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(54) **MARKER FOR ARRHYTHMIA RISK**

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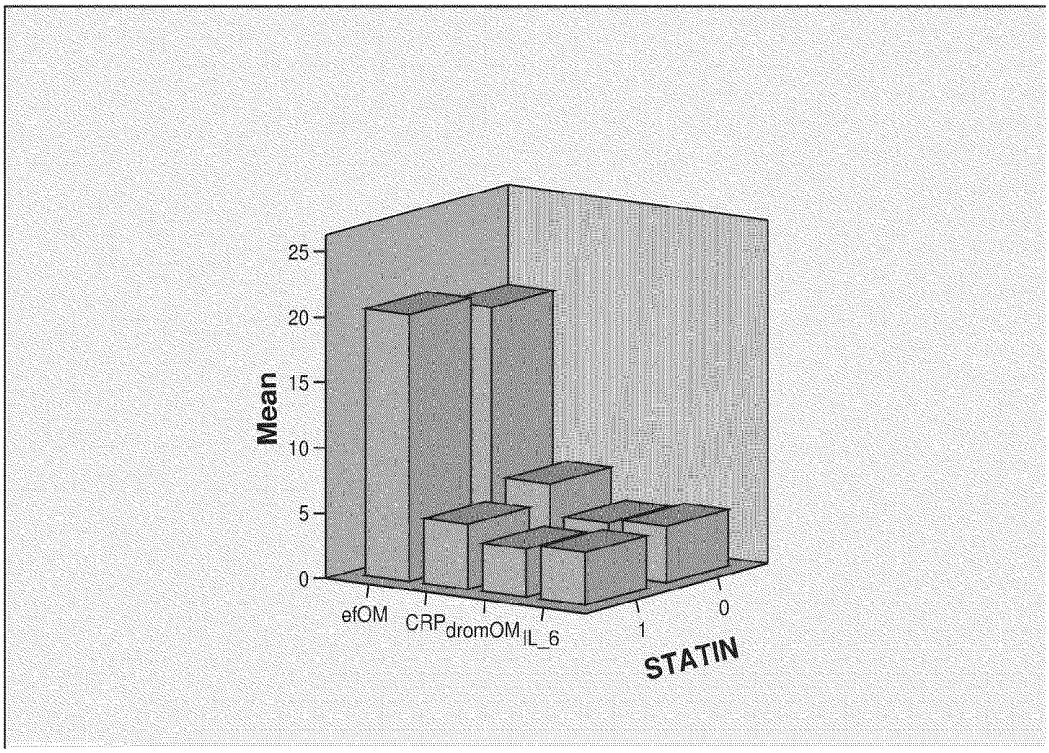
(57) **ABSTRACT**

The present invention relates to markers and methods for determining risk of ventricular arrhythmia in an individual. By using the markers of the present invention, individual with high risk of ventricular arrhythmia can properly be detected and treated. The present inventors have discovered that IL-6 and/or DROMs have strongly positive correlation with the risk of ventricular arrhythmia.

EF, hsCRP, DROM and IL-6 by Statin Use



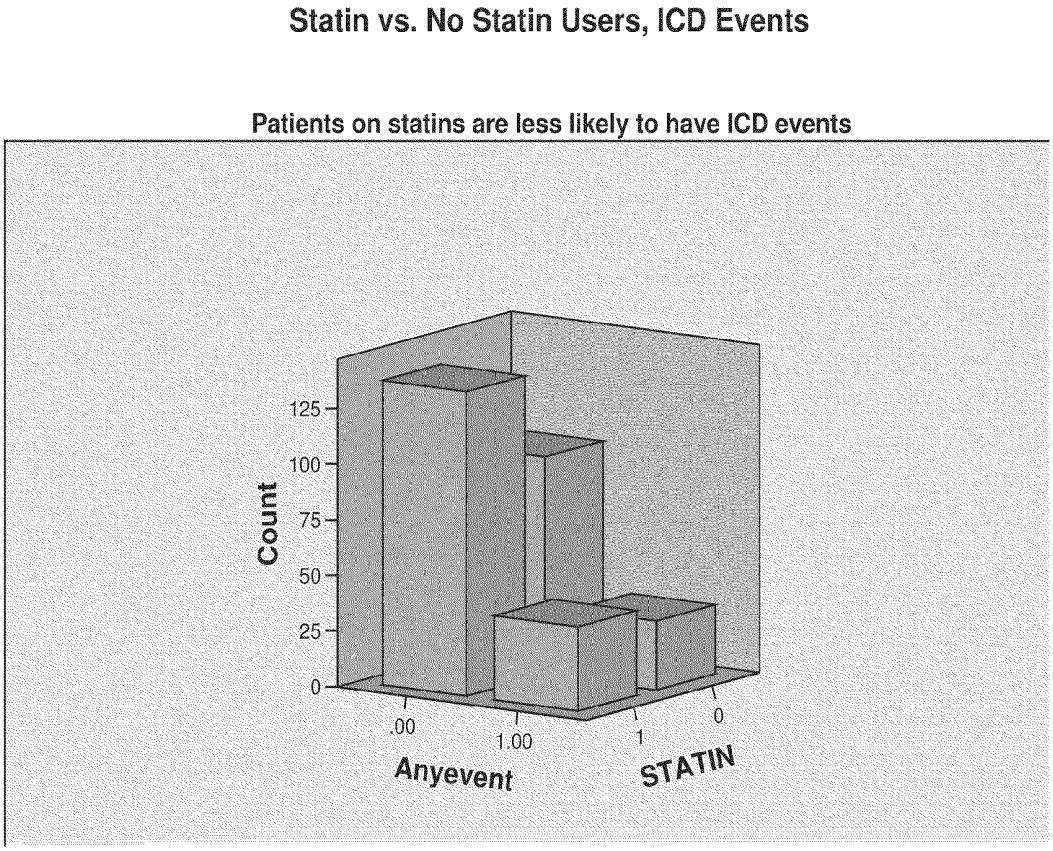

Statin vs. No Statin Users, ICD Events
Patients on statins are less likely to have ICD events
Count
125
100
75
50
25
0
.00
1.00
Anyevent
1
0
STATIN

Figure 1

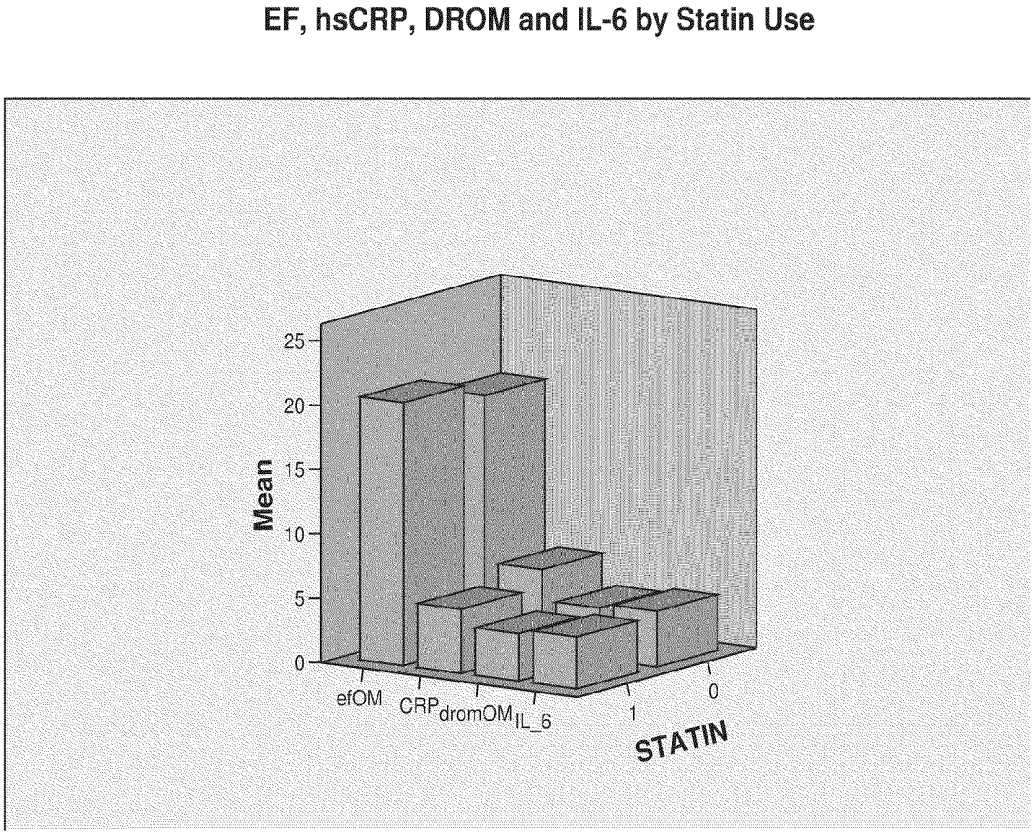

EF, hsCRP, DROM and IL-6 by Statin Use
Mean
25
20
15
10
5
0
efOM
CRP
dromOM
IL_6
1
0
STATIN

Figure 2

MARKER FOR ARRHYTHMIA RISK

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 60/960,013, entitled "Marker for Arrhythmia Risk," filed Sep. 11, 2007, the disclosure of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to markers and methods for determining risk of ventricular arrhythmia in an individual. By using the markers of the present invention, individual with high risk of ventricular arrhythmia can properly be detected and treated.

BACKGROUND OF THE INVENTION

[0003] Sudden Cardiac death (SCD) accounts for more than 50% of cardiac-related death[1], numbering over 400,000 deaths per year[2] in the United States. Ventricular arrhythmias cause most of these deaths[3]. The only treatment for ventricular arrhythmias with proven mortality benefit is the internal cardioverter-defibrillator (ICD). Two recent observational trials have demonstrated that Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) decrease the incidence of ventricular arrhythmias and increase survival in patients with ICDs[4;5]. This survival benefit exists for both ischemic (MADITII) and non-ischemic cardiomyopathy (DEFINITE). The reduction in ICD discharges is independent of the cholesterol-lowering effects.

[0004] One proposed mechanism for the anti-arrhythmic effect of statins is their anti-oxidant properties[4]. Statins reduce the generation of reactive oxygen species by inhibition of vascular NAD(P)H oxidase[6;7], inhibit the respiratory burst of phagocytes[8], antagonize the pro-oxidant effect of angiotensin II and endothelin-1[9], and increase the synthesis of vascular nitric oxides[10;11]. In addition, some statins and their metabolites are direct free radical scavengers. Statins may also have important anti-inflammatory effects. As inflammation is closely linked to the production of reactive oxygen species (ROS), the molecular basis of the observed anti-inflammatory effects of statins may relate to their ability block the production and/or activity of ROS.[12]

[0005] Several lines of evidence link oxidative stress with arrhythmias. [13-15] H_2O_2, a form of oxidative stress, causes alterations in cellular electrophysiology resulting in increased ventricular arrhythmias. H_2O_2 reduces sodium channel current and prevents its complete inactivation, causing a persistent current during the action potential plateau. This effect appeared to be the result of lipid peroxidation[16]. Patch clamp experiments in rat myocytes have also observed a H_2O_2-induced augmentation of sodium current via a slowing of the inactivation kinetics, producing a marked prolongation of the cellular action potential[17]. This provides good reason to believe that statins act to reduce arrhythmic risk, in part, by reducing lipid peroxidation.

[0006] Treatment with statins and/or ICD, however, is not always necessary. Currently, ventricular arrhythmic risk is determined by the ejection fraction. Generally, an ejection fraction (EF) lower than about 35% is a risk factor for ventricular arrhythmia; however, many patients with EF less than about 35% do not have ventricular arrhythmia. Nevertheless, out of an abundance of caution, these patients receive ICD and/or statin treatment. Therefore, there remains a need for an independent and simple test for diagnosing and assessing ventricular arrhythmic risk, possibly as a supplement to EF, to reduce the number of unnecessary treatment.

SUMMARY OF THE INVENTION

[0007] An object of the present invention is to provide a method for assessing or diagnosing the risk of ventricular arrhythmia in a subject.

[0008] Another object of the present invention is to provide a method for preventing or substantially reducing the risk of ventricular arrhythmia in a subject.

[0009] The present invention relates to markers and methods for determining risk of ventricular arrhythmia in a subject, preferably a person. The present inventors have discovered that derivatives of reactive oxidative metabolites (DROMs) and/or interleukin-6 (IL-6) are significant markers for ventricular arrhythmic risk. Thus, an abnormally high concentration of DROMs and/or IL-6 indicates a high risk of ventricular arrhythmia. "Abnormally high" is used herein to mean that the concentration is significantly higher than the average concentration in normal individuals without ventricular arrhythmia, preferably>5% higher than the normal concentration. In accordance with the present invention, a sample, preferably a blood sample, is taken from a subject. The concentration of DROMs and/or IL-6 in the sample is measured and compared to concentrations of these factors in normal subjects. If the concentration is abnormally high, then the subject is assessed or diagnosed as having a high risk of ventricular arrhythmia.

[0010] The method of the present invention can be used alone or in conjunction with the commonly used ejection fraction (EF) to assess or diagnose ventricular arrhythmic risk. When used in conjunction with the EF test, patients at risk for ventricular arrhythmia would have abnormally high concentrations of DROMs and/or IL-6 and an EF less than about 35%. The present methods are best suited to confirm assessment and diagnosis by EF measurement.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] FIG. **1** is a graph comparing ICD event for statin and non-statin users.

[0012] FIG. **2** is a graph comparing EF, hsCRP, DROM and IL-6 by statin use.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0013] To practice the present invention, the following steps are performed: 1) taking a sample, preferably a blood sample from a subject; 2) determine the concentration of reactive oxidative metabolites (DROMs) and/or interleukin-6 (IL-6) in the sample; and 3) diagnosing or assessing high ventricular arrhythmia risk when the DROMs and/or IL-6 concentration is abnormally high.

[0014] The concentration of DROMs can be determined as disclosed by Cessarone et al (Int. Angio. 2:127-130, 1999), Alberti et al. (Res. Chem. Intermed. 26:253-267, 2000), and Cornelli et al. (Journal of Nutrition 131:3208-3211, 2001), which are incorporated herein by reference. This test is a spectrophotometric test that determines the concentration of hydroperoxides (ROOH). Such compounds are generated into the cells by the oxidative attack of reactive oxidative species (ROS) on a number of organic substrates (e. g. car-

bohydrates, lipids, amino acids, proteins, nucleotides, etc.). During the test the hydroperoxides of a sample, e. g. the blood serum, after reacting with a chromogenic substrate develop a colored derivative (pink to red). Such colored complex is detectable and then quantifiable by a spectrophotometric methodic. Hydroperoxides concentration, which directly correlates with detected color intensity, is expressed as Carratelli Unit (CARR U), where 1 CARR U correspond to 0.08 mg/100 mL H_2O_2.

[0015] In the DROMs test, hydroperoxides of a sample are exposed to the same conditions of the Fenton's reaction to generate in vitro alkoxyl and peroxyl radicals. By diluting the sample with an acidic buffered solution (pH ~4.8). At these conditions, iron previously bonded to serum proteins becomes available to catalyze the breakdown of blood hydroperoxides to alkoxyl and peroxyl radicals. A compound (chromogen) having the ability to change its color when oxidized by hydroperoxyl and alkoxyl radicals is then added to this solution. The chromogenic substrate used in the DROMs test is preferably N,N,-diethylparaphenylen-diamine, which is capable of being oxidized by hydroperoxyl and alkoxyl radicals, thus transforming itself into a pink to a red colored cation. The color development can be monitored spectrophotometrically at wavelength 505 or 546 nm. The concentration of colored complex is directly related to the hydroperoxide levels of the tested sample.

[0016] An automated DROM test is disclosed by Iamelle et al. (Clinical Chemistry and Laboratory Medicine 40(7):673-676, 2002). DROM tests are commercially available from Diacron International s.r.l. in Grosseto, Italy.

[0017] IL-6 concentration can be determined by various methods available in the prior art. Typically, an immunoassay, such as ELISA, is appropriate for determining IL-6 concentration. The availability of antibodies that are capable of specifically binding IL-6 has permitted the development of sensitive immunoassays of IL-6 concentration. Such antibodies can be obtained from Genzyme Corp. (Boston, Mass.), or from R&D Systems, Inc. (Minneapolis, Minn.).

[0018] Immunoassays are assay systems that exploit the ability of an antibody to specifically recognize and bind to a particular target molecule, which are used extensively in modern diagnostics (Fackrell, Clin. Immunoassay 8:213-219, 1985, which is incorporated herein by reference). A large number of different immunoassay formats have been described (Yolken, Rev. Infect. Dis. 4:35, 1982; Collins, In: Alternative Immunoassays, John Wiley & Sons, NY, 1985; Ngo et al., In: Enzyme Mediated Immunoassay, Plenum Press, NY, 1985, all of which are incorporated herein by reference).

[0019] Corcoran et al. (Clin. Chem. 37:1046, 1991), which is incorporated herein by reference, disclose an enzyme immunoassay for the quantification of IL-6 in serum. The assay is stated to be capable of detecting 2.6 pg/ml.

[0020] Other IL-6 immunoassay protocols have been described by Buyalos et al. (Fertil. Steril. 57:1230-1234, 1992), and by Thavasu et al. (J. Immunol. Meth. 153:115-124, 1992), which are incorporated herein by reference. The assay of Buyalos et al. is used to measure IL-6 levels in follicular fluids with a detection limit of 50 pg/ml. The assay of Thavasu et al. is used to assay IL-6 in blood, and has a detection level of 70 pg/ml. A solid phase monoclonal immunoassay for IL-6 has also been described by Helle et al. (J. Immunol. Meth. 138:47-56, 1991), which is incorporated herein by reference.

[0021] Commercial immunoassay kits for IL-6 are also available (Human IL-6 ELISA kit, Cell Sciences, Inc., Canton, Mass.; IL-6 EIA and IL-6 ELISA kits, Cayman Chemicals, Ann Arbor, Mich.; Human High Sensitivity IL6 ELISA Kit, Abcam, Inc., Cambridge, Mass.; and Human IL-6 ELISA Ready-SET-Go!, eBioscience, Inc., San Diego, Calif.).

[0022] Various samples can be collected from a subject suspected of having ventricular arrhythmia risk. The samples can be whole blood, blood plasma, blood serum, or cell extract. The preferred samples are blood based, such as whole blood, blood plasma, and blood serum.

[0023] Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. The following example is given to illustrate the present invention. It should be understood that the invention is not to be limited to the specific conditions or details described in this example.

EXAMPLE

Methods

[0024] To select patients at high risk for ventricular arrhythmia, this retrospective study was performed by examining patients either undergoing ICD implantation or generator exchange. This study protocol was approved by the Emory University Internal Review Board. These patients were enrolled in the Genetic Risk Assessment for Defibrillator Events (GRADE) trial, and were undergoing new ICD implant or who had undergone ICD placement or generator exchange within the last 5 years and were enrolled from the four Emory University Hospitals. Patients met the inclusion criteria of being age 18 or older, able to give informed consent and had depressed left ventricular ejection fraction (LVEF) <30%. Exclusion criteria included patient refusal, patients with a life expectancy less than 6 months, patients who had ongoing class IV heart failure symptoms, patients who were post-cardiac transplant or with left ventricular assist devices. Demographic and medical information obtained on enrollment included: age, gender, race, history of smoking, medications, New York Heart Association (NYHA) class, etiology of heart disease, hypercholesterolemia, history of myocardial infarction (MI) history of coronary artery bypass (CABG) surgery, family history of heart disease, history of arrhythmias, history of syncope, echocardiogram results, cardiac catheterization results, nuclear imaging results, electrocardiograms, blood pressure, heart rate, electrolytes and date of ICD implantation surgery and any ICD generator exchanges.

[0025] Biomarker data: A single blood draw was performed at the time of enrollment and analyzed for markers of oxidative stress and inflammation in the Emory Biomarkers Core Laboratory. Markers used to measure oxidative stress were: ratios of oxidized to reduced glutathione (E_h GSH) and cystiene (E_h CySH) in plasma (thiol ratios) [18] and derivatives of reactive oxygen species (DROMs). [19;20;31] Detailed methods to prevent rapid oxidation of samples have been delineated previously. [21] Blood was collected from an antecubital vein and transferred immediately to a micro-centrifuge tube containing 0.5 mL of a preservation solution of 100 mM serine-borate (pH 8.5) containing (per mL) 0.5 mg sodium heparin, 1 mg bathophenanthroline disulfonate sodium salt, and 2 mg iodoacetic acid. Use of this procedure minimizes auto-oxidation and hemolysis.[22] All blood was drawn between 7:30 am

and 3:00 pm in non-fasting patients. Following centrifugation to remove blood cells, aliquots (200 μL) were transferred to tubes containing 200 μL of 10% (w/v) perchloric acid containing 0.2 M of boric acid and 10 μM γ-Glu-Glu as internal standard. Samples were stored at −80° C. (<2 months) prior to further processing to form N-dansyl derivatives and analysis by HPLC with fluorescence detection. Reduced glutathione, cystine, and cystiene levels in plasma were greater than 1,000 times the level of detection (~1 nM). Oxidized glutathione levels were approximately 10 times this limit. Previous data have shown stable measurements over this length of storage 23 Metabolites were identified by co-elution with standards, and quantified by integration relative to the internal standard.

[0026] The redox states (E_h) of the thiol/disulfide pools were calculated with the Nernst equation, $E_h=E_o+RT/nF \ln [disulfide]/[thiol]^2$. E_o is the standard potential for the redox couple, R is the Rydberg constant, T is the absolute temperature, n is 2 for the number of electrons transferred, and F is Faraday's constant. The standard potential E_o used for the glutathione and cystiene redox couples was −264 mV and −250 mV, respectively [24]. Less negative E_h numbers imply a more oxidized state. DROMs were measured in Carr units with higher values indicating higher levels of oxidative stress. DROMs (Diacron International, Grosseto, Italy) and inflammatory markers, high sensitivity C-reactive protein (hsCRP; Life Diagnostics, West Chester, Pa.), interleukin-1-β (IL-1β; R&D Systems, Minneapolis, Minn.), interleukin-6 (IL-6; R&D Systems), and tumor necrosis factor α (TNFα; R&D Systems), were measured using commercially available kits.

[0027] Ventricular arrhythmias: Routine device interrogations and chart review were performed. All history of appropriate therapies for ventricular fibrillation (VF) or ventricular tachycardia (VT) were recorded. Dates, times, types and number of therapies were all documented. As the study was retrospective, there was no standardization of ICD programming; some patients had antitachycardia pacing (ATP) programmed on and some did not. Thus both ATP and shock therapies were recorded (further referred to as "ICD events"). All therapies were adjudicated by an independent cardiologist as appropriate therapy for ventricular arrhythmias or inappropriate therapy, for a non-VT/VF. Only appropriate therapies documented to be for ventricular arrhythmias were included in the analysis. Due to high variability of event rates and discrepancy in follow up time, events were analyzed as a function of time and analyzed as "event-months".

[0028] Data analysis: Statistical analysis was performed using SPSS software version 14.0 (SPSS Inc., Chicago, Ill. 60606). Baseline characteristics of patients who received and did not receive ICD therapies were compared using a paired t-test for continuous variables (expressed as mean±SD) and Fisher's exact test for categorical variables. Baseline characteristics of patients who received and did not receive statins were compared using a paired t-test for continuous variables (expressed as mean±SD) and Fisher's exact test for categorical variables. Marker data were presented as the mean±SD, except as noted. All statistical tests were two-tailed, and significance was taken to be $\rho \leqq 0.05$. Patient characteristics and all oxidative and inflammatory markers were examined for links to ICD events using Pearson's correlation coefficients. Multivariate models were used to examine the association between each oxidative marker and the occurrence of ICD therapies while controlling for other inflammatory markers and significant characteristics. Due to the wide range of follow up times, events were examined as a function of time, in "event-months."

Results

[0029] 304 patients were enrolled and had blood tests performed and received 3 months or more of follow up (range: 3 months to 135 months, mean 29 months). Demographic data is presented in Table 1.

TABLE 1

Baseline demographics	
Age	62 ± 12
Gender	252 men (83%)
CAD	196 (65%)
DM	114 (38%)
ICD therapies	68 (23%)
Average EF	20% ± 7%
Statins	175 (58%)
Smokers	202 (67%)
Afib	87 (29%)
ACE	177 (58%)
ARB	71 (23%)
PPAR	28 (9.2%)
Biomarker	**Value**
CRP	5.7 ± 4.67
IL-6	4.3 ± 3.2
IL1β	0.52 ± 0.37
TNF-α	4.4 ± 2.8
DROM	383 ± 95
EhGSH	−126 ± 13
EhCYS	−66 ± 9

[0030] There were 252 men (83%) and 52 women (17%). Average age was 63±11, EF 20%±7%, 114 (38%) had diabetes, 175 (58%) were on statins, 234 (80%) had no ICD therapies, 200 (67%) were smokers. 196 (65%) had coronary artery disease (CAD). Medication use examined included ACE-inhibitors (177/58%), ARBs (71 23%) and PPARs (28, 9.2%), all of which are known to affect oxidative stress. Mean biomarker values were high for all patients (Table 1). Table 2 shows compares patients using statins to those who were not using statins.

TABLE 2

	Statin Use (n = 175)	No Statin Use (n = 129)	ρ
Age	59 ± 13	65 ± 9	.00
Gender	146 (83%)	106 (82%)	.46
DM	101 (57%)	40 (31%)	.055
Smokers	127 (72%)	75 (58%)	.01
CAD	138 (78%)	58 (45%)	.00
EF	20% ± 7%	19% ± 7%	
CRP	5.2 ± 4.4	6.3 ± 5.0	.05
DROM	373 ± 87	397 ± 102	.03
IL-β	0.52 ± 0.37	0.53 ± 0.36	.90
IL-6	4.3 ± 3.4	4.5 ± 3.0	.88
TNF-α	4.5 ± 3.0	4.3 ± 2.6	.64
EhGSH	−126 ± 12	−126 ± 13	.82
EhCYS	−66 ± 9	−67 ± 9	.93
Afib	37 (30%)	50 (29%)	.87

[0031] There is a significant difference in incidence of CAD ($\rho=0.00$) and cigarette smoking ($\rho=0.01$) in patients on statins. However, cigarette smoking correlates directly with CAD and is not an independent variable. DROM and hsCRP

are significantly lower in the statin group. FIG. **2** shows EF, hsCRP, DROM and IL-6 by statin use. Table 3 shows the Pearson correlation coefficients and ρ values for the characteristics that correlated with ICD therapy events.

TABLE 3

	ICD events*	
	Pearson's Correlation Coefficient	ρ value
Age	−.058	.37
Gender	−.033	.57
DM	.052	.37
Cigs	0.079	.17
CAD	0.37	.52
EF	−.120	.04
CRP	.057	.37
DROM	.188	.003
IL-6	.129	.043
IL-β	−.065	.30
TNF-α	−.111	.08
EhGSH	.064	.32
EhCYS	−.005	.94
Statin	.037	−.114

*Analysis by event-months

[0032] Ejection fraction, IL-6 levels, statins, TNF-α and DROMs all were significant. FIG. **1** shows the relationship between statin use and ICD events.

[0033] Multivariate cross-correlation analysis confirms the significant relationships of IL-6, DROMs, statins and EF with events. For IL-6: ρ=0.024, Pearson coefficient of 0.124; DROM: ρ=0.001, Pearson coefficient of 0.183; statins: ρ=0.047, Pearson coefficient of −0.107; TNF-α: ρ**32** 0.040, Pearson coefficient of −0.112; and EF: ρ**32** 0.015, Pearson coefficient of −0.132. Multivariate linear regression shows DROMs to be the dominant predictive factor of events, with a regression coefficient of 0.164 (ρ=0.026).

CONCLUSIONS

[0034] For these high risk patients, we confirm the previous observation that statin medication use correlates with decreased rates of ventricular arrhythmias as measured by ICD therapies. We also demonstrate the independence of ejection fraction as a risk factor for ventricular arrhythmias. When we examined biomarkers to assess inflammation and oxidative stress burden, we found that hsCRP and DROM were decreased in the statin users group and that IL-6 and DROMS correlate with decreased event risk. IL-6 correlates with events, but not with statin use, suggesting IL-6 is unaffected by statin use. The only factor dependent on statin use and associated with decreased ICD events is DROM. That DROMs are the single most predictive indicator of future events, coupled with their statin correlation, provides strong evidence that the mechanism by which statins lower rates of ventricular arrhythmias is via their antioxidant effect.

Discussion

[0035] Each patient considered had cardiac disease that qualified them for an ICD, giving them a high risk for ventricular arrhythmias. Our patient demographics do not differ significantly from those in the two large trials, previously cited, that demonstrate decreased ICD events with statins. Average patient age, gender, EF, rates of diabetes, and rates of ACE/ARB use were all similar. Perhaps unsurprisingly, a difference was seen in the rates of cigarette smokers. In the ischemic cardiomyopathy group (MADITII), the rate of smoking was 81%, in the non-ischemic group (DEFINITE), 38% were smokers. In our mixed ischemic and non-ischemic population, 67% of patients were smokers. Of our smokers, 76% had CAD, (and 73% of our CAD patients were smokers).

[0036] Our patients' biomarkers are elevated. Elevated inflammatory markers and markers of oxidative stress have been correlated with increased mortality in cardiac disease. hsCRP, for example, is considered a "high risk" marker (per AHA/CDC consensus document)[25] when the levels are >3.0 mg/dl. Our mean value was 5.7 In a study recently accepted for publication, we compare case-matched biomarkers for patients with and without atrial fibrillation. In that study we demonstrate that patients with AF are more oxidized compared to the controls. These ICD patients are similarly oxidized when compared our AF patients: DROMS are similar at 388 vs. 383, EhC−66 vs. −68, EhG−126 vs. −133. For our inflammatory markers hsCRP is higher (5.7 vs 3.9), as is IL-6 (5.5 vs. 4.3), TNF alpha is lower 4.4 vs. 6.4, and ILB was the same 0.5 vs. 0.5.

[0037] In these high-risk patients, statin use correlates with decreased arrhythmia risk. Decreases in DROMs correlate with decreased ICD events, and with statin use. This suggests that statin use decreases ventricular arrhythmias in part due to its anti-oxidant properties, possibly via ion channel alterations.

[0038] That IL-6 with does not change with statin use has been somewhat controversial in the literature. It has been previously documented to be unchanged with pravastatin, simvastatin, and atorvastatin in several studies[26-28]. Others, however, have seen a change in Il-6 with statin use.[29] As IL-6 is known to exhibit great circadian variation, this particular marker may be more sensitive to the variable follow-up time courses in our study. However, the lack of correlation with statin use further suggests that statins are acting through an IL-6 independent mechanism.

[0039] Measuring oxidative stress in humans is difficult because free radicals are reactive and thus short-lived. Products of free radical damage to DNA proteins and lipids may provide such markers. Additionally, measurements of O_2-generating enzymes can be easily quantified(already said measured). We chose several markers to examine: quantifying thio-disulfide redox couples, reduced and oxidized glutathione disulfide, and cysteine/cystine ratios. These redox states represent the plasma oxidation state. To reflect the lipid compartment, we used a measure of plasma lipid peroxides known as the d-ROMs test. The positive correlation of reduced ICD events with DROMs may reflect changes in the lipid compartment, as opposed to the other markers of oxidative stress, which reflect changes in plasma oxidative stress. This finding demonstrates that the tissue oxidative state and the plasma oxidative state are not necessarily equivalent. That DROMs reflect the tissue state, and are significant is further circumstantial evidence to support a tissue-level mechanistic change.

[0040] Although certain presently preferred embodiments of the invention have been specifically described herein, it will be apparent to those skilled in the art to which the invention pertains that variations and modifications of the various embodiments shown and described herein may be made without departing from the spirit and scope of the invention.

Accordingly, it is intended that the invention be limited only to the extent required by the appended claims and the applicable rules of law.

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What is claimed is:

1. A method for assessing or diagnosing a risk of ventricular arrhythmia in an individual comprising the step of

a. obtaining a sample from a patient;

b. determining DROMs or IL-6 concentration in the sample; and

c. assessing or diagnosing the risk of ventricular arrhythmia from said concentration

2. The method of claim **1**, wherein the concentration of IL-6 is determined by immunoassay.

3. The method of claim **1**, wherein the concentration of DROM is determined by measuring the amount of hydroperoxides in the blood.

4. The method of claim **1**, wherein an increased risk of heart disease is assessed or diagnosed when the concentration of DROM or IL-6 is elevated when compared to normal individuals.

5. The method of claim **1**, wherein an increased risk of heart disease is assessed or diagnosed when the concentration of DROM or IL-6 is increased or is abnormally high.

6. The method of claim **1**, wherein the sample is blood.

7. The method of claim **6**, where in the sample is whole blood, blood serum, or blood plasma.

8. A method for monitoring the treatment of an individual with ventricular arrhythmia risk comprising the steps of

administering a pharmaceutical composition for treating heart disease to the individual; and

determining the blood level of DROM or IL-6 in the individual.

9. The method of claim **8**, wherein a decrease in DROM or IL-6 levels indicate effectiveness of the pharmaceutical composition.

10. The method of claim **8**, wherein the levels of IL-6 is determined by immunoassay.

11. The method of claim **8**, wherein the levels of DROM is determined by measuring the amount of hydroperoxides in the blood.

12. The method of claim **8**, wherein the sample is blood.

13. The method of claim **12**, where in the sample is whole blood, blood serum, or blood plasma.

14. A method for screening for an agent capable of decreasing the risk of ventricular arrhythmia comprising the steps of

exposing an individual to the agent; and

determining the blood level of DROM or IL-6 in the individual.

15. The method of claim **14**, wherein a decrease in DROM or IL-6 levels indicate effectiveness of the agent in decreasing the risk of ventricular arrhythmia.

16. The method of claim **14**, wherein the levels of IL-6 is determined by immunoassay.

17. The method of claim **14**, wherein the levels of DROM is determined by measuring the amount of hydroperoxides in the blood.

18. The method of claim **14**, wherein the sample is blood.

19. The method of claim **18**, where in the sample is whole blood, blood serum, or blood plasma.

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专利名称(译)	心律失常风险标记		
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申请(专利权)人(译)	美利坚合众国系退伍军人事务		
当前申请(专利权)人(译)	埃默里大学 美洲的美国为代表的退伍军人事务署		
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摘要(译)

本发明涉及用于确定个体中心室心律失常的风险的标志物和方法。通过使用本发明的标志物，可以适当地检测和治疗具有心室心律失常的高风险的个体。本发明人已经发现IL-6和/或DROM与心室心律不齐的风险具有强正相关。