lead electrocardiogram (ECG) to those with no evidence of clinical cardiovascular disease. This analysis also examines the predictive value of Silent MI in those with diabetes, diagnosed by oral glucose tolerance test, and those without diabetes.

Methods

Population

Participants were members of the Rancho Bernardo Study, a California community-based study of a geographically defined, predominantly upper-middle class white adult community. In 1984-1987, 82% of residents aged 50-85 years participated in a clinic visit that included a 75g oral glucose tolerance test performed after a 12-h overnight fast, fasting plasma glucose measurements, as well as a resting ECG. Participants were evaluated for ischemic heart disease as defined by Rose Questionnaire, and resting ECG evaluated according to the Minnesota Code. Diabetes status was determined by oral glucose tolerance test using WHO 1999 criteria[19]. This study was approved by the UCSD Institutional Review Board and all participants gave informed consent prior to participation.

Exclusion Criteria

This analysis excluded participants who were younger than 50 years of age, did not have a resting ECG, did not have diabetes status confirmed, or who had a history of coronary artery bypass graft surgery (CABG), myocardial infarction (MI), or angina pectoris (as assessed by the Rose Questionnaire or previous diagnosis), leaving 1882 participants available for this analysis.

Statistical Analysis

Silent Myocardial Ischemia was defined as one or more ischemic resting ECG abnormalities:

i. "ECG coronary probable" major Q or QS wave [Minnesota Code 1.1, 1.2]; complete left bundle branch block [Minnesota Code 7.1.1]

ii. "ECG coronary possible" small Q or QS wave [Minnesota Code 1.3]; ST depression [Minnesota Code 4.1 – 4.3]; T wave items [Minnesota Code 5.1 – 5.3]

No Evidence of Cardiovascular Disease was defined as:

No ECG changes and no history of MI (Major Q wave), angina pectoris (Grade 1, Grade 2) or chest pain (> 30 min) or revascularization

Vital status was ascertained annually for all participants. More than 99% were followed for vital status by annual mailer through December 2007. Death certificates were obtained and underlying causes of death were coded by a certified nosologist according to the International Classification of Diseases, Ninth Revision. Deaths due to cardiovascular disease included ICD-9 codes 390.0 – 459.0. Descriptive statistics compared those without CVD to those with Silent MI using Student's t-test for continuous variables and chi-square analysis for categorical variables. Survival analysis utilized Kaplan-Meier curves and log rank tests to compare median survival by sex and disease status. Multivariate Cox proportional hazards regression analysis was used to determine the association of Silent MI with CVD death adjusting for other CVD risk factors. HDL level and triglycerides were not normally distributed; therefore a log transformation was used for the Cox proportional hazards models. Statistical significance was defined as $p<0.05$ or 95% confidence intervals that excluded 1. Three separate Cox Models were generated examining the effect of Silent MI on CVD death. Model 1 controlled for age alone. Model 2 controlled for age and all characteristics differing between those with and without Silent MI at the $p\leq0.001$ level of significance. Model 3 controlled for all characteristics in Model 2 as well as health behaviors (exercise ≥3 times per week, alcohol intake ≥3 drinks per week, and smoking (ever)).

Results:

The study population consisted of 1882 community dwelling adults ≥50 years of age at baseline (57.3% women) followed for a mean of 14.2 years (range 0.01 – 23.4 years). Compared to those without known CVD (n=1532), those with Silent MI (n=350) were significantly older (73.7 vs. 69.5 years) at baseline (Table 1). After adjusting for age, on average they had significantly higher waist/hip ratio (WHR) (0.86 vs. 0.84), systolic blood pressure (SBP) (146 vs. 137 mmHg), triglycerides (129 vs. 113 mg/dL), fasting glucose (103 vs. 100 mg/dL), and 2 hour glucose (150 vs. 134 mg/dL), less alcohol intake (>3 drinks/week, 48% vs. 55%), HDL cholesterol (60 vs. 64 mg/dL), and higher prevalence of hypertension (71% vs. 54%) and diabetes (21% vs. 12%). There were no differences in total cholesterol or LDL cholesterol levels between those with and without Silent MI. Regarding ideal health behaviors, overall 81.8% of the participants exercised >3x per week, 55.3% had a Body Mass Index <25, and 57.7% had a fasting plasma glucose <100 mg/dL.

Significantly reduced survival free of CVD death was seen in participants with Silent MI (16.4 vs. 19.4 years), diabetes (17.4 vs. 19.1), hypertension (17.6 vs. 20.3), and in men versus women (18.2 vs. 19.4) using log rank Mantel Cox comparison ($p<0.001$, $p=0.008$, $p<0.001$, and $p<0.001$ respectively) (Figures 1-4).

In Cox proportional hazards models, Silent MI was independently associated with CVD death after adjusting for age alone (HR 1.67, 95% CI 1.36-2.04, $p<0.001$). This held true after adjusting for risk factors differing at the $p\leq0.001$ level between those with and without Silent MI at baseline (age, SBP, HDL, triglycerides, and diabetes status: HR 1.54, 95% CI 1.25-1.90, $p<0.001$). Silent MI also remained a significant risk factor after adding key health behaviors (smoking (ever), exercise ≥3 times/week, alcohol intake >3 drinks/day) into the model (HR 1.56, 95% CI 1.27-1.92) (Table 2). These associations remained significant when adjusting for hypertension instead of SBP, or when adding BP medication use to the model. Additionally, utilizing fasting plasma glucose or 2 hour glucose levels in place of diabetes status did not change the significance of any of the associations. Having diabetes defined by OGTT or history did not increase the risk of CVD death in this model.

Among participants with diabetes, the observed higher risk of fatal CVD with Silent MI was not statistically significant in the adjusted analyses (HR 1.32, 95% CI 0.82-2.14) with a sample size of 257 participants with diabetes compared to 1625 without (Table 2). Among those with diabetes, age, SBP, and male sex increased the risk of CVD death. Among those without diabetes the results were similar to those for all participants, with Silent MI, age, SBP, and male sex all independently increasing the risk of CVD death, and with physical exercise displaying a protective effect.

Silent MI, male sex, older age, and a higher SBP all significantly increased the risk of CVD death, while exercise decreased the risk of CVD death in the fully adjusted model (Table 3). Silent MI was independently associated with CVD death in both men and women (Table 4). Among men, older age, SBP, and Silent MI were independently associated with CVD death. Among women, older age, SBP, and Silent MI were independently associated with CVD death, while exercise was associated with a decreased risk of CVD death.

Overall among the participants 57 died within 2 years of their study visit and 164 died within 5 years of their study visit. A repeat analysis excluded these participants as they may have had symptoms but did not report them at the time. The repeated analysis did not differ from the initial analysis, except that exercise was no longer a protective factor in Cox proportional models.

Discussion:

In this analysis Silent MI was a risk factor for CVD death in both men and women even when adjusting for other CVD risk factors. The finding of Silent MI on resting ECG, even in an apparently healthy individual, should therefore initiate further cardiac testing as well as intensive risk factor modification. These findings are consistent with recent analyses of the importance of minor ECG abnormalities in other cohorts such as the Women's Health Initiative as well as recent results from the Cardiovascular Health Study.[6;20] In the later study, minor ECG abnormalities led to increased CVD mortality (1.53 (1.12–2.08)) when adjusted for age, sex, race, diabetes status, smoking status, baseline level of total cholesterol, high-density lipoprotein cholesterol, systolic and diastolic blood pressures, body mass index, creatinine, and C-reactive protein. Additionally, an analysis of a Finnish cohort of nearly 6,000 participants found that T-wave morphology dispersion significantly predicted CVD and all-cause mortality after 6 years of follow-up.[21] Another Finnish cohort of 559 persons over the age of 85 years

found no significant increase in mortality with left axis deviation (counterclockwise and clockwise rotation) after 5 years of follow-up, but a significant increase in mortality with a Q-QS pattern, ST-junction segment depression, T-wave inversion, second or third degree AV block, left or right bundle branch block, or atrial fibrillation.[22] However, a third Finnish cohort of 697 men age 65 and greater found that Q waves alone or T wave inversion/flattening alone did not significantly increase the risk of future myocardial infarction (MI) or mortality, while Q waves with ST depression or ST depression alone did increase MI risk after 5 years of follow-up.[23]

This current analysis improves upon these prior studies in that the diabetes status of each individual was known by OGTT or history of diagnosis by a physician. In the prior studies, participants may have had undiagnosed diabetes as none of the studies obtained oral glucose tolerance tests and instead utilized fasting plasma glucose[21] or clinical history[24 5] or failed to control for diabetes status in their analysis.[22 23]

The finding that diabetes does not increase the excess risk associated with Silent MI may be due to a smaller sample size of those with diabetes (n=257) and especially those with diabetes and Silent MI (n=76) as the HR is in the positive direction in all analyses and sub-analyses. Another smaller study using 48 hour Holter monitoring in 678 asymptomatic community-dwelling adults with and without diabetes. found that while Silent MI resulted in a 3-fold increased risk of a cardiac event in the following 5 years, diabetes did not contribute to excess risk of overall mortality and first acute MI.[25] Conflicting evidence also exists regarding the cardiovascular consequences of silent myocardial ischemia in patients with diabetes.[26] One previous analysis of the prognosis of silent MI in 1269 patients with type 2 diabetes followed for an average of 7 years found no increased mortality compared to patients with diabetes but without silent MI.[27]

Diabetes status also may have reduced importance when cardiovascular risk factors are appropriately treated and controlled. In a study of asymptomatic patients with diabetes and at least 2 additional risk factors that examined the benefit of screening for Silent MI via bicycle exercise test or dipyridamole single photon emission computed tomography the authors found no reduction in all-cause mortality between those who were screened and those who received standard care aimed at reducing cardiovascular risk factors.[28] Similarly the DIAD study did not find a significant benefit in preventing

cardiac death or MIfrom screening diabetic patients for silent myocardial ischemia using adenosine-stress radionuclide myocardial perfusion imaging (MPI).[29] Additionally, a prior finding of the DIAD study indicated that silent myocardial ischemia seen in patients with diabetes resolved in 79% of the patients upon subsequent testing using repeat adenosine-stress myocardial perfusion imaging following 3 years of intensified medical treatment.[30]

Further contributing to the difficulty in demonstrating the significance of diabetes in CVD deaths is that death certificates for patients with diabetes are increasingly attributing cause of death to cardiovascular complications, as the association of diabetes with CVD has become more widely known.[31] This may lead to an over attribution of deaths among those with diabetes to CVD.

Despite the lack of statistical significance in this analysis, an abnormal ECG in those with diabetes should still prompt further investigation with a more sensitive tool. As outlined by Dweck et al, Silent MI is often under-recognized but when detected it should prompt further investigation, especially in a diabetic population.[32] For example, the detection of silent myocardial ischemia through stress myocardial scintigraphy has been shown to be predictive of cardiovascular events in patients with type 2 diabetes with at least one additional risk factor.[33]

Sex specific analyses including all participants found Silent MI to increase the risk of CVD death for both men and women, with exercise a significant protective factor for women and trending towards significance in men. A previous analysis of the Rancho Bernardo participants had found that the excess ischemic heart disease mortality for women with diabetes was partially explained by their HDL and VLDL levels.[34] However, in this analysis the impact of Silent MI on CVD death was significant for men and women even after controlling for dyslipidemias and exercise. Diabetes status did not explain the excess risk associated with Silent MI in neither men nor women.

Limitations of this study include limits in the ability to generalize these findings as the Rancho Bernardo Study population captures the experience of white older adults, over 80% of whom exercise ≥3 times per week. Additionally, lipid lowering medications were not widely available at the beginning of this study, and today many persons with diabetes take statins.

That many of these participants meet several of the American Heart Association guidelines' key metrics of cardiovascular health and still had Silent MI as a risk factor for CVD death speaks to the

importance of Silent MI even in a relatively healthy population. Therefore, Silent MI on a resting ECG should prompt further evaluation and risk factor reduction.

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Disclosures

None.

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Figure Legends:

Figure 1: Kaplan-Meier curve for survival free of cardiovascular disease death with Silent MI compared to those with no Silent MI (No Silent MI).

Figure 2: Kaplan-Meier curve for survival free of cardiovascular disease death with diabetes compared to those without diabetes.

Figure 3: Kaplan-Meier curve for survival free of cardiovascular disease death in women compared to men.

Figure 4: Kaplan-Meier curve for survival free of cardiovascular disease death in those with hypertension compared to those without.

Table 1. Age-Adjusted Mean ± SD or Prevalence of Baseline Characteristics

	No Silent MI† (n =1532)	Silent MI‡ (n =350)	p-value
Age, years*	69.5 ± 9.5	73.7 ± 9.2	<.0001
Male, %*	42.0	45.4	0.247
Body Mass Index (kg/m^2)	24.8 ± 3.7	25.1 ± 3.6	0.180
Waist / Hip Ratio	0.84 ± 0.09	0.86 ± 0.08	0.028
Systolic BP, mmHg	137 ± 20	146 ± 24	<.0001
Total Cholesterol, mg/dL	220 ± 38	220 ± 43	0.853
LDL Cholesterol, mg/dL	134 ± 36	136 ± 39	0.477
HDL Cholesterol, mg/dL	64 ± 19	60 ± 19	0.001
Triglycerides, mg/dL	113 ± 73	129 ± 83	0.001
Fasting glucose, mg/dL	100 ± 18	103 ± 27	0.008
2 hour glucose, mg/dL	134 ± 53	150 ± 68	<.0001
Smoking (ever), %	59.0	58.7	0.921
Alcohol (≥3 drinks/wk), %	54.5	48.4	0.042
Exercise (≥3x per wk), %	81.8	82.1	0.869
BP Medications, %	25.0	39.9	<.0001
Hypertension, %	53.6	70.6	<.0001
Diabetes, %	12.1	20.6	<.0001

*Not adjusted for age. †Cardiovascular Disease ‡Silent Myocardial Ischemia

Table 2: Multivariate Cox Proportional Hazards for Association Between Silent MI and Cardiovascular Disease Death by Sex and Diabetes Status.

	All Participants (n=1882)			No Diabetes (n= 1625)			Diabetes (n=257)		
	HR	**CI 95%**	**p-value**	**HR**	**CI 95%**	**p-value**	**HR**	**CI 95%**	**p-value**
All participants									
Model 1	1.67	1.36 – 2.04	<0.001	1.76	1.41-2.21	<0.001	1.31	0.82-2.11	0.260
Model 2	1.54	1.25 – 1.90	<0.001	1.60	1.27-2.02	<0.001	1.33	0.82-2.14	0.247
Model 3	1.56	1.27 – 1.92	<0.001	1.62	1.29-2.04	<0.001	1.32	0.82-2.14	0.256
Men (n= 803)									
Model 1	1.61	1.20 – 2.17	0.002	1.61	1.16 – 2.25	0.005	1.48	0.76-2.83	0.234
Model 2	1.42	1.04 – 1.93	0.026	1.41	0.99 – 2.00	0.054	1.36	0.70-2.65	0.358
Model 3	1.40	1.03 – 1.90	0.033	1.38	0.97 – 1.96	0.072	1.28	0.66-2.48	0.474
Women (n=1079)									
Model 1	1.72	1.31 – 2.27	<0.001	1.88	1.39 – 2.54	<0.001	1.16	0.57-2.36	0.686
Model 2	1.66	1.25 – 2.21	<0.001	1.78	1.31 – 2.42	<0.001	1.17	0.57-2.40	0.677
Model 3	1.73	1.30 – 2.31	<0.001	1.85	1.35 – 2.52	<0.001	1.23	0.58-2.59	0.590

Model 1: Adjusting for age

Model 2: Adjusting for age, SBP, HDL, Trig, Diabetes

Model 3: Adjusting for age, SBP, HDL, Trig, Diabetes, Exercise, Alcohol, Smoking

Table 3: Multivariate Cox Proportional Hazards for Cardiovascular Disease Mortality for all participants. All factors with significant difference (p<0.001) between those with and without Silent MI are included as well as behaviors and sex.

	All Participants (n = 1882)		
	HR	**95% CI**	**p-value**
Silent Myocardial Ischemia	1.56	1.27 – 1.92	<0.001
Age	1.15	1.14 – 1.17	<0.001
Male Sex	1.55	1.24 – 1.94	<0.001
Systolic BP, mmHg	1.01	1.005 – 1.014	<0.001
HDL Cholesterol, mg/dL	0.79	0.28 – 2.29	0.655
Triglycerides, mg/dL	1.37	0.83 – 2.25	0.222
Diabetes	0.93	0.72 – 1.19	0.555
Exercise (≥3x per wk)	0.72	0.57 – 0.90	0.004
Alcohol (≥3 drinks/wk)	1.04	0.86 – 1.27	0.681
Smoking (ever)	1.03	0.85 – 1.26	0.736

Table 4: Multivariate Cox-proportional Hazards Model for Silent MI and Cardiovascular Disease Mortality for women and for men. All factors with p<0.01 significant difference between those with and without Silent MI are included as well as behaviors.

	Women (n= 1079)			**Men (n= 803)**		
	HR	**CI 95%**	**p-value**	**HR**	**CI 95%**	**p-value**
Silent MI	1.73	1.30 – 2.31	<0.001	1.40	1.03 – 1.90	0.033
Age	1.16	1.14 – 1.19	<0.001	1.15	1.12 – 1.17	<0.001
Systolic BP, mmHg	1.01	1.002 – 1.015	0.006	1.01	1.005– 1.019	0.001
HDL Cholesterol, mg/dL	0.52	0.12 – 2.16	0.365	1.19	0.25 – 5.73	0.827
Triglycerides, mg/dL	1.04	0.51 – 2.10	0.923	1.61	0.79 – 3.28	0.190
Diabetes	0.85	0.58 – 1.23	0.391	0.99	0.70 – 1.39	0.935
Exercise (≥3x per wk)	0.67	0.50 – 0.90	0.008	0.77	0.53 – 1.12	0.170
Alcohol (≥3 drinks/wk)	0.98	0.74 – 1.29	0.865	1.12	0.84 – 1.50	0.429
Smoking (ever)	1.19	0.91 – 1.55	0.197	0.90	0.68 – 1.20	0.487

Figure 1: Kaplan-Meier curve for survival free of cardiovascular disease death with Silent MI compared to those with no Silent MI (No Silent MI).

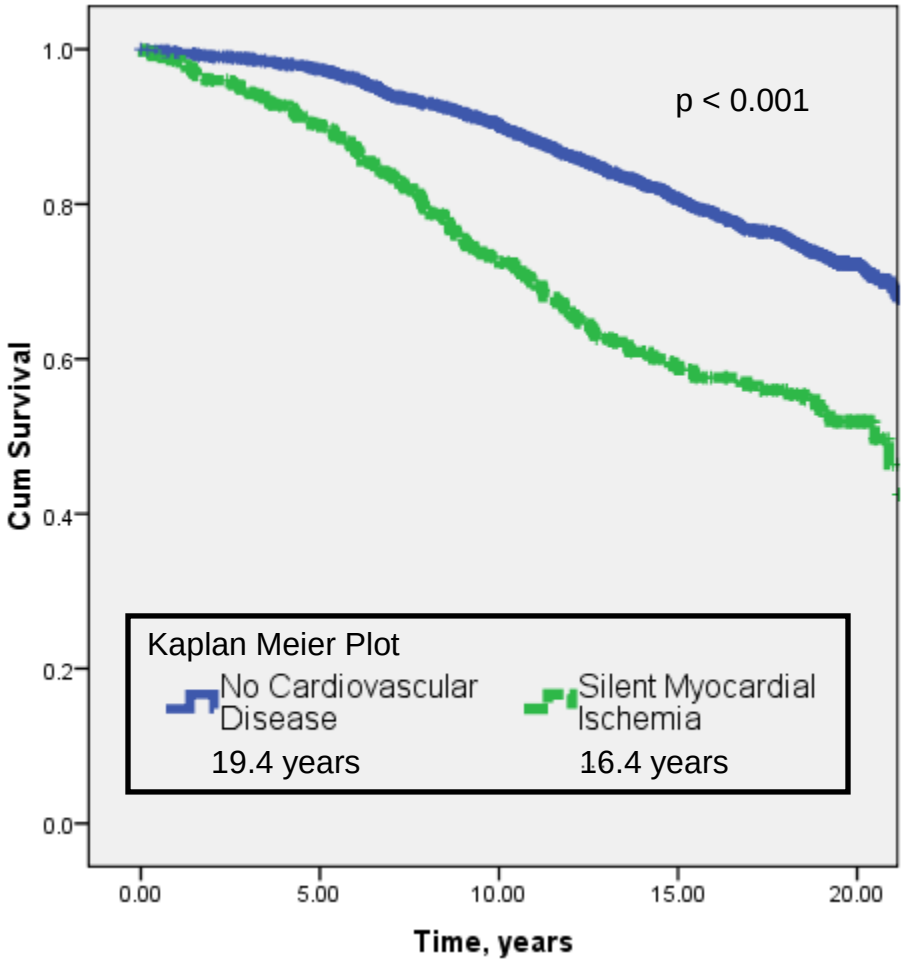

Figure 2: Kaplan-Meier curve for survival free of cardiovascular disease death with diabetes compared to those without diabetes.

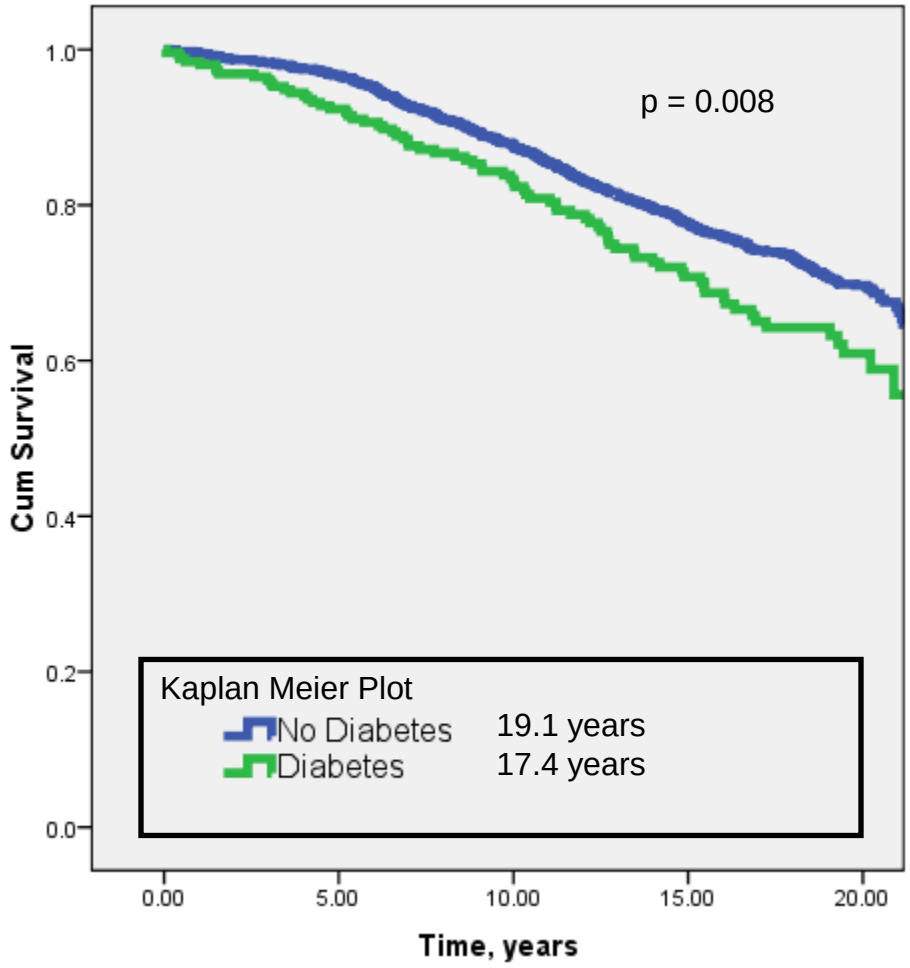

Figure 3: Kaplan-Meier curve for survival free of cardiovascular disease death in women compared to men.

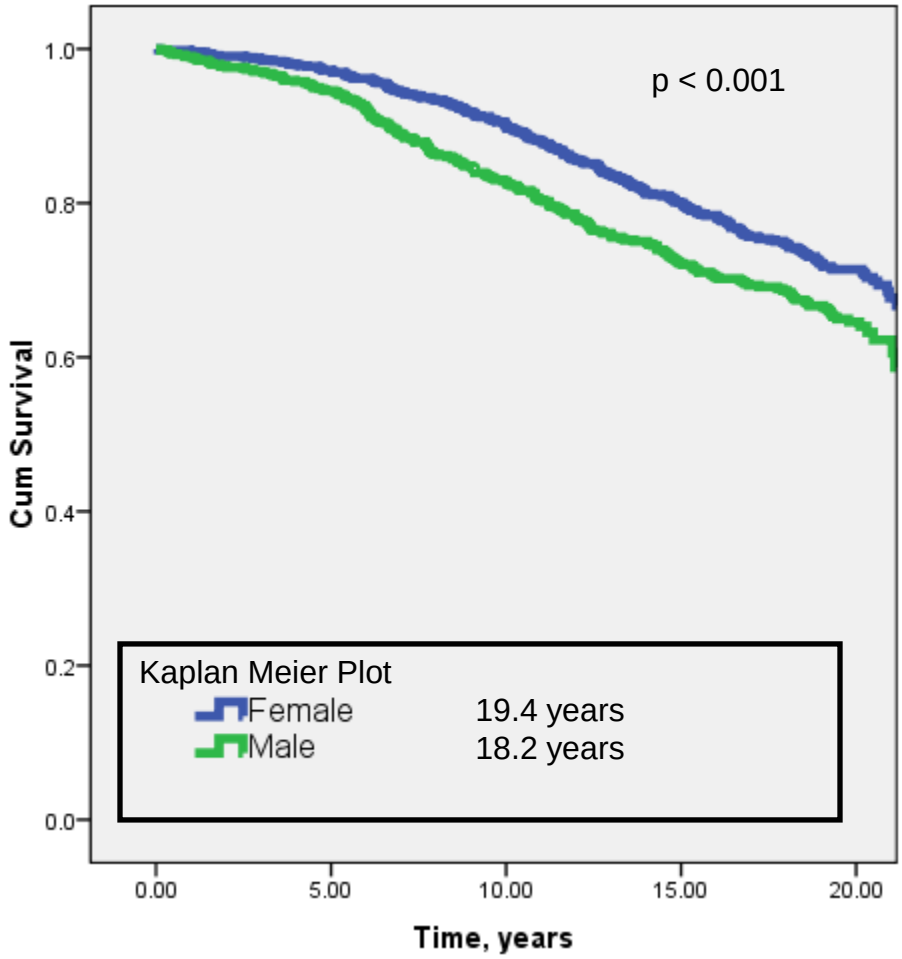

Figure 4: Kaplan-Meier curve for survival free of cardiovascular disease death in those with hypertension compared to those without.