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# Serum Calcium and Risk of Sudden Cardiac Arrest in the General Population

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## Abstract

**Objective—**To evaluate the potential role of low serum calcium (Ca) levels toward occurrence of SCA in the community.

**Patients and Methods—**We compared 267 SCA cases (73% male) and 445 controls (71% male) from a large population based study (catchment population almost 1 million) in the US Northwest from February 1st, 2002 to December 31st, 2015. Subjects were included if their age was ≥18 years with available creatinine clearance (CrCl) and serum electrolyte levels for analyses, to enable adjustment for renal function. For cases, CrCl and electrolytes were required to be measured within 90 days of the SCA event.

**Results—**Cases of SCA had higher proportions of African-Americans (12% vs. 3%, $P<.001$), diabetes mellitus (46% vs. 28%, $P<.001$) and chronic kidney disease (38% vs. 16%, $P<.001$) compared to controls. In multivariable logistic regression analysis, a one-unit decrease in Ca level was associated with 1.6-fold increase in odds of SCA (odds ratio [OR] =1.63, 95% confidence interval [CI]: 1.06–2.51). Blood Ca levels lower than 8.95 mg/dL were associated with 2.3-fold increase in odds of SCA comparing to levels higher than 9.55 mg/dL (OR= 2.33, 95% CI: 1.17–4.61). SCA cases had significantly prolonged QTc intervals on the 12-lead ECG compared to controls (465±37 ms vs. 425±33 ms, $P<.001$).

**Conclusions—**Lower serum Ca levels were independently associated with increased risk of SCA in the community.

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**Keywords**

sudden cardiac arrest; electrolytes abnormality; calcium

## Introduction

It is estimated that approximately 300,000 individuals die from sudden cardiac arrest (SCA) annually in the US[1]. However, over half of men and close to 70% of women that die from SCA have no clinical history of heart disease prior to their cardiac arrest[2,3]. Hence, it is important to identify other risk factors and mediators for SCA to improve risk stratification and preventive strategies in the general population.

Electrolyte abnormalities are known to induce or facilitate clinical arrhythmia even in normal cardiac tissue and they can lead to SCA[4]. Calcium (Ca) is an essential cation for the myocardial action potential and excitation/contraction coupling of cardiac muscle[5]. Importantly, low serum Ca is associated with increased risk of SCA in dialysis patients[6]. However, the evidence for the relationship between Ca intake and cardiovascular events is mixed and at times contradictory. In some observational studies a strong inverse or neutral relation was noted between Ca intake and mortality from ischemic heart disease[7,8]. In addition, communities with a Ca-rich water supply also seem to have a lower incidence of cardiovascular events[9]. On the other hand, there are reports of an upward trend in cardiovascular event rates including myocardial infarction and sudden death in postmenopausal women that received Ca supplementation resulting in higher blood Ca levels[10,11]. In summary it is not clear whether blood Ca levels are related to SCA in the general population. Therefore, we evaluated the association between serum Ca and SCA in a large community-based study, also adjusting for renal function.

## Methods

### Data Sources and Study Population

Case and control subjects were ascertained in the Oregon Sudden Unexpected Death Study, a prospective, ongoing population-based study of SCA started on February 1st 2002 in the Portland, Oregon metropolitan region (catchment population around 1 million individuals). The details of the design and ascertainment of cases and controls have been reported previously[12,13]. In brief, cases of out-of-hospital cardiac arrest are identified from multiple sources including: county medical examiner's office, emergency medical response system (EMS-ambulance and fire services), and local hospital emergency rooms. Cases also included survivors of SCA. Since 2002, the Oregon Sudden Unexpected Death Study has reviewed all SCAs with EMS response, as well as additional cases from the medical examiner and hospitals. SCA was defined as a sudden unexpected pulseless condition if witnessed or unexpected death within 24 hours of last having been observed in the usual state of health (if unwitnessed). SCA was adjudicated by 3 in-house physicians after reviewing all available medical records/autopsy reports for each subject[12], and all SCAs meeting inclusion criteria were enrolled. Non-cardiac etiologies such as trauma, chronic terminal illness and drug overdose were excluded. Control subjects were enrolled during the

same time period and from the same geographical region as the cases from multiple sources within the Portland metro region including: emergency medical services that treated patients with chest pain, outpatient local hospital clinics, patients undergoing coronary angiogram at a participating hospital system, and a local large health maintenance organization (HMO). From the first three sources, all potential control subjects were identified, contacted, consented, and enrolled if they had documented coronary artery disease (CAD), defined by history of myocardial infarction, revascularization, or angiogram with ≥50% stenosis in a major coronary artery. Controls were excluded if they had a history of prior ventricular arrhythmia or SCA[12]. For the HMO controls, a random sample of HMO members (half with documented CAD, half without) were frequency matched to cases by age and sex, and were enrolled using the same procedures described above. The control population was selected to represent the source population of the cases, with a predominance of individuals with documented CAD to adequately control for CAD in case-control comparisons. Eighty percent of control subjects had a diagnosis of CAD, to match the estimate of CAD among the cases reported in previous community based studies[14].

For both cases and controls, electrolyte levels were obtained from clinical laboratory results performed during routine clinical practice, if available in patients' medical records. Cases for this analysis were included if they were enrolled from February 1st, 2002 to December 31st, 2015 and their electrolyte levels were measured within the 90 days prior to the SCA. Subjects were excluded if their age was < 18 years or if there were no available creatinine clearance (CrCl), serum Ca, or serum albumin level measurements. CrCl was calculated using the Cockcroft-Gault formula[15]. While free (ionized) Ca is more physiologically relevant than total Ca, measured ionized Ca was not available from most routine clinical labs. Therefore, Ca serum levels were corrected using the concomitant measured serum albumin levels and employing a widely used formula (corrected Ca level in mg/dL=uncorrected value in mg/dL + (0.8*(4-albumin level in g/dL))[16,17]. Normal albumin levels were set at 4 g/dL. Detailed clinical information was obtained for all subjects from review of all available medical records. The QT interval was measured from archived standard resting 12-lead ECGs with paper speed of 25mm/s and calibration of 10mm/mV (prior and unrelated to the cardiac arrest in cases), and corrected for heart rate using Bazett's formula. Only ECGs performed within 90 days prior to the arrest were included.

For this analysis, labs obtained within 90 days of the arrest were chosen for SCA cases because results would indicate the patient's electrolyte status shortly before the arrest. Overall, cases with labs available within 90 days of arrest were somewhat older and had a higher comorbidity burden (mean age 66.1 yrs, 67% male, 77% hypertension, 45% diabetes, 38% CRI) than cases with labs available more than 90 days prior to arrest (mean age 65.0 yrs, 68% male, 69% hypertension, 37% diabetes, 23% CRI).

## Statistical Analysis

Continuous variables are presented as mean ± SD and categorical variables are reported as frequencies and percentages (Table 1). Categorical and continuous variables including demographics and lab results were compared between cases and controls using chi-square and student *t*-tests. Examination of continuous variables indicated that all were relatively

normally distributed, with median values close to mean values. Nonparametric Wilcoxon rank sum tests for case-control comparisons for Ca, K, CrCl, and albumin produced similar results, and thus we have used *t*-tests for all continuous variables. As expected in a case-control study, cases had a higher burden of risk factors for SCD than control subjects whose risk factor burden should be representative of the larger source population from which cases arose. To adjust for these differences, multivariable logistic regression was used to estimate the independent association of Ca with SCA. The association was adjusted for confounders in three models (Table 2). The confounders were chosen from the covariates listed in table 1, because of their potential association with both Ca and SCA. A two-tailed p value of ≤.05 was considered statistically significant. Statistical analyses were performed using STATA version 11 (College Station, Texas). Quartiles of plasma corrected Ca were created based on the distribution of plasma corrected Ca among the controls, and cases were assigned to the appropriate category. Median levels of plasma Ca in each quartile were used as a continuous variable for estimating the linear trend across all quartiles.

## Results

A total of 712 subjects were included in this study: 267 cases (66% male) and 445 controls (71% male) (Table 1). Cases had a significantly higher percentage of African-Americans, diabetes mellitus, chronic obstructive pulmonary disease and chronic kidney disease compared to controls (all $P<.001$). Cases were also more likely than controls to be on hemodialysis (12% vs 1%, $P<.001$). In addition, diuretics, especially loop diuretics were prescribed more for cases compared to controls ($P<.001$) with no differences in the rate of utilization of beta blockers ($P=.11$). Among the lab values, cases had lower corrected Ca levels compared to controls (9.18±0.56 vs. 9.27 ±0.56, $P=.03$). Ca values ranged from 7.28 to 11.3 mg/dL in cases and 7.7 to 12.5 mg/dL in controls. In individuals not undergoing hemodialysis, results were nearly identical, with Ca 9.16 ± 0.54 mg/dL for cases and 9.27 ± 0.56 for controls, p=.02. In addition, cases had lower CrCl ($P<.001$), higher serum potassium levels ($P<.001$), and lower albumin levels ($P<.001$).

Evaluation of EKGs demonstrated significantly longer QRS and heart rate adjusted QT intervals in cases compared to controls ($P=.01$ & $P<.001$, respectively). Echocardiograms were performed in 171 (64%) of the cases and 255 (57%) of the controls and the mean left ventricular ejection fraction (LVEF) was significantly lower among the cases (mean = 48 vs. 54%; $P<.001$). However, only 40 (23% of all that had echocardiogram results) of the cases and 26 (10%) of controls had LVEF less than 35%.

In the age, gender, race and BMI adjusted model (model 1), Ca level was inversely associated with SCA ($P$ for trend<.001) and the patients in the lowest quartile of blood Ca level (Ca level <8.95 mg/dl) compared to highest quartile (Ca level >9.55 mg/dL) had a significantly higher risk of SCA (Odds ratio (OR): 1.91; 95% CI: 1.22–2.99) (Table 2). Further adjustment for history of hypertension, diabetes, chronic obstructive pulmonary disease, hypothyroidism and CrCl demonstrated higher OR for SCA (model 2) when comparing the lowest quartile to the highest. Finally, upon adding LVEF, potassium level and use of diuretics (loop and non-loop) and beta blockers to the model, the lowest quartile

(Ca level < 8.95 mg/dL) showed a significant increase in odds of SCA (2.3 fold) compared to the highest quartile (model 3).

As a sensitivity analysis, we repeated the analysis excluding subjects on hemodialysis. Results were very similar to the overall results, with odds ratios of ~2.0 comparing the lowest vs. highest quartile of Ca, with a significant linear trend ($P$<.02) in all three multivariable models.

In multivariable regression analysis, with a one-unit decrease in Ca level there was a 1.6 fold increase in odds of SCA (OR=1.63, 95% CI: 1.06–2.51), when Ca level was treated as a continuous variable (after adjustment for all the variables included in model 3). As compared with the cases constituting the highest quartile of blood Ca level (cases with Ca level >9.55 mg/dL), those in the lowest quartile had lower rate of beta blocker use and a trend towards a higher CrCl ($P$=.04 and .05, respectively) (Table 3). However, there was no significant difference between these quartiles in their demographics, comorbidities, LVEF and potassium levels ($P$ values >.05). Heart rate adjusted QT interval was somewhat longer in the lowest quartile, but this difference was not statistically significant ($P$=.52).

## Discussion

In this large prospective population-based study, lower Ca levels measured within 90 days prior to SCA were associated with a higher risk of SCA. These findings demonstrate that patients with Ca levels lower than 8.95 mg/dL have a 2.3-fold higher risk of SCA compared to those with Ca levels higher than 9.55 mg/dL. This inverse relationship between Ca level and SCA is consistent with the hypothesis that lower Ca levels may independently modify the risk of SCA.

A review of the literature demonstrates limited information available regarding the correlation between blood Ca level and SCA in the general population. Ca intake or level has mainly been studied in relation to bone health and in regards to its supplementation and cardiovascular safety[18]. Nevertheless, multiple cohort studies with long duration of follow up using baseline Ca levels have investigated the association of Ca serum levels and cardiovascular or all-cause mortality in different populations and subgroups[19–28]. These reports demonstrated conflicting results, with both high and low levels of Ca reported to be associated with increase in cardiovascular events. Leifsson *et al* found that the risk of premature death, which was largely attributed to cardiovascular disease, increases in men younger than 50 years of age with rising Ca levels even in the normal range. They followed these patients for 11 years[19]. In another study reported by Grandi *et al*, a cohort of patients with stable CAD were followed for 8 years and they reported significantly higher all-cause mortality in patients with higher adjusted baseline Ca levels. Grandi *et al* suggested that the higher Ca level might contribute to progressive vascular calcification and its related morbidities resulting in higher cardiovascular adverse events[20]. Furthermore, Lundgren *et al* reported that mild hypercalcemia is associated with premature cardiovascular death. These patients were followed for approximately two decades[21]. In contrast to the above mentioned studies, Ogard *et al* were unable to demonstrate any correlation between upper quintiles of serum ionized Ca levels and higher incidence of cardiovascular diseases in 45 year old men

and women followed for 18 years[22]. Similar to Ogard *et al*, Palmer *et al* conducted a meta-analysis study to assess the association between all-cause mortality and serum Ca levels in patients with chronic kidney disease, and reported no significant association[23]. However, Palmer *et al* do list some concerns regarding the studies included in their meta-analysis, stating that few of the studies had met their criteria for completeness.

More recently, a study reported that lower Ca levels increase the risk of cardiovascular death among men and decrease the risk in women[29]. However, the test for interaction by sex was not statistically significant and therefore, the authors stated that this reverse association might be due to chance. In addition, Zittermann *et al* showed that Ca levels were significantly higher in event-free survivors than in non-survivors of end-stage heart failure in short term follow up[26,27]. Similarly, Miura *et al* reviewed patients with heart failure and chronic kidney disease and reported that cardiac and all-cause mortality was significantly higher in the low-Ca group compared to the normal-high Ca group[27]. Finally, in patients with ST-elevated myocardial infarction lower Ca levels at the time of admission were associated with higher in-hospital mortality[28]. An important caveat to majority of the above mentioned studies is the focus on overall cardiovascular disease mortality, with limited data on association of Ca levels specifically with SCA. Additionally, the cohort studies have a long duration of follow up after the baseline measured Ca and therefore may not reflect the patients' Ca status in the months and days prior to the event. In the current study, the level of Ca was evaluated within 90 days prior to the event.

There are some potential explanations for the association of lower Ca levels, even within the normal range of values, with increased risk of SCA. First, low serumCa level can prolong the action potential duration.[4,5]. If the serum Ca is low enough or when other factors that can prolong QT interval exist, life-threatening arrhythmias like torsades de pointes can occur[30,31]. The current study supports this possibility as the QTc intervals were longer among our cases when compared to controls. Second, low Ca levels have been associated with heart failure and diastolic dysfunction[32]. Gromadzinski *et al* reported that low serum Ca is the only independent predictive factor for left ventricular diastolic dysfunction (independent from parathyroid hormone) in patients with chronic kidney disease[32]. Third, low extracellular Ca effect on cell death and stroke was studied in preclinical models and the low levels paradoxically increased the overloading of intracellular Ca which could potentiate apoptosis during ischemic episodes[33]. The same phenomena may exist in cardiac tissues in the setting of ischemia. Fourth, lower Ca levels may increase parathyroid hormone levels, also linked with a variety of deleterious cardiovascular effects[34–36].

## Limitations

This analysis is based on a single measurement of plasma Ca. While the study demonstrated a statistically significant inverse relationship between Ca level and SCA, serial measurements may provide a better assessment of this correlation. The second limitation of this study is the observational design. Similar to other observational studies, residual confounding could contribute to the relationship observed. A third limitation of this study is lack of complete data on drug therapies, their dosage and level of compliance. To assess whether a bias was introduced by choosing the patients with available Ca serum levels we

compared two groups (subjects with available Ca levels vs. no levels available) by age, BMI and CrCl and no significant differences were found ($P$=.8). Nevertheless, this analysis doesn't eliminate the possibility of bias based on other uncontrolled factors. Overall, it seems that further study is required to elucidate the mechanisms underlying the adverse associations with lower Ca levels and to determine whether controlling Ca levels improves the prognosis in the general population, or in high risk patients.

## Conclusions

Lower serum Ca levels were independently associated with increased risk of SCA in this population. These findings have potential implications for mechanisms as well as prevention of SCA and warrant further evaluation.

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## Abbreviations

| | |
|---|---|
| **Ca** | Calcium |
| **CAD** | Coronary artery disease |
| **CrCl** | Creatinine clearance |
| **HMO** | Health maintenance organization |
| **LVEF** | Left ventricular ejection fraction |
| **OR** | Odds ratio |
| **SCA** | Sudden cardiac arrest |

## References

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics–2015 update: A report from the american heart association. Circulation. 2015; 131(4):e29–322. [PubMed: 25520374]
2. Albert CM, Chae CU, Grodstein F, et al. Prospective study of sudden cardiac death among women in the united states. Circulation. 2003; 107(16):2096–2101. [PubMed: 12695299]
3. Kannel WB, Schatzkin A. Sudden death: Lessons from subsets in population studies. J Am Coll Cardiol. 1985; 5(6 Suppl):141B–149B.
4. El-Sherif N, Turitto G. Electrolyte disorders and arrhythmogenesis. Cardiol J. 2011; 18(3):233–245. [PubMed: 21660912]
5. Fisch C. Relation of electrolyte disturbances to cardiac arrhythmias. Circulation. 1973; 47(2):408–419. [PubMed: 4567871]
6. Pun PH, Horton JR, Middleton JP. Dialysate calcium concentration and the risk of sudden cardiac arrest in hemodialysis patients. Clin J Am Soc Nephrol. 2013; 8(5):797–803. [PubMed: 23371957]
7. Knox EG. Ischaemic-heart-disease mortality and dietary intake of calcium. Lancet. 1973; 1(7818): 1465–1467. [PubMed: 4123137]

8. Hsia J, Heiss G, Ren H, et al. Calcium/vitamin D supplementation and cardiovascular events. Circulation. 2007; 115(7):846–854. [PubMed: 17309935]
9. Dawson EB, Frey MJ, Moore TD, McGanity WJ. Relationship of metal metabolism to vascular disease mortality rates in texas. Am J Clin Nutr. 1978; 31(7):1188–1197. [PubMed: 665571]
10. Bolland MJ, Barber PA, Doughty RN, et al. Vascular events in healthy older women receiving calcium supplementation: Randomised controlled trial. BMJ. 2008; 336(7638):262–266. [PubMed: 18198394]
11. Reid IR, Schooler BA, Hannan SF, Ibbertson HK. The acute biochemical effects of four proprietary calcium preparations. Aust N Z J Med. 1986; 16(2):193–197. [PubMed: 3463271]
12. Chugh SS, Jui J, Gunson K, et al. Current burden of sudden cardiac death: Multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. J Am Coll Cardiol. 2004; 44(6):1268–1275. [PubMed: 15364331]
13. Havmoeller R, Reinier K, Teodorescu C, et al. Low rate of secondary prevention ICDs in the general population: Multiple-year multiple-source surveillance of sudden cardiac death in the oregon sudden unexpected death study. J Cardiovasc Electrophysiol. 2013; 24(1):60–65. [PubMed: 22860692]
14. Adabag AS, Peterson G, Apple FS, Titus J, King R, Luepker RV. Etiology of sudden death in the community: Results of anatomical, metabolic, and genetic evaluation. Am Heart J. 2010; 159(1): 33–39. [PubMed: 20102864]
15. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976; 16(1):31–41. [PubMed: 1244564]
16. Figge J, Jabor A, Kazda A, Fencl V. Anion gap and hypoalbuminemia. Crit Care Med. 1998; 26(11):1807–1810. [PubMed: 9824071]
17. Payne RB, Little AJ, Williams RB, Milner JR. Interpretation of serum calcium in patients with abnormal serum proteins. Br Med J. 1973; 4(5893):643–646. [PubMed: 4758544]
18. Reid IR, Bolland MJ. Calcium supplements: Bad for the heart? Heart. 2012; 98(12):895–896. [PubMed: 22626897]
19. Leifsson BG, Ahren B. Serum calcium and survival in a large health screening program. J Clin Endocrinol Metab. 1996; 81(6):2149–2153. [PubMed: 8964843]
20. Grandi NC, Brenner H, Hahmann H, et al. Calcium, phosphate and the risk of cardiovascular events and all-cause mortality in a population with stable coronary heart disease. Heart. 2012; 98(12):926–933. [PubMed: 22301505]
21. Lundgren E, Lind L, Palmer M, Jakobsson S, Ljunghall S, Rastad J. Increased cardiovascular mortality and normalized serum calcium in patients with mild hypercalcemia followed up for 25 years. Surgery. 2001; 130(6):978–985. [PubMed: 11742326]
22. Ogard CG, Petersen J, Jorgensen T, Almdal T, Vestergaard H. Serum ionised calcium and cardiovascular disease in 45-years old men and women followed for 18 years. Eur J Epidemiol. 2006; 21(2):123–127. [PubMed: 16518680]
23. Palmer SC, Hayen A, Macaskill P, et al. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: A systematic review and meta-analysis. JAMA. 2011; 305(11):1119–1127. [PubMed: 21406649]
24. Van Hemelrijck M, Michaelsson K, Linseisen J, Rohrmann S. Calcium intake and serum concentration in relation to risk of cardiovascular death in NHANES III. PLoS One. 2013; 8(4):e61037. [PubMed: 23593383]
25. Cubbon RM, Thomas CH, Drozd M, et al. Calcium, phosphate and calcium phosphate product are markers of outcome in patients with chronic heart failure. J Nephrol. 2015; 28(2):209–215. [PubMed: 24615401]
26. Zittermann A, Fuchs U, Kuhn J, et al. Parameters of mineral metabolism predict midterm clinical outcome in end-stage heart failure patients. Scand Cardiovasc J. 2011; 45(6):342–348. [PubMed: 21905973]
27. Miura S, Yoshihisa A, Takiguchi M, et al. Association of hypocalcemia with mortality in hospitalized patients with heart failure and chronic kidney disease. J Card Fail. 2015; 21(8):621–627. [PubMed: 25982827]

28. Lu X, Wang Y, Meng H, et al. Association of admission serum calcium levels and in-hospital mortality in patients with acute ST-elevated myocardial infarction: An eight-year, single-center study in china. PLoS One. 2014; 9(6):e99895. [PubMed: 24926660]
29. Van Hemelrijck M, Michaelsson K, Linseisen J, Rohrmann S. Calcium intake and serum concentration in relation to risk of cardiovascular death in NHANES III. PLoS One. 2013; 8(4):e61037. [PubMed: 23593383]
30. Akiyama T, Batchelder J, Worsman J, Moses HW, Jedlinski M. Hypocalcemic torsades de pointes. J Electrocardiol. 1989; 22(1):89–92. [PubMed: 2921582]
31. Drew BJ, Ackerman MJ, Funk M, et al. Prevention of torsade de pointes in hospital settings: A scientific statement from the american heart association and the american college of cardiology foundation. Circulation. 2010; 121(8):1047–1060. [PubMed: 20142454]
32. Gromadzinski L, Januszko-Giergielewicz B, Pruszczyk P. Hypocalcemia is related to left ventricular diastolic dysfunction in patients with chronic kidney disease. J Cardiol. 2014; 63(3): 198–204. [PubMed: 24012332]
33. MacDonald JF, Xiong ZG, Jackson MF. Paradox of Ca2+ signaling, cell death and stroke. Trends Neurosci. 2006; 29(2):75–81. [PubMed: 16376999]
34. Schluter KD, Weber M, Piper HM. Parathyroid hormone induces protein kinase C but not adenylate cyclase in adult cardiomyocytes and regulates cyclic AMP levels via protein kinase C-dependent phosphodiesterase activity. Biochem J. 1995; 310(Pt 2):439–444. [PubMed: 7654180]
35. Schluter KD, Piper HM. Trophic effects of catecholamines and parathyroid hormone on adult ventricular cardiomyocytes. Am J Physiol. 1992; 263(6 Pt 2):H1739–46. [PubMed: 1481899]
36. Saleh FN, Schirmer H, Sundsfjord J, Jorde R. Parathyroid hormone and left ventricular hypertrophy. Eur Heart J. 2003; 24(22):2054–2060. [PubMed: 14613742]

## Table 1

Characteristics of the study population

| Total (*N*=712) | Case (*N*=267) | Control (*N*=445) | *P* Value |
|---|---|---|---|
| Age (y), mean ± SD | 66 ± 14 | 67 ± 10 | .33 |
| Male (%) | 177 (66) | 314 (71) | .23 |
| Race-ethnicity (%) | | | |
| White | 216 (80) | 411 (92) | <.001 |
| Black | 31 (12) | 14 (3) | |
| Asian | 7 (3) | 4 (1) | |
| Hispanic | 3 (1) | 5 (1) | |
| Others & Unknown | 10 (4) | 11 (3) | |
| BMI[a] (kg/m2), mean ± SD | 30.1±10.4 | 29.8±6.3 | .67 |
| Comorbidities (%) | | | |
| Hypertension | 209 (78) | 342 (77) | .66 |
| Diabetes | 122 (46) | 126 (28) | <.001 |
| COPD | 77 (29) | 47 (11) | <.001 |
| CKD | 102 (38) | 73 (16) | <.001 |
| On hemodialysis | 31 (12) | 5 (1) | <.001 |
| Hypothyroidism | 39 (15) | 64 (14) | .93 |
| Documented coronary artery disease | 165 (62) | 358 (80) | <.001 |
| EKG[b] intervals (msec) | (*N*=115) | (*N*=436) | |
| QRS interval, mean ± SD | 106±27 | 100±23 | .01 |
| QTc interval, mean ± SD | 465±37 | 425±32 | <.001 |
| Drug therapy (%) | (N=254) | (N=425) | |
| All diuretics | 136 (54) | 162 (38) | <.001 |
| Loop diuretic | 116 (46) | 69 (16) | <.001 |
| Beta blockers | 133 (52) | 249 (59) | .11 |
| Clinical labs/blood levels | | | |
| Potassium (mg/dL), mean ± SD | 4.23±0.62 | 4.11±0.45 | <.001 |
| Albumin (g/dL), mean ± SD | 3.61±0.63 | 3.88±0.54 | <.001 |
| CrCl (ml/min), mean ± SD | 55±34 | 63±23 | <.001 |
| Ca (mg/dL), mean ± SD | 8.86±0.64 | 9.18±0.54 | <.001 |
| Corrected Ca (mg/dL), mean ± SD | 9.18±0.56 | 9.27±0.56 | .03 |
| LVEF[c] (%), mean ± SD | 48±17 | 54±13 | <.001 |

[a] BMI = body mass index; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CrCl= creatinine clearance; LVEF = left ventricular ejection fraction.

[b] EKGs were recorded within 90 days prior to sudden cardiac arrest;

[c] Echocardiogram was done in 171 (64%) of the cases and 255 (57%) of the controls.

**Table 2**

Risk of sudden cardiac death by quartile of plasma calcium

| | Plasma calcium (mg/dL) | | | | |
|---|---|---|---|---|---|
| | **Q1** | **Q2** | **Q3** | **Q4** | ***P-value[a] for trend*** |
| Range of calcium levels | <8.95 | 8.95–9.25 | 9.26–9.55 | > 9.55 | |
| Cases/Controls (n) | 91/113 | 64/112 | 63/109 | 49/111 | |
| Multivariable model 1 | **1.91 (1.22–2.99)** | 1.29 (0.81–2.07) | 1.34 (0.84–2.15) | 1.0 (ref) | <.001 |
| Multivariable model 2 | **2.38 (1.47–3.85)** | 1.52 (0.92–2.52) | 1.49 (0.89–2.46) | 1.0 (ref) | <.001 |
| Multivariable model 3 | **2.33 (1.17–4.61)** | 1.58 (0.76–3.27) | 1.21 (0.57–2.53) | 1.0 (ref) | <.001 |

Model 1: adjusted for age, race, gender and BMI.

Model 2: adjusted for age, race, gender, BMI, hypertension, diabetes, chronic obstructive pulmonary disease, hypothyroidism and creatinine clearance.

Model 3: Model 2 & loop diuretics use, non-loop diuretics use, beta blockers, left ventricular ejection fraction and potassium level.

[a]Median levels of plasma calcium in each quartile were used as a continuous variable for linear trend estimation

## Table 3

Characteristics of cases in lowest vs. highest quartiles of calcium levels

| | Plasma calcium (mg/dL) | | |
|---|---|---|---|
| | **Q1 (<8.95) (N=91)** | **Q4 (> 9.55) (N=49)** | ***P* Value** |
| Age (y), mean ± SD | 68 ± 15* | 68 ± 14 | .86 |
| Male (%) | 64 (70) | 31 (63) | .39 |
| Race-ethnicity (%) | | | |
| White | 73 (81) | 41 (84) | .41 |
| Black | 9 (10) | 6 (12) | |
| Asian | 4 (4) | 0 | |
| Hispanic | 1 (1) | 0 | |
| Others & Unknown | 4 (4) | 2 (4) | |
| BMI[a] (kg/m2), mean ± SD | 29 ±7.7 | 29 ±9.5 | .79 |
| Comorbidities (%) | | | |
| Hypertension | 68 (75) | 41 (84) | .22 |
| Diabetes | 37 (41) | 22 (45) | .63 |
| COPD | 25 (27) | 11 (22) | .52 |
| CKD | 29 (32) | 22 (45) | .12 |
| Hypothyroidism | 14 (15) | 9 (18) | .65 |
| EKG[b] intervals (msec) | (*N*=35) | (*N*=23) | |
| QRS interval, mean ± SD | 109±27 | 107±25 | .79 |
| QTc interval, mean ± SD | 462±38 | 453±41 | .52 |
| Drug therapy (%) | (N=86) | (N=46) | |
| All diuretics | 42 (49) | 22 (48) | .91 |
| Loop diuretic | 37 (43) | 19 (41) | .85 |
| Beta blockers | 38 (44) | 29 (63) | .04 |
| Potassium blood levels (mg/dL) | 4.1±0.6 | 4.2±0.6 | .26 |
| CrCl (ml/min), mean ± SD | 59 ± 37 | 47 ± 32 | .05 |
| LVEF[c] (%), mean ± SD | 50 ±19 | 48±17 | .65 |

[a]BMI = body mass index; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CrCl = creatinine clearance; LVEF = left ventricular ejection fraction.

[b]EKGs were recorded within 90 days prior to sudden cardiac arrest

[c]Echocardiogram was done in 58 (64%) of cases in quartile 1 and 35 (71%) of cases in quartile 4