Authored by

**Gary L. Murray**\(^1\)\(^*\) and **Joseph Colombo**\(^2\),\(^3\)

\(^1\) Director of Clinical Research, The Heart and Vascular Institute, Germantown, TN-USA.

\(^2\) Parasympathetic & Sympathetic Nervous System Consultant, Franklin Cardiovascular Associates, Sewell, New Jersey – USA

\(^3\) Physio PS, Inc., Atlanta, Georgia – USA

**Published Date**

October 16, 2020

Published in the Journal of

Clinical Cardiology and Cardiovascular Interventions

**Auctores Publishing, LLC**

16192 Coastal Highway

Lewes, DE 19958,

USA
Re-print: Maintenance (r) Alpha Lipoic Acid Reduces Sudden Cardiac Death in Geriatric Diabetes Mellitus II Patients

Gary L Murray1* and Joseph Colombo2,3
1Director of Clinical Research, The Heart and Vascular Institute, Germantown, USA
2Parasympathetic & Sympathetic Nervous System Consultant, Franklin Cardiovascular Associates, Sewell, New Jersey – USA
3Physio PS, Inc., Atlanta, Georgia – USA
*Corresponding author: Gary L Murray, The Heart and Vascular Institute, 7205 Wolf River Blvd, Germantown,
Received date: September 30, 2020; Accepted date: October 09, 2020; Published date: October 16, 2020
Citation: Gary L Murray and Joseph Colombo., (2020) Re-print: Maintenance (r) Alpha Lipoic Acid Reduces Sudden Cardiac Death in Geriatric Diabetes Mellitus II Patients. J. Clinical Cardiology and Cardiovascular Interventions, 3(9); Doi: 10.31579/2641-0419/094
Copyright: © 2020 Gary L Murray, This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Background: Diabetes carries a two-fold risk of Sudden Cardiac Death (SCD). Diabetic Autonomic Neuropathy (DAN), often progressing to Cardiovascular Autonomic Neuropathy (CAN, critically low parasympathetic tone [P]), increases death 3.5-fold over 5 years, half sudden or non-renal. Oxidative stress is a major cause of DAN. Also, increased sympathetic tone (S), High Sympathovagal Balance [SB>2.5] increases SCD risk.

Objective: Dysautonomic diabetic II patients were treated with the antioxidant (r) Alpha Lipoic Acid (ALA), autonomic function followed, and Sudden Death (SD) compared to untreated patients.

Methods: 133 patients (mean age 66y/o) with DAN or CAN, diagnosed using the ANX 3.0 Autonomic Monitor (Physio PS, Inc., Atlanta, GA) was offered (r)-ALA: 83 agreed (Group 1), and 50 refused (Group 2). P and S were re-measured up to 3 times/yr (mean f/u 6.31 yrs); SCDs were recorded.

Results: A 43% Relative Risk Reduction (RRR) in SCD occurred with (r)-ALA: 25% SCD Group 1 vs. 44% SCD Group 2, p=0.0076. Initial to final patients with high SB or CAN were 21.7%-12% (p=0.010), 10.8%-15.7% (p=0.045), Group 1 vs. 24%-22% (p=ns), 6%-12% (p=0.083), Group 2. Only Group 1 survivors increased mean resting P. The progressive increase in P’s decline, increasing CAN risk, in the other patients correlated with mortality (p<0.001) and (r) ALA dose. Initially, Group 1 had insignificantly less high SB (p=0.449) and significantly more CAN (p=0.013) vs. Group 2. Finally, Group 1 had significantly less high SB (p=0.0967) vs. Group 2, also improving to insignificantly more CAN (p=0.261).

Conclusion: (r)-ALA was associated with a 43% RRR of SCD and favorable P and S changes.

Keywords: Alpha Lipoic Acid, Diabetic Autonomic Neuropathy, Sudden Death.

Abbreviations:

SCD-Sudden Cardiac Death,
DAN-Diabetic Autonomic Neuropathy,
CAN-Cardiovascular Autonomic Neuropathy,
P-Parasympathetic tone,
S-Sympathetic tone,
ALA-Alpha Lipoic Acid,
SD-Sudden Death,
NOH-Neurogenic Orthostatic Hypotension,
DMII-Type 2 Diabetics,
RA-Respiratory Activity,
HRV-Heart Rate Variability,
RFa-Respiratory Frequency area,
FRF-Fundamental Respiratory Frequency,
LFa-Low Frequency area,
ACS-Acute Coronary Syndromes,
VT/VF-Ventricular Tachycardia/Fibrillation,
CART-Cardiovascular Autonomic Reflex Test,
BMI-Body Mass Index, Bx-Baseline,
dBP-Diastolic Blood Pressure,
Introduction

Diabetics have a two-fold increased risk of Sudden Cardiac Death (SCD), the most common cause of death in adult diabetics. Subgroup analyses have not explained this adequately [1]. Diabetic Autonomic Neuropathy (DAN) [2], carries a 53% 5yr. mortality, half of the deaths sudden [3]. DAN can progress to Cardiovascular Autonomic Reflex Test (CART) w/o isometric grip (grip variability, as we detailed previously [11-17]. P&S were computed simultaneously and independently by concurrent, continuous time-frequency analysis of Respiratory Activity (RA) and Heart Rate Variability (HRV), as we detailed previously [11-17].

Methods

In 2006, 133 consecutive DMII referrals for cardiovascular evaluation underwent P and S testing via ANX 3.0 Autonomic Monitoring (P&S Monitoring, Physio PS, Inc., Atlanta, GA). P&S were computed simultaneously and independently by concurrent, continuous time-frequency analysis of Respiratory Activity (RA) and Heart Rate Variability (HRV), as we detailed previously [11-17]. P&S were computed simultaneously and independently by concurrent, continuous time-frequency analysis of Respiratory Activity (RA) and Heart Rate Variability (HRV), as we detailed previously [11-17]. P&S were computed simultaneously and independently by concurrent, continuous time-frequency analysis of Respiratory Activity (RA) and Heart Rate Variability (HRV), as we detailed previously [11-17]. P&S were computed simultaneously and independently by concurrent, continuous time-frequency analysis of Respiratory Activity (RA) and Heart Rate Variability (HRV), as we detailed previously [11-17]. P&S were computed simultaneously and independently by concurrent, continuous time-frequency analysis of Respiratory Activity (RA) and Heart Rate Variability (HRV), as we detailed previously [11-17]. P&S were computed simultaneously and independently by concurrent, continuous time-frequency analysis of Respiratory Activity (RA) and Heart Rate Variability (HRV), as we detailed previously [11-17]. P&S were computed simultaneously and independently by concurrent, continuous time-frequency analysis of Respiratory Activity (RA) and Heart Rate Variability (HRV), as we detailed previously [11-17]. P&S were computed simultaneously and independently by concurrent, continuous time-frequency analysis of Respiratory Activity (RA) and Heart Rate Variability (HRV), as we detailed previously [11-17]. P&S were computed simultaneously and independently by concurrent, continuous time-frequency analysis of Respiratory Activity (RA) and Heart Rate Variability (HRV), as we detailed previously [11-17].

Out of hospital SCD was defined as pulse less SD of cardiac origin. The cause of SD was determined from hospital records if clinically indicated: Groups AA 60%, AD 57.1%, NA 60.7%, ND 31.8%

The abbreviations are: Δ, change from initial to final; A1C, glucose form hemoglobin; (r) ALA (r)Alpha-Lipoic Acid) (the r-isomer functional in humans); BMI (Body Mass Index); Bx (Baseline); CAN; DAN; dBP (Diastolic Blood Pressure); HL (Hyperlipidemia); HR (Heart Rate); Init (Initial); LFa ((Low Frequency area)=S); LVEF (Left Ventricular Ejection Fraction); mg (milligrams); N (number); Nml (normal); ns (not significant); P (Parasympathetic tone); PE (Parasympathetic Excess); QTc (corrected QT); RFa ((Respiratory Frequency area)=P); S (Sympathetic tone); SB (Systolic BP); SW (Sympathetic Withdrawal). Given the size of the cohort, statistical significance is p<0.100. Statistical significance was determined with either a two-tailed, student T-test or a Pearson correlation.

25% of (r)-ALA patients experienced SCD vs. 44% non-(r)-ALA patients, a 43% Relative Risk Reduction (RRR, p=0.0076 [Figure 1]), altering the natural history of DAN [3].

Results

Demographics

Table 1 Survivor demographics Group AA had significantly more males and higher final A1C; their initial LVEF was insignificantly lower, factors not favoring survival [20-24]; tending to favor survival were insignificantly fewer with CAD (although all AA and NA patients were vascularized with normal stress tests), less Chronic Kidney Disease (CKD); and significantly more Angiotensin blocker therapy (ACEI or ARB, p<0.100) [20,25]. 11% more (r)-ALA patients required insulin. Control Group NA had significantly more females and lower final A1C; there were insignificantly higher initial LVEFs and insignificantly more patients on Empagliflozin, Liraglutid, and Metformin, tending to favor survival [26-29].
re SD patients had CAD causes most adult SDs [24]. Although more hypertensive (p<0.086); had greater use of Empagliflozin (p<0.100), Metformin (p<0.100), Liraglutid (p<0.100), higher final BMI (p<0.100), with more CAD (p<0.100); all were revascularized (normal myocardial perfusion stress tests). Fewer in Group AA took insulin (p<0.100). Initially, Group AA had 18.4% VT (1sustained) vs. 14.3% non-sustained in Group ND, p=0.3559.

| Group   | Group 5 | p    |
|---------|---------|------|
| N       | 62      | 28   |
| Male    | 61%     | 39%  | p<0.100 |
| Age (mean yrs) | 67   | 64   | p>0.100 |

Ethnicity
- Caucasian: 74% vs. 73% ns
- African Am: 23% vs. 24% ns
- Other: 3% vs. 2% ns

2 Dxs
- HTN: 95.00% vs. 86.00% ns
- HL: 80.00% vs. 82.00% ns

| Group   | Group 5 | p    |
|---------|---------|------|
| N       | 21      | 22   |
| Male    | 91%     | 41%  | p<0.100 |
| Age (mean yrs) | 66 ± 12.3 | 70 ± 11.5 | p<0.100 |

Ethnicity
- Caucasian: 81% vs. 73% ns
- African Am: 11% vs. 28% ns

SUPPLEMENTAL TABLES

Table 1: Survivor Patient Demographics.

Table 2 Non-Survivors. Group AD had significantly more males and higher AIC; there were insignificantly higher final BMI [24], lower LVEFs, more CHF, and less Metformin use, all tending unfavorably regarding survival. But 9% more took ACEI/ARBs (p<0.100). Control Group ND was 4 years older (p>0.100); QTc had no significance on SD, as SD increases when QTc is >450ms in males or >470ms in females [30]. Insignificantly more Group ND African Americans tends to favor SD [31]. CAD causes most adult SDs [24]. Although more SD patients had CAD vs. survivors, CAD prevalence was insignificantly different in Groups AD, ND.

Group AA vs. Group ND: Improved Group AA survival occurred despite Group ND having a normal final BMI (p=0.067), less HTN (p=0.021), greater use of Empagliflozin (p<0.100), Metformin (p<0.100), lower final AIC (p=0.034), and fewer males (p<0.100), all favoring less SCD in Group ND. DMII attenuates gender differences in SD [22]. Group ND was 3 yrs. Older (p=0.067) with more CAD (p<0.100); all were revascularized (normal myocardial perfusion stress tests). Fewer in Group AA took insulin (p<0.100). Initially, Group AA had 18.4% VT (1sustained) vs. 14.3% non-sustained in Group ND, p=0.3559.

| Group   | Group 5 | p    |
|---------|---------|------|
| N       | 21      | 22   |
| Male    | 91%     | 41%  | p<0.100 |
| Age (mean yrs) | 66 ± 12.3 | 70 ± 11.5 | p<0.100 |

Ethnicity
- Caucasian: 81% vs. 73% ns
- African Am: 11% vs. 28% ns

Note: 2° Dxs=Secondary Diagnosis; ACEI=Angiotensin Converting Enzyme Inhibitor; ARB=Angiotensin Renin Blocker; BB=Beta-Blocker; CCB=Calcium Channel Blocker; HL=Hyperlipidemia; Rx=therapy.

Table 2: Non-Survivor Patient Demographics (Sudden Death Patients).

| Group   | Group 5 | p    |
|---------|---------|------|
| N       | 21      | 22   |
| Male    | 91%     | 41%  | p<0.100 |
| Age (mean yrs) | 66 ± 12.3 | 70 ± 11.5 | p<0.100 |

Ethnicity
- Caucasian: 81% vs. 73% ns
- African Am: 11% vs. 28% ns

Note: HCTZ, hydrochlorothiazide. See Table 1 or Methods for other abbreviations.
LVEFs (60% vs. 48%, p<0.100), fewer males (p<0.100), and less CAD (p<0.100; revascularized with normal stress tests), mostly favoring survival. Fewer in Group NA took insulin (p<0.100). Initially, Group NA had 0% non-sustained VT vs. 16.7% in Group AD, p=0.1661.

**Autonomic Measures:** Table 3: Survivors and SCD patients initial to final autonomic Measures. Mean Bx LFa, decreased in survivors (p=0.045), increasing in SACD (p=0.039). Bx RFa, increased in 5590 patients (60%), by a mean 12.5% in survivors and severely decreased in 29/43 (67%) non-survivors, mean -59.5%, (p<0.0001). SB increased 17.6% in survivors, but had a greater increase in SACD to >2.5: +29.5% (p=0.064).

Non-Survivors demonstrated a more abnormal final alpha-S-response standing, SW (-24.4% vs. -13.8% [p=0.066]), indicating greater Bar receptor Reflex dysfunction, which increases SCD risk. PE upon standing developed more significantly in survivors (+65%) vs. SACD (+29%) because initial to final standing RFa increased in survivors vs. decreasing in SACD (p=0.022). In parallel, SACD patients experienced a dramatic 59.5% decrease in resting P in addition to SW. All P- and S-final values were lower in SACD, the lowest being resting P. Since HRV=S+P, HRV was lower in SACD (p<0.0001) mainly due to lower P.

**Survivors**

**Group-AA, Survivors with (r)-ALA:** (Table 4) A1C increased (increasing oxidative stress, p=0.047), inversely proportional to (r)-ALA dosage (p=0.071); but resting RFa increased proportionally (p=0.014). Average resting Bx LFa increased (p=0.095) as did resting Bx RFa (p=0.070). HRV increased. The mean initial standing response was SW. At final testing, 4 patients’ SW were relieved (p=0.097); Consequently, BRS improved. One more patient demonstrated PE (p=0.098) (standing RFa increased) proportional to (r)-ALA dosage.

![Table 3](https://www.auctoresonline.org)

**Table 3: Comparison between Survivors and Sudden Cardiac Death patients, Mean P&S Measures. See Methods for parameters’ normal ranges.**
Survivors’ Mortality Risk: 13% Group AA patients demonstrated CAN initially, improving to 8.1%, proportional to (r)-ALA dose (p=0.004). Group AA was the only Group that increased resting BxRFa (Table 4). Group AA’s final RFa increased 36.2%, correlating with the dose of (r)-ALA (p=0.014). Group AA’s increase in resting BxLFa (Table 4) was mitigated by the increase in resting BxRFa, so the SB change was insignificant. Group NA had no CAN initially; increasing to 3.6%. This group’s average resting BxLFa decreased (34.5%); BxRFa fell 7.6%. SB (the average of 4 sec. ratios, not the ratio of these reported averages) significantly increased 3.6% (p=0.088), increasing MACE risk. In Tables 4 and 5, Group AA’s BxLFa and BxRFa were initially lower than Group NA’s (p<0.100), indicating lower HRV. Group AA increased both, decreasing mortality risk (Table 4). Group NA decreased both BxLFa (Table 5) (p=0.075) and BxRFa (p=ns), indicating an accelerated progression towards increased mortality risk (decreased HRV).

Non-Survivors

Group AD, Non-Survivors with (r)-ALA: (Table 6) Initial P&S levels are below normal and lowest of all Groups (lowest HRV). Given their age, SB is high (but not >2.5). Final LFa increased (p=0.047); RFa decreased (p=0.098); and SB increased to 2.72. Resting P protects against VT/VF and silent ischemia [21,32-36]; seven progressed to CAN (p=0.080), not surprising since initial BxRFa was so severely depressed. Group AD was beyond help. Standing, 57% of Group AD initially demonstrated PE; 33% ended with PE (p=0.061) and 57% ended with SW (p=0.080), not surprising since initial BxRFa was so severely depressed.

Survivors’ Mortality Risk: Resting BxRFa decreased in both Groups (Tables 6&7): 10.5%, Group AD and 67.5%, Group ND (p=0.033); a higher risk of developing CAN. Final SB was >2.5 in both, which we have shown increases MACE 700% [18]. SB greater than 2.5 with CAN is particularly deadly in both Groups, and final average standing response was SW (impaired BRS), increasing SCD as well. BxLFa increased in Group AD (Table 6) by 109.1% vs. decreasing 38.6% in Group ND (Table 7, p=0.100), causing increased SB in Group AD.

In Group ND, despite the decrease in S, the severe decrease in resting BxRFa increased SB anyway. Two more patients had CAN. Non-survivors’ (r)ALA preserved their severely lowest P and S (LOWEST HRV) even in death. Group ND’s final BxLFa and BxRFa fell severely to the 2nd lowest among all Groups. CAN and high SB were most frequent in Groups AD and ND.

Traditional Standards Comparison: Comparing the gold standard of CARTs, without isometric hand-grip, to any abnormality of P&S

Note: (+), improved; (-), declined; Δ, change demonstrated; ns, not significant (p>0.100); See Table 1or Methods for other abbreviations.
of Group 1 and 30.0% of Group 2 patients; an overall unsatisfactory sensitivity of 41.4%.

**Discussion**

Administration of (r)ALA resulted in a 43% RRR of SCD, rather than the demographics that may have favored survival in Controls. Rapid separation of the SCD curves (Figure 1) strongly implies treatment effect. Lower initial HRV, Group 1 vs. Group 2, p<0.0001, predicted SCD: AA 1.83 vs. AD 0.82, p=0.0171; NA 4.14 vs. ND 3.09, p=0.0051. More initial CAN ((r)ALA 10.8% vs. Controls 6%, p=0.0013) and initial BRS dysfunction ((r)ALA 63.9% vs. Controls 58%, p=0.0044) predicted SCD better than recorded VT. (r)ALA preserved P and S vs. Controls. Those with the lowest P&S (HRV) died. Reduced HRV is a common thread in SCD Only Group AA demonstrated an increase in final, resting P (and HRV); P reduces VT/VF and silent ischemia [21,32-36], increasing 36.2% vs. a 7.6% decrease for Group NA, a 10.5% decrease for Group AD, and a 67.5% decrease for Group ND.

The progressive increase in the decline of resting P indicated mortality, from the lowest decline in resting P in Group NA, to the next greater decline in Group AD, to those with the greatest decline, Group ND (p<0.001). Changes in P were proportional to (r)ALA dose. These trends are not found in the other physiologic measures: BMI, LVEF, and QTc; and only different between the survivors’ A1Cs (Group AA vs. Group NA, p=0.034). Since SW and PE can cause both NOH and systemic HTN [9,10], DMII patients not on (r)ALA might experience orthostasis, or labile HTN. HTN could be secondary (neurogenic), and is over twice as well controlled treating the primary SW ± PE [9] than treating the BP per se. (r)ALA preserved P and S, especially P, in survivors and nonsurvivors. (r)ALA is a natural, powerful thiol antioxidant. (r)ALA restores and recycles vitamins A,C,E and glutathione [9,10,34].

It improves hyperglycemia, endothelial dysfunction, nitric oxide levels (protective against VT/VF, silent ischemia [37-40]), reduces nuclear kappa B, and is essential for certain mitochondrial oxidative enzymes. (r)ALA prevents diabetic-induced reduction of the afferent limb function of the baroreceptor reflex (BR) [41], reducing MACE. SW, found in 50% to 74% of patients, failed to correct in 88% of Group NA and all SCD patients. SW disappeared substantially only in Group AA, 59.7% reduced to 53.2%, p=0.097, decreasing SCD risk. The other most common, and most important, P&S finding was low resting P in 56% to 81% of patients, improving only in Group AA (initial 56%, final 9%; p=0.070), vs. Group NA (initial 29%, final 43%; p=0.098), and worsening most severely in Group ND patients, a 67% reduction in RFa vs. 10.5% reduction in Group AD (p=0.020).

CAN decreased 37.5% in Group AA vs. an increase of 67% in Group ND. 29% of Group AD had high SB vs. 50% in Group ND (p=0.037). More CAN in Group 2 increased mortality; high SB increased mortality risk in Group 1. Group 1’s autonomic profiles generally stabilized or improved (HRV); Group 2’s deteriorated, especially a 59.5% decrease in resting P, reducing Group 2’s ability to combat VT/VF, silent ischemia, and life stresses. Standard deviations decreased over time, with the most decreases correlating with the (r)ALA dosage. The pleotropic effects of (r)ALA likely contributed to SCD reduction. Increased nitric oxide improves P&S, endothelial dysfunction, protects against VT/VF and silent ischemia [37-40]. Decreased nitric oxide levels prolong QTc [37]. Improved mitochondrial function should reduce SCD also [42]. Asymptomatic SW (BR dysfunction) was the most common presentation of DAN. Approximately 90% of patients had HTN, presumed to be essential (primary), not possibly secondary to DAN. Ultimately, CAN with, or without, dangerously high SB can develop while under our care. How simple it is to diagnose and treat dysautonomia early; how tragic it may be not to.

**References**

1. Aune D, Schlesinger S, Norat T and Riboli E. Diabetes mellitus and the risk of sudden cardiac death: a systematic review and meta-analysis of prospective studies (2018) Nutr Metab Cardiovasc Dis 28:543-556. https://doi.org/10.1016/j.numecd.2018.02.011
2. Vinik A, Mitchell B, Maser R and Freeman R. Diabetic Autonomic Neuropathy (2003) Diabetes Care 26: 1553-1579. https://doi.org/10.2337/diacare.26.5.1553
3. Ewing D, Campbell I and Clarke B. The natural history of diabetic autonomic neuropathy (1980) Q J Med Winter 49: 95-108.
4. Spallone V, Ziegler D, Freeman R, Bernardi L, Frontoni S, et al. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management (2011) Diabetes Metab Res Rev 27: 639-653. https://doi.org/10.1002/dmr.1239
5. Tsuchi H, Larson M, Venditti F, Manders E, Evans J, et al. Impact of reduced heart rate variability on risk of cardiac events: The Framingham Heart Study (1996) Circulation 94: 2850-2855. https://doi.org/10.1161/01.cir.94.11.2850
6. Rolo A and Palmeira C. Diabetes and mitochondrial function: role of hyperglycemia and oxidative stress (2006) Toxicol Appl Pharmacol 212: 167-178. https://doi.org/10.1016/j.taap.2006.01.003
7. Hussain N and Adrian T. Diabetic Neuropathy: Update on pathophysiological mechanism and the possible involvement of glutamate pathways (2017) Curr Diabet Rev 13: 488-497. https://doi.org/10.2174/1573399812666160624122605
8. Yorek M. The role of oxidative stress in diabetic vascular and neural disease (2003) Free Radic Res 37: 471-480.
9. Murray G and Colombo J. The feasibility of blood pressure control with autonomic-assisted hypertension therapy versus JNC8 therapy (2020) Clinical Cardiol Cardiovascular Med 4:1-5. https://doi.org/10.31579/2641-0419/01595
10. Murray G and Colombo J. (r)Alpha lipoic acid is a safe, effective pharmacologic therapy of chronic orthostatic hypotension associated with low sympathetic tone (2019) Int J Angiol 28: 188-193. https://doi.org/10.31579/2641-0419/0155
11. Aysin B, Colombo J and Aysin E. Comparison of HRV analysis methods during orthostatic challenge: HRV with respiration or without? 2007 29th Int Conf IEEE EMBS Lyon, France. https://doi.org/10.1109/embs.2007.4353474
12. Akselrod S, Gordon D, Ubel F, Shannon D, Berger A, et al. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control (1981) Sci 213: 220-222. https://doi.org/10.1126/science.6166045
13. Akselrod S, Gordon D, Madwed J, Snidman N, Shannon D, et al. Hemodynamic regulation: Investigation by spectral analysis of heart rate fluctuation: a quantitative tool for the investigation of the baroreceptor reflex (BR) (1981) J Physiol 220: H873-880. https://doi.org/10.1126/j.numecd.6166045
14. Akselrod S, Eliash S, Oz O and Cohen S. Hemodynamic function should reduce SCD also (1987) Am J Physiol 253: H176-H183. https://doi.org/10.1152/ajpheart.1987.253.1.h176
15. Akselrod S. Spectral analysis of fluctuations in cardiovascular parameters: a quantitative tool for the investigation of mitochondrial dysfunction, protects against VT/VF and silent ischemia [37-40]. Decreased nitric oxide levels prolong QTc [37]. Improved mitochondrial function should reduce SCD also [42]. Asymptomatic SW (BR dysfunction) was the most common presentation of DAN.
autonomic control. Trends Pharmacol Sci 9: 6-9.
https://doi.org/10.1016/0165-6147(88)90230-1

16. Colombo J, Arora R, DePace N and Vinik A. Clinical Autonomic Dysfunction: Measurement, Indications, Therapies, and Outcomes (2014) Springer Science, USA.

17. Bloomfield DM, Kaufman ES, Bigger JT Jr, Fleiss J, Rolnitzky L, et al. Passive head-up tilt and actively standing up produce similar overall changes in autonomic balance (1997) Am Heart J 134: 316-320. https://doi.org/10.1016/s0002-8703(97)70140-6

18. Murray G and Colombo J. Routine measurements of cardiac parasympathetic and sympathetic nervous systems assists in primary and secondary risk stratification and management of cardiovascular clinic patients (2019) Clinical Cardiovascular Med 3: 27-33. https://doi.org/10.33805/2639.6807.122

19. Korei A, Kempler M, Istenes I, Vagi D, Putz Z, et al. Why not use the handgrip test in the assessment of cardiovascular autonomic neuropathy among patients with diabetes mellitus? (2017) Curr Vasc Pharmacol 15: 66-73. https://doi.org/10.2174/1570161114666160822154351

20. Kannel W and Schatzkin A. Sudden death: lessons from subsets in population studies (1985) J Am Coll Cardiol 5: 141B-149B. https://doi.org/10.1016/s0735-1097(85)80545-3

21. Umetani K, Singer DH, McGraty R, and Atkinson M. Twenty-four hour time domain heart rate variability and heart rate: Relations to age and gender over nine decades (1998) JACC 31: 593-601. https://doi.org/10.1016/s0735-1097(97)00554-8

22. Kucharska-Newton A, Couper D, Pankow J, Prineas R, Rea T, et al. Diabetes and the risk of sudden cardiac death, the Atherosclerosis Risk in Communities Study (2010) Acta Diabetol 47: 161-168.

23. Patel R, Moorthy M, Chiuve S, Pradhan A, Cook N, et al. Hemoglobin A1c levels and risk of sudden cardiac death: A nested case-control study (2017) Heart Rhythm 14: 72-78. https://doi.org/10.1016/j.hrthm.2016.08.044

24. Kuriachan V, Sumner G and Mitchell L. Sudden cardiac death (2015) Curr Probl Cardiol 40: 133-200.

25. Aljaroudi W, Refaat M, HabibR Al-Shaar L, Singh M, Gutmann R, et.al. Effect of angiotensin-converting enzyme inhibitors and receptor blockers on appropriate implantable cardiac defibrillator shock in patients with severe systolic heart failure (from the GRADE Multicenter Study (2015) Am J Cardiol 1: 924-931. https://doi.org/10.3410/f.725363020.793512706

26. Suttar N, McLaren J, Kristensen S, Priess D and McMurray J. SGLT2 inhibition and cardiovascular events: why did EMPA-REG outcomes surprise and what were the likely mechanisms? Diabetologia (2016) 59: 1333-1339. https://doi.org/10.1007/s00125-016-3956-x

27. Roussel R, Travert F, Pasquet B, Wilson P, Smith S, et al. Metformin use and mortality among patients with diabetes and atherothrombosis (2010) Arch Intern Med 170: 1892-1899. https://doi.org/10.1001/archinternmed.2010.409

28. Simard P, Presse N, Rov L, Dorais M, White-Guay B, et al. Association between metformin adherence and all-cause mortality among new users of metformin: A nested case-control study (2018) Ann Pharmacother 52: 305-313. https://doi.org/10.1177/1060028017743517

29. Costa E, Goncalves A, Areas M and Morgabel R. Effects of metformin on QT and QTc interval dispersion of diabetic rats (2008) Arg Bras Cardiol 90: 232-238.

30. Straus S, Kors J, De Bruin M, van der Hooft C, Hofman A, et al. Prolonged QTc interval and risk of sudden cardiac death in a population of older adults (2006) J Am Coll Cardiol 47: 362-367. https://doi.org/10.1016/j.jacc.2005.08.067

31. Reiner K, Rusinaru C and Chugh S. Race, ethnicity, and the risk of sudden death (2019) Trends Cardiovasc Med 29: 120-126.

32. Curtis BM and O’Keefe JH. Autonomic tone as a cardiovascular risk factor: The dangers of chronic fight or flight (2002) Mayo Clin Proc 77: 45-54. https://doi.org/10.4065/77.1.45

33. Kalla M, Herring N and Patterson D. Cardiac sympatho-vagal balance and ventricular arrhythmia (2016) Auton Neurosci 199: 29-37. https://dx.doi.org/10.1016%2Fj.autneu.2016.08.016

34. Gomes M and Negrato C. Alpha lipoic acid as a pleotropic compound with potential therapeutic use in diabetes and other chronic diseases (2014) Diabetol Metab Syndr 6: 80-89. https://doi.org/10.1186/1758-9966-6-80

35. MaserR and Lenhard M.An overview of the effect of weight loss on cardiovascular autonomic function (2017) Curr Diabetess Rev 3: 204-211.

36. Kurpeta M, Trzos E, Drozdz J, Bednarkiewicz Z and Kuzmenska- Pakuta M. Myocardialischimia and autonomic activity in dippers and non-dippers with coronary artery disease: Assessment of normotensive and hypertensive patients (2002) Int J Cardiol 83: 133-142. https://doi.org/10.1016/s0167-5273(02)00031-1

37. Eijgelsheim M, Aamoudas A, Rivadeneira F, Kors J, Wittman J, et.al. Identification of a common variant at the NOS1AP locus strongly associated to QT-interval prolongation (2009) Human Mol Genet 18: 347-357. https://doi.org/10.1093/hmg/ddn341

38. Rakhit A, Maguire C, Wakimoto H, Gehrmann J, Li G, et.al. In vivo electrophysiologic studies in endothelial nitric oxide synthase (eNOS)-deficient mice (2001) J Cardiovasc Electrophysiol 12: 1295-1301. https://doi.org/10.1046/j.1540-8167.2001.01295.x

39. Horinaka S, Kobayashi N, Yabe A, Asakawa H, Yagi H, et.al. Nicorandil protects against lethal ventricular arrhythmias and up-regulates endothelial nitric acid synthase expression and sulfonyleura receptor 2 mRNA in conscious rats with acute myocardial infarction (2004) Cardiovasc Drugs Ther 18: 13-22. https://doi.org/10.1023/b/card.0000025751.82774.a9

40. Hino V, Ohkubo T, Katsub Y and Ogawa S. Changes in endothelium-derived vascular regulatory factors during dolutabamine-stress-induced silent myocardial ischemia in patients with Kawasaki disease (1999) Jpn Circ J 63: 503-508. https://doi.org/10.1253/jcj.63.503

41. Gouty S, Regalia J, Cai F and Helke C. Alpha-lipoic acid treatment prevents the diabetes- induced attenuation of the afferent limb of the baroreceptor reflex in rats (2003) Auton Neurosci 108: 32-44. https://doi.org/10.1016/j.autneu.2003.08.004

42. DePace NL and Colombo J. Autonomic and Mitochondrial Dysfunction in Clinical Diseases: Diagnostic, Prevention, and Therapy (2019) Springer Science + Business Media, United States.