Published in final edited form as:

J Electrocardiol. 2017 ; 50(6): 798–801. doi:10.1016/j.jelectrocard.2017.08.012.

Risk stratification of sudden cardiac death in hypertension

Larisa G. Tereshchenko, MD, PhD¹, Elsayed Z. Soliman, MD, MSc, MS², Barry R. Davis, MD, PhD³, and Suzanne Oparil, MD⁴

The Knight Cardiovascular Institute, Oregon Health & Science University, Portland, OR

²Epidemiological Cardiology Research Center (EPICARE), Division of Public Health Sciences and Department of Medicine, Cardiology Section, Wake Forest School of Medicine, Winston Salem, NC

³University of Texas School of Public Health, Houston, TX

⁴University of Alabama at Birmingham, Department of Medicine, School of Medicine, Birmingham, AL

Abstract

In the United States, up to 450,000 people per year die suddenly; an average of 1 sudden death every 70 seconds. Strategies for preventing sudden cardiac death are urgently needed. Systemic arterial hypertension is a major risk factor for sudden cardiac death and the increasing burden of hypertension is a worldwide problem. The lifetime risk of sudden cardiac death at 30 years of age is higher by 30% in individuals with hypertension. Each 20/10 mm Hg increase in systolic/diastolic blood pressure, is associated with a 20% additional increase in sudden cardiac death risk. Theoretically, antihypertensive treatment should be an effective strategy for sudden cardiac death prevention. However, a recent meta-analysis of 15 randomized controlled trials showed that antihypertensive treatment does not reduce the incidence of sudden cardiac death. This manuscript reviews ECG predictors of sudden cardiac death and the importance of risk stratification for appropriate management of hypertension.

Despite advances in the treatment and prevention of cardiovascular disease (CVD) and reduction in total cardiovascular mortality, the incidence of SCD remains high. In the United States, up to 450,000 sudden cardiac deaths (SCDs) [1], and an estimated 347,000 out-of-hospital sudden cardiac arrests (SCAs) in adults occur annually[2]. Survival to discharge has been very low (7–8%) over the last three decades[3], although a slightly positive trend for improvement was observed recently[4]. Thus, development of SCA/SCD prevention is urgently needed. In up to half of SCDs, cardiac arrest is the first manifestation of CVD[5]. While overall cardiovascular mortality in the community has declined about 30% [6; 7], the

Correspondence: Larisa Tereshchenko, 3181 SW Sam Jackson Park Rd; UHN62; Portland, OR, 97239. tereshch@ohsu.edu. Phone: 503-494-7400; Fax: 503-494-8550.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflict of interest: none

incidence of SCD has not[8]. The San Francisco POstmortem Systematic InvesTigation of Sudden Cardiac Death (POST SCD) Study[9; 10], which performed comprehensive pre- and post- mortem investigation (83% autopsy rate) of SCD cases in 2011–2014 in the San Francisco area confirmed that sudden arrhythmic death due to ventricular tachyarrhythmia remains the most frequent underlying cause of SCD in the general population. Failure to reduce the rate of arrhythmic SCD despite the successful reduction of cardiovascular mortality suggests that electrophysiological substrate and electrophysiological mechanisms of SCD in the community are incompletely understood and therefore, have not been appropriately targeted. Individuals at risk have not been timely identified.

Hypertension (HTN) is a major risk factor for SCD and CVD [11; 12]. The lifetime risk of SCA/SCD at 30 years of age is significantly (30%) higher in individuals with HTN [12]. Each 20/10 mm Hg increase in systolic/diastolic blood pressure (BP), adjusted for age and sex, is associated with a 20% additional increase in SCD/SCA risk [12]. HTN is associated with a significant and ever rising burden of morbidity, mortality, loss of productivity, and cost. A comprehensive global scale study[13] demonstrated a 1.4-fold increase in HTN-associated mortality in 2015, as compared to 1990. In 2015 an estimated 3.5 billion adults had elevated systolic blood pressure (SBP) 110–115 mm Hg, and 874 million adults had SBP of 140 mm Hg. The increasing burden of HTN is a worldwide problem. Aging of the population and increasing prevalence of obesity are important contributors to the increasing prevalence of HTN. In 2015 7.8 million deaths and 143 million disability-adjusted-life-years were estimated to be related to SBP of 140 mmHg or higher[13]. Per the 2016 AHA statistics[2], the overall prevalence of HTN among U.S. adults aged 20 and older is about 33%, representing an estimated 80 million US adults, of whom an estimated 50% have uncontrolled HTN. Moreover, more than 12% of U.S. adults have masked HTN: nearly 1 in 8 adults with non-elevated clinic SBP may be misclassified as not having HTN[14]. However, in spite of a well-known fact that HTN is the number one risk factor for SCD, blood pressure control is not mentioned in a new 2016 AHA/ACC Clinical Performance and Quality Measures for Prevention of Sudden Cardiac Death[15].

Multiple mechanisms participate in arrhythmogenesis associated with HTN. HTN triggers cardiac remodeling and development of left ventricular hypertrophy (LVH), causing subclinical organ damage, which eventually leads to clinically manifest CVD, acute cardiovascular events, and ultimately, cardiovascular death[16]. LVH affects ventricular repolarization[17–19] and increases the risk of ventricular arrhythmias. LVH[20], fibrosis[21], and inflammation[22] are well-known mechanisms of the development of an abnormal electrophysiological substrate, associated with high risk of life-threatening ventricular arrhythmias as an underlying cause of SCD. The beneficial effect of BP reduction on CVD risk is well-known[23; 24].

Large cohort studies [e.g. Framingham Heart Study[25], MRFIT[26]] showed continuous linear relationships between SBP and CVD risk. Consistently with observational data, the recent randomized controlled trial (RCT) SPRINT[27] showed that among patients at high risk for cardiovascular events but without diabetes, targeting an SBP of less than 120 mm Hg, as compared with less than 140 mm Hg, is more beneficial: it resulted in lower rates of fatal and nonfatal major cardiovascular events and all-cause mortality. Meta-analysis of 147

randomized trials showed that HTN treatment is associated with approximately a 25% reduction in initial risk of CVD development[28]. The beneficial effect of BP lowering was observed in patients of all ages with moderate to severe HTN[29; 30]. However, previous studies did not focus on prevention of SCD by anti-hypertensive treatment. A recent comprehensive meta-analysis by Taverny et al[31] is the only meta-analysis, which focused on the SCD outcome. Strikingly, Taverny et al[31] showed that while HTN treatment reduces the incidence of fatal and non-fatal myocardial infarction (MI), antihypertensive drugs do NOT reduce the incidence of SCD. Taverny et al[31] included RCTs that compared first line antihypertensive drugs to placebo or control (no therapy). For successful primary prevention of SCD in HTN patients, it is crucial to characterize associations between BP response on treatment (visit-to-visit variability, degree of BP reduction) and electrophysiological substrate in order to understand causes of failure to reduce SCD incidence by antihypertensive drugs, and identify subgroup(s) of patients in whom BP reduction DOES reduce the incidence of SCD.

Widely used major classes of antihypertensive drugs include angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), and diuretics. Current guidelines for Management of High Blood Pressure in Adults[32] developed by the Eighth Joint National Committee (JNC 8) suggest that any of these medications (thiazide-type diuretic, ACEi, ARB, or CCB) might be used for initial antihypertensive treatment in whites without diabetes or chronic kidney disease (CKD). Blacks without CKD have a choice of thiazide-type diuretic or CCB. Renin inhibitors, beta-adrenergic blockers (BB), alpha-adrenergic blockers (AB), combined alpha- and beta-blockers (ABB), central sympatholytics, and direct vasodilators are used less frequently. ALLHAT was the largest randomized double-blinded trial that compared treatment with different classes of antihypertensive drugs [33–35]. ALLHAT showed that benefits of CCB (represented by amlodipine), ACEi (represented by lisinopril), and a diuretic (represented by chlorthalidone) in reducing the incidence of coronary heart disease (CHD) events did not differ between treatment arms.

The Losartan Intervention for End Point Reduction in Hypertension (LIFE) RCT demonstrated reduction of SCD risk in patients who responded to antihypertensive treatment by reducing ECG-LVH [36]. The effect of ECG-LVH reduction was independent of treatment arm (BB atenolol vs. ARB losartan), BP reduction, prevalent CHD, and other cardiovascular risk factors in hypertensive patients with LVH. Similarly to ALLHAT, LIFE did not show the difference in life-saving benefit between the treatment arms (BB vs. ARB). Importantly, LIFE showed that antihypertensive therapy targeted at regression or prevention of ECG-LVH might reduce the risk of SCD. Reversal of end-organ damage with antihypertensive drugs has been studied for many years. It has been shown that all classes of antihypertensive drugs (diuretics, BB, ACEi, ARB, CCB) reverse LVH and reduce left ventricular (LV) mass measured by echocardiography [37]. Moreover, some data suggest that ACEi, ARB, and CCB are more potent reducers of LVH than BB and diuretics [37].

Differences between LVH measured by ECG vs. LV mass measured by imaging modalities[38] are well known, and likely reflect true differences between the cardiac anatomy and the electrophysiological substrate. Two hearts with the same LV mass, one in a

healthy endurance athlete, and another in a HTN patient, have clear differences in the electrophysiological substrate and risk of SCD. Adaptive/physiologic LVH has no signs of interstitial fibrosis, and, therefore, can reverse after approximately three months of complete cessation of vigorous sporting activity [39; 40]. In contrast, pathological LVH is characterized by the presence of fibrosis [41–43]. There is strong evidence that ECG-LVH characterizes an abnormal electrophysiological substrate, which is associated with SCD and other cardiovascular outcomes independent of LV mass and BP control [44–46]. However, there are limitations of ECG-LVH as a measure of the electrophysiological substrate, as there are more than a dozen of ECG-LVH definitions with poor agreement among them [38].

The abnormal electrophysiological substrate is a complex phenomenon. Electrocardiography is built on the assumption of a heart represented by a dipole vector, rotating around a virtual electrical center within the heart. By the design, surface 12-lead ECG is a powerful tool for characterization of global electrophysiological properties of the heart. Recently, we conceptualized the ECG-GEH phenomenon [11; 47], quantified by 5 ECG parameters: spatial ventricular gradient [47] (SVG) magnitude, azimuth, and elevation, spatial QRS-T angle [48], and sum absolute QRST integral (SAI QRST) [49–55]. In two large community-based prospective cohorts (Atherosclerosis Risk In Communities [ARIC], and Cardiovascular Health Study [CHS]) GEH was independently associated with SCD (after adjustment for prevalent CVD, its risk factors, and traditional ECG markers of SCD risk, including ECG-LVH [11]. Moreover, we showed that ECG-GEH is dynamic [11]. Increase in GEH was associated with an incremental increase in SCD risk, whereas decreasing GEH over time was associated with a trend towards lower SCD risk. Further studies are needed to answer a question whether antihypertensive treatment can decrease ECG-GEH and whether decreasing GEH mediates SCD risk reduction in HTN.

Acknowledgments

Funding Sources:

This research was supported in part by the National Institute of Health #1R01HL118277.

References

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, 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. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, et al. Writing Group M. Executive Summary: Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation*. 2016; 133(4):447–54. [PubMed: 26811276]
3. Sasson C, Rogers MA, Dahl J, Kellermann AL. Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes*. 2010; 3(1):63–81. [PubMed: 20123673]
4. Daya MR, Schmicker RH, Zive DM, Rea TD, Nichol G, Buick JE, et al. Out-of-hospital cardiac arrest survival improving over time: Results from the Resuscitation Outcomes Consortium (ROC). *Resuscitation*. 2015; 91:108–15. [PubMed: 25676321]
5. Myerburg RJ, Junttila MJ. Sudden cardiac death caused by coronary heart disease. *Circulation*. 2012; 125(8):1043–52. [PubMed: 22371442]

6. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics-2012 update: a report from the American Heart Association. *Circulation*. 2012; 125(1):e2–e220. [PubMed: 22179539]
7. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Executive summary: heart disease and stroke statistics-2012 update: a report from the American Heart Association. *Circulation*. 2012; 125(1):188–97. [PubMed: 22215894]
8. Kong MH, Fonarow GC, Peterson ED, Curtis AB, Hernandez AF, Sanders GD, et al. Systematic Review of the Incidence of Sudden Cardiac Death in the United States. *Journal of the American College of Cardiology*. 2011; 57(7):794–801. [PubMed: 21310315]
9. Steinhaus DA, Vittinghoff E, Moffatt E, Hart AP, Ursell P, Tseng ZH. Characteristics of sudden arrhythmic death in a diverse, urban community. *American Heart Journal*. 2012; 163(1):125–31. [PubMed: 22172446]
10. Kim AS, Moffatt E, Ursell PC, Devinsky O, Olgin J, Tseng ZH. Sudden neurologic death masquerading as out-of-hospital sudden cardiac death. *Neurology*. 2016; 87(16):1669–73. [PubMed: 27638923]
11. Waks JW, Sitlani CM, Soliman EZ, Kabir M, Ghafoori E, Biggs ML, et al. Global Electric Heterogeneity Risk Score for Prediction of Sudden Cardiac Death in the General Population: The Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health (CHS) Studies. *Circulation*. 2016; 133(23):2222–34. [PubMed: 27081116]
12. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *Lancet*. 2014; 383(9932):1899–911. [PubMed: 24881994]
13. Forouzanfar MH, Liu P, Roth GA, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm hg, 1990–2015. *JAMA*. 2017; 317(2):165–82. [PubMed: 28097354]
14. Wang YC, Shimbo D, Muntner P, Moran AE, Krakoff LR, Schwartz JE. Prevalence of Masked Hypertension Among US Adults With Nonelevated Clinic Blood Pressure. *Am J Epidemiol*. 2017; doi: 10.1093/aje/kww237
15. Al-Khatib SM, Yancy CW, Solis P, Becker L, Benjamin EJ, et al. Writing Committee M. 2016 AHA/ACC Clinical Performance and Quality Measures for Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *J Am Coll Cardiol*. 2016; doi: 10.1016/j.jacc.2016.09.933
16. Zanchetti A. Hypertension: Cardiac hypertrophy as a target of antihypertensive therapy. *Nat Rev Cardiol*. 2010; 7(2):66–7. [PubMed: 20104240]
17. Marionneau C, Brunet S, Flagg TP, Pilgram TK, Demolombe S, Nerbonne JM. Distinct cellular and molecular mechanisms underlie functional remodeling of repolarizing K⁺ currents with left ventricular hypertrophy. *Circ Res*. 2008; 102(11):1406–15. [PubMed: 18451341]
18. Xu X, Rials SJ, Wu Y, Salata JJ, Liu T, Bharucha DB, et al. Left ventricular hypertrophy decreases slowly but not rapidly activating delayed rectifier potassium currents of epicardial and endocardial myocytes in rabbits. *Circulation*. 2001; 103(11):1585–90. [PubMed: 11257089]
19. Yang KC, Foeger NC, Marionneau C, Jay PY, McMullen JR, Nerbonne JM. Homeostatic regulation of electrical excitability in physiological cardiac hypertrophy. *J Physiol*. 2010; 588(Pt 24):5015–32. [PubMed: 20974681]
20. Samak M, Fatullayev J, Sabashnikov A, Zerrouh M, Schmack B, Farag M, et al. Cardiac Hypertrophy: An Introduction to Molecular and Cellular Basis. *Med Sci Monit Basic Res*. 2016; 22:75–9. [PubMed: 27450399]
21. Jalil JE, Doering CW, Janicki JS, Pick R, Shroff SG, Weber KT. Fibrillar collagen and myocardial stiffness in the intact hypertrophied rat left ventricle. *Circ Res*. 1989; 64(6):1041–50. [PubMed: 2524288]
22. Frohlich ED, Gonzalez A, Diez J. Hypertensive left ventricular hypertrophy risk: beyond adaptive cardiomyocytic hypertrophy. *Journal of hypertension*. 2011; 29(1):17–26. [PubMed: 21045723]
23. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. *Jama*. 1967; 202(11):1028–34. [PubMed: 4862069]

24. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. *Jama*. 1991; 265(24):3255–64. [PubMed: 2046107]
25. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J 3rd. Factors of risk in the development of coronary heart disease--six year follow-up experience. The Framingham Study. *Ann Intern Med*. 1961; 55:33–50. [PubMed: 13751193]
26. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks. US population data. *Arch Intern Med*. 1993; 153(5):598–615. [PubMed: 8439223]
27. Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med*. 2015; 373(22):2103–16. [PubMed: 26551272]
28. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. 2009; 338:b1665. [PubMed: 19454737]
29. Musini VM, Tejani AM, Bassett K, Wright JM. Pharmacotherapy for hypertension in the elderly. The Cochrane database of systematic reviews. 2009; :Cd000028. 2009/10/13. doi: 10.1002/14651858.CD000028.pub24 [PubMed: 19821263]
30. Gueyffier F, Bulpitt C, Boissel JP, Schron E, Ekblom T, Fagard R, et al. Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. INDANA Group. *Lancet*. 1999; 353(9155):793–6. [PubMed: 10459960]
31. Taverny G, Mimouni Y, Ledigarcher A, Chevalier P, Thijs L, Wright JM, et al. Antihypertensive pharmacotherapy for prevention of sudden cardiac death in hypertensive individuals. The Cochrane database of systematic reviews. 2016; 3:Cd011745. [PubMed: 26961575]
32. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014; 311(5):507–20. [PubMed: 24352797]
33. Davis BR, Cutler JA, Gordon DJ, Furberg CD, Wright JT Jr, Cushman WC, et al. Rationale and design for the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT Research Group. *Am J Hypertens*. 1996; 9(4 Pt 1):342–60. [PubMed: 8722437]
34. Davis BR, Cutler JA, Furberg CD, Wright JT, Farber MA, Felicetta JV, et al. Relationship of antihypertensive treatment regimens and change in blood pressure to risk for heart failure in hypertensive patients randomly assigned to doxazosin or chlorthalidone: further analyses from the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial. *Ann Intern Med*. 2002; 137(5 Part 1):313–20. [PubMed: 12204014]
35. Davis BR, Furberg CD, Wright JT Jr, Cutler JA, Whelton P. ALLHAT: setting the record straight. *Ann Intern Med*. 2004; 141(1):39–46. [PubMed: 15238369]
36. Wachtell K, Okin PM, Olsen MH, Dahlöf B, Devereux RB, Ibsen H, et al. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive therapy and reduction in sudden cardiac death: the LIFE Study. *Circulation*. 2007; 116(7):700–5. [PubMed: 17664372]
37. Klingbeil AU, Schneider M, Martus P, Messerli FH, Schmieder RE. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. *Am J Med*. 2003; 115(1):41–6. [PubMed: 12867233]
38. Jain A, Tandri H, Dalal D, Chahal H, Soliman EZ, Prineas RJ, et al. Diagnostic and prognostic utility of electrocardiography for left ventricular hypertrophy defined by magnetic resonance imaging in relationship to ethnicity: the Multi-Ethnic Study of Atherosclerosis (MESA). *Am Heart J*. 2010; 159(4):652–8. [PubMed: 20362725]
39. Basavarajaiah S, Wilson M, Junagde S, Jackson G, Whyte G, Sharma S, et al. Physiological left ventricular hypertrophy or hypertrophic cardiomyopathy in an elite adolescent athlete: role of detraining in resolving the clinical dilemma. *Br J Sports Med*. 2006; 40(8):727–9. discussion 9. [PubMed: 16864569]

40. Maron BJ, Pelliccia A, Spataro A, Granata M. Reduction in left ventricular wall thickness after deconditioning in highly trained Olympic athletes. *Br Heart J.* 1993; 69(2):125–8. [PubMed: 8435237]
41. Pelliccia A, Maron MS, Maron BJ. Assessment of left ventricular hypertrophy in a trained athlete: differential diagnosis of physiologic athlete's heart from pathologic hypertrophy. *Prog Cardiovasc Dis.* 2012; 54(5):387–96. [PubMed: 22386289]
42. Kahan T, Bergfeldt L. Left ventricular hypertrophy in hypertension: its arrhythmogenic potential. *Heart.* 2005; 91(2):250–6. [PubMed: 15657259]
43. Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. *Circulation.* 1991; 83(6):1849. [PubMed: 1828192]
44. Leigh JA, O'neal WT, Soliman EZ. Electrocardiographic Left Ventricular Hypertrophy as a Predictor of Cardiovascular Disease Independent of Left Ventricular Anatomy in Subjects Aged 65 Years. *American Journal of Cardiology.* 117(11):1831–5.
45. Oseni AO, Qureshi WT, Almahmoud MF, Bertoni AG, Bluemke DA, Hundley WG, et al. Left ventricular hypertrophy by ECG versus cardiac MRI as a predictor for heart failure. *Heart.* 2017; 103(1):49–54. [PubMed: 27486144]
46. Bang CN, Devereux RB, Okin PM. Regression of electrocardiographic left ventricular hypertrophy or strain is associated with lower incidence of cardiovascular morbidity and mortality in hypertensive patients independent of blood pressure reduction - A LIFE review. *J Electrocardiol.* 2014; 47(5):630–5. [PubMed: 25052475]
47. Waks JW, Tereshchenko LG. Global electrical heterogeneity: A review of the spatial ventricular gradient. *J Electrocardiol.* 2016; 49(6):824–30. [PubMed: 27539162]
48. Oehler A, Feldman T, Henrikson CA, Tereshchenko LG. QRS-T Angle: A Review. *Ann Noninvasive Electrocardiol.* 2014; 19(6):534–42. [PubMed: 25201032]
49. Tereshchenko LG, Cheng A, Fetis BJ, Marine JE, Spragg DD, Sinha S, et al. Ventricular arrhythmia is predicted by sum absolute QRST integral but not by QRS width. *J Electrocardiol.* 2010; 43(6):548–52. [PubMed: 20832820]
50. Tereshchenko LG, Cheng AA, Fetis BJ, Butcher B, Marine JE, Spragg DD, et al. A new electrocardiogram marker to identify patients at low risk for ventricular tachyarrhythmias: sum magnitude of the absolute QRST integral. *Journal of Electrocardiology.* 2011; 44(2):208–16. [PubMed: 21093871]
51. Tereshchenko LG, McNitt S, Han L, Berger RD, Zareba W. ECG marker of adverse electrical remodeling post-myocardial infarction predicts outcomes in MADIT II study. *PLoS One.* 2012; 7(12):e51812. [PubMed: 23251630]
52. Tereshchenko LG, Cheng A, Park J, Wold N, Meyer TE, Gold MR, et al. Novel measure of electrical dyssynchrony predicts response in cardiac resynchronization therapy: Results from the SMART-AV Trial. *Heart Rhythm.* 2015; 12(12):2402–10. [PubMed: 26272523]
53. Tereshchenko LG, Ghafoori E, Kabir MM, Kowalsky M. Electrical Dyssynchrony on Noninvasive Electrocardiographic Mapping correlates with SAI QRST on surface ECG. *Computing in cardiology.* 2015; 42:69–72. [PubMed: 27011950]
54. Jacobsson J, Borgquist R, Reitan C, Ghafoori E, Chatterjee NA, Kabir M, et al. Usefulness of the Sum Absolute QRST Integral to Predict Outcomes in Patients Receiving Cardiac Resynchronization Therapy. *Am J Cardiol.* 2016; 118(3):389–95. [PubMed: 27265674]
55. Tereshchenko LG, Feeny A, Shelton E, Metkus T, Stolbach A, Mavunga E, et al. Dynamic Changes in High-Sensitivity Cardiac Troponin I Are Associated with Dynamic Changes in Sum Absolute QRST Integral on Surface Electrocardiogram in Acute Decompensated Heart Failure. *Ann Noninvasive Electrocardiol.* 2017; 22(1)