Regular wine consumption in chronic heart failure: impact on outcomes, quality of life and circulating biomarkers

(Article begins on next page)

17 May 2024

iris - AperTO

Regular Wine Consumption in Chronic Heart Failure. Impact on Outcomes, Quality of Life, and Circulating Biomarkers

Franco Cosmi, MD; Paola Di Giulio, MSc; Serge Masson, PhD; Andrea Finzi, MD;
Rosa Maria Marfisi, MS; Deborah Cosmi, MD; Marco Scarano, ScD; Gianni Tognoni, MD;
Aldo P. Maggioni, MD; Maurizio Porcu, MD; Silvana Boni, MD; Giovanni Cutrupi, RN;
Luigi Tavazzi, MD; Roberto Latini, MD; on behalf of the GISSI-HF Investigators

Background—Moderate, regular alcohol consumption is generally associated with a lower risk of cardiovascular events but data in patients with chronic heart failure are scarce. We evaluated the relations between wine consumption, health status, circulating biomarkers, and clinical outcomes in a large Italian population of patients with chronic heart failure enrolled in a multicenter clinical trial.

Methods and Results—A brief questionnaire on dietary habits was administered at baseline to 6973 patients enrolled in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF) trial. The relations between wine consumption, fatal and nonfatal clinical end points, quality of life, symptoms of depression, and circulating biomarkers of cardiac function and inflammation (in subsets of patients) were evaluated with simple and multivariable-adjusted statistical models. Almost 56% of the patients reported drinking at least 1 glass of wine per day. After adjustment, clinical outcomes were not significantly different in the predefined 4 groups of wine consumption. However, patients with more frequent wine consumption had a significantly better perception of health status (Kansas City Cardiomyopathy Questionnaire score, adjusted $P<0.0001$), less frequent symptoms of depression (Geriatric Depression Scale, adjusted $P=0.01$), and lower plasma levels of biomarkers of vascular inflammation (osteoprotegerin and C-terminal proendothelin-1, adjusted $P<0.0001$, and pentraxin-3, $P=0.01$) after adjusting for possible confounders.

Conclusions—We show for the first time in a large cohort of patients with chronic heart failure that moderate wine consumption is associated with a better perceived and objective health status, lower prevalence of depression, and less vascular inflammation, but does not translate into more favorable clinical 4-year outcomes.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT0033633.

Alcohol consumption and its effect on health is a complex topic largely influenced by nationality, ethnicity, age, social, and family status of patients forming study populations. Wine can be considered a unique example of this complexity because it is customarily a daily component of a

standard meal in some areas and populations, but only an occasional event in others, and formally forbidden because of religious constraint in large populations. In the absence of randomized controlled trials, observational studies suggest that moderate and regular alcohol consumption but not binge drinking[1] is associated with lower risk of cardiovascular events, particularly myocardial infarction,[2] and incident heart failure (HF).[3] Moreover, in 2006, the AHA suggested that after a cardiovascular event patients may continue drinking moderate amounts of alcohol, if they already did before.[4] The bulk of evidence for a protective effect of moderate wine intake on incident cardiovascular events comes from studies in the general population without cardiovascular disease or in hypertensive, post myocardial infarction (MI), diabetic patients.[3–9] Recently, data have been obtained within the INTERHEART case-control study in >27 000 individuals from 52 countries showing that this protection may not be effective across different countries.[2] A significantly lower incidence of all-cause deaths and cardiovascular events was reported in 11 248 Italian post MI patients enrolled in the GISSI Prevenzione trial.[10] However, the issue is still controversial, as there are no controlled prospective trials.[11,12]

Four studies previously addressed this subject in patients with HF or left ventricular (LV) dysfunction: 6313 patients from the Studies of Left Ventricular Dysfunction (SOLVD) trial,[13] 2231 post MI patients from the Survival and Ventricular Enlargement (SAVE) trial,[8] 449 male US physicians,[14] and 117 Italian patients aged ≥65 years.[15] In chronic HF, dietary indications and control are of paramount importance but, at the same time, different pathophysiologic determinants and variability in clinical profiles are unavoidable confounding factors.[16]

GISSI-HF, a double-blind randomized trial found that n-3 polyunsaturated fatty acids (1 g/d), but not rosuvastatin (10 mg/d), slightly but significantly reduced mortality and hospital admissions for cardiovascular reasons in patients with symptomatic chronic HF of any cause.[17,18] Because all patients completed a brief diet questionnaire at baseline, including daily wine, beer, and spirits intake, we investigated the possible relationship between the latter and the clinical outcome indicators, with the aim of verifying whether the benefit of moderate wine consumption shown in a population of post-MI patients from GISSI Prevenzione applied also to patients with symptomatic chronic HF. In addition, in 2 subgroups of patients from the same study, we assessed the relations between wine consumption and several circulating biomarkers or indicators of health status perception. This enabled us to search for relations between wine, outcomes, biohumoral, and behavioral factors in a contemporary population of patients with chronic HF with any level of LV ejection fraction (LVEF).

Methods

The GISSI-HF trial was a randomized, double-blind, placebo-controlled, multicenter study that enrolled 6975 patients with clinical evidence of chronic, stable HF (New York Heart Association II–IV), of any cause and level of LVEF.[17,18] The trial investigated the effect of adding 1 g of n-3 polyunsaturated fatty acids per day or placebo to standard therapy in patients with moderate-to-severe HF. In the prospectively planned biomarker substudy, blood samples were collected at randomization and 3 months later from 1235 patients recruited in 51 clinical centers. Investigators participated on a voluntary basis and ensured that all eligible patients would have been enrolled in the present substudy, to minimize selection bias. The study was approved by the local ethics committee and informed consent was obtained from all patients before the study started. The other predefined substudy was quality of life (QoL), depression, and cognitive function, which enrolled 1465 patients to whom questionnaires on QoL, depression, and cognitive function were serially administered by attending nurses.[19]

Wine Consumption. In the main GISSI-HF study, a brief questionnaire on dietary habits was administered to each patient at study entry. Wine consumption was divided into 4 categories, such as patients who did not drink wine, those who drank it occasionally, and those with low to moderate (1–2 glasses per day) and high (≥3 glasses per day) consumption. In the general study population, baseline data included patient's characteristics, cardiovascular risk factors, medical history, causes and New York Heart Association class of HF, physical examination and medical treatment. Primary end points were total mortality, cardiovascular mortality and hospital admissions, total and for cardiovascular reasons, specifically for worsening HF, arrhythmias, myocardial infarction, and stroke.

Health Status Perception and Depression. The validated Italian version of the Kansas City Cardiomyopathy Questionnaire[20] was used to define the perception of health status. This specific 23-item health status measure encompasses several domains, including physical limitations, symptoms (frequency, severity, and recent changes) self-efficacy, social interference, and QoL.[21] The summary score ranges from 0 to 100, higher scores denoting better health. Health status was defined as good (76–100), fair (51–75), poor (26–50), and worst (0–25). The Geriatric Depression Scale is a 15- item well-validated questionnaire that measures emotional factors in depression.[22] Each yes/no item corresponds to a depressive symptom.
Subjects with 5 to 8 symptoms were considered to have mild depression and those with >9 symptoms moderate-to-severe depression.

Circulating Biomarkers

In the subgroup of 1235 patients enrolled in the biological substudy, a blood sample was collected at randomization; EDTA-plasma was stored at −70°C in a centralized biological repository. The circulating levels of adiponectin, high-sensitivity C-reactive protein, pentraxin-3 (PTX3), osteoprotegerin, N-terminal pro B-type natriuretic peptide, midregional proatrial natriuretic peptide, high-sensitivity cardiac troponin T, midregional proadrenomedullin, C-terminal provasopressin (copeptin), mannose-binding lectin, and C-terminal proendothelin- 1 were measured, blind, in a central laboratory, as previously reported.[23–27]

Statistical Analyses

All the statistical analyses were done on the imputed data set. A multiple imputation technique based on a Markov chain Monte Carlo approach[28] was used to estimate the missing values for each missing data point. For most variables, ≈1% of the data were missing. However, data were missing in 9.5% of the study population for fibrinogen, 5.9% for bilirubin, 4.2% for uricemia, 4.1% for low-density lipoprotein-cholesterol, 3.5% for high-density lipoprotein cholesterol, and 3.0% for CK total. Trends across categories were analyzed using respectively the Cochran–Armitage trend tests and linear regression analysis for categorical and continuous variables. Cox proportional hazard models were used to evaluate the independent associations between wine intake and outcome events. Hazard ratios were evaluated in an unadjusted model and then in an adjusted one for major potential risk factors based on biological plausibility and associations with exposures/outcomes in the present population, for example, demographic, clinical, and lifestyle risk factors. Trends in hazard ratios across categories of wine consumption were examined using the variable as continuous (eg, coded 0, 1, and 2). The Geriatric Depression Scale score and the Kansas City Cardiomyopathy Questionnaire score were expressed as median (interquartile range) and the median test was used for their analysis across wine consumption categories. Survival curves were adjusted by Cox-regression according to corrected group prognosis method. This method calculates the survival curve for each unique combination at all levels of the covariates with a Cox model and obtains the adjusted survival curve as a weighted average of those individual curves, in which weights are based on the sample sizes in each combination.[29,30]

All probability values are 2-sided. All computations used the SAS statistical package (SAS Institute Inc, Cary, NC).

Results

Patients' Characteristics in Relation to Wine Consumption

The patients declared a low consumption of alcoholic beverages other than wine: 2.4% drank at least 1 glass of beer per day, whereas only 1.0% drank 1 glass of spirits. For this reason, we limited our main analyses to wine consumption. The distribution of wine consumption of the 6973 patients in the GISSI-HF study is shown in Table 1. Age showed no specific trends across groups, although the difference between wine consumption groups reached statistical significance. Among cardiovascular risk factors, smoking was positively correlated with wine consumption and the incidence of chronic obstructive pulmonary disease and neoplasia was higher in groups with higher wine consumption; an inverse correlation was observed with history of hypertension. Wine consumption was positively associated with a more favorable New York Heart Association functional class. Hospital admission in the year before study entry or a history of diabetes mellitus was more frequent in patients with no wine consumption. These clinical characteristics were consistent with greater severity of HF in patients who never or seldom drank wine, as evidenced by physical examination and more frequent treatment with agents, such as angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, diuretics, spironolactone, digitalis, and nitrates. Among laboratory values, hemoglobin and glomerular filtration rate were positively correlated with increasing frequencies of wine consumption (Table 1). In the absence of a statistically significant difference in history or presence of atrial fibrillation, oral anticoagulant agents and amiodarone were prescribed significantly more often to wine consumers.

Wine Consumption and Outcomes

Clinical events during the 3.9-year follow-up showed a lower incidence in patients with the highest wine consumption, with 1 exception, all-cause hospitalizations, which were somewhat more frequent in the ≥3 glasses of wine/d group (Table 2). Nonetheless, after adjustment for confounders, the differences were no longer significant for any of the clinical outcomes (Table 3). Adjusted survival curves by wine consumption categories are presented in Figure 1. Two interaction terms were added to the Cox multivariable models, rosuvastatin × wine consumption and n-3 polyunsaturated fatty acids × wine consumption: interactions with rosuvastatin, but not with n-3 polyunsaturated fatty acids were statistically significant for both all-cause death and the combined end point (Table 3). In other words, the analysis of the direction of the interaction suggests that rosuvastatin tended to be associated with worse outcomes than placebo in patients drinking wine, than in those not drinking it at all or just occasionally.

QoL and Depression Substudy

The distribution of wine consumption of the 1465 patients participating in the QoL, depression, and cognitive function substudy is shown in Table 4. The characteristics of this subpopulation of GISSI-HF were similar to those of the main study population in terms of medical history, clinical

presentation, and pharmacological treatment.17 Kansas City Cardiomyopathy Questionnaire score showed a significant correlation between wine consumption and better health status perception ($P<0.0001$), so that patients with a score <50 (poor or worst) were 21.0% in those who never drank, while they were only 7.4% in those drinking at least 3 glasses of wine a day (Table 4). The depression score, Geriatric Depression Scale, showed an inverse correlation ($P=0.01$), with 18.4% of the nondrinkers being classified as having moderate-to-severe depression, while they were only 5.0% among those drinking ≥3 glasses a day (Table 4). All these differences were statistically significant after full adjustments (Table 4).

Circulating Biomarkers

Figure 2 shows the baseline levels of several circulating biomarkers related to cardiovascular function or inflammation, according to wine consumption. The plasma levels of osteoprotegerin, a member of the tumor necrosis factor superfamily, and of the endothelin precursor C-terminal proendothelin-1, a powerful endogenous vasoconstrictor, were inversely related to wine consumption (adjusted $P<0.0001$). A similar but less significant trend was observed for PTX3, a marker of vascular inflammation ($P=0.01$). The concentrations of 2 cardiac markers, N-terminal pro B-type natriuretic peptide and highsensitivity cardiac troponin T, tended to be lower in patients drinking ≥3 glasses of wine per day ($P=0.04$ and 0.002, respectively).

Discussion

In the whole population of patients with symptomatic chronic HF enrolled in the GISSI-HF trial, ≥2 glasses of wine daily as assessed with a diet questionnaire, were associated to lower severity of HF, better perceived QoL, and more favorable profile of inflammatory circulating biomarkers. However, the multivariate analyses adjusted for patient's characteristics abolished the relation of wine consumption with fatal and nonfatal clinical outcomes.

Wine Consumption and Clinical Outcomes

These Italian patients aged 67 years on the average, declared a low consumption of alcoholic beverages other than wine. This is consistent with the Italian culture, more so of elderly people. The neutral results on clinical outcomes should be compared with the existing data in HF because the largest study reported that light-to-moderate alcohol consumption was not associated with adverse outcomes in 6313 US patients with LV dysfunction, and even reduced the risk of fatal MI in patients with ischemic cause of HF.10 In 2231 patients from SAVE trial, with an LVEF <40% after MI, light-to-moderate alcohol intake did not alter the risk of hospitalization for HF.8 In 449 male US physicians with HF a J-shaped relation between alcohol intake and mortality was reported, so the risk was significantly lower only in those drinking 1 to 2 glasses per day.14

In contrast, the study on 1332 Italian subjects aged ≥65 years found that alcohol consumption was associated with a 21% lower risk of death in subjects without HF, but a 29% higher risk of death in patients with chronic HF.15This study, the largest to date, supports a neutral effect of alcohol intake on the outcomes in chronic HF, after adjusting for several factors, including ischemic cause of HF. LVEF, and hypertension. A previous study from the GISSI collaboration showed that moderate wine intake, as collected with the same questionnaire, could even reduce cardiovascular events in patients after MI but substantially without overt HF.10 The reduction observed in GISSI Prevenzione was mainly because of a decrease in ischemic events such as incident MI, a potential target of wine protective action. In the placebo group of GISSI-HF, incident MI was only 0.7%, while worsening of HF was 9.5% and sudden death, presumably arrhythmic, 8.7%, thus reducing the potential benefits of wine.10

Wine Consumption and Circulating Biomarkers

In the subgroup of 1235 patients in whom circulating biomarkers were assayed, there was a consistent decrease in markers of inflammation with higher regular wine consumption even after adjustment for age, sex, and severity of HF. The independent association between wine consumption and markers of systemic inflammatory activation, known to play a role in chronic HF,31 has already been reported in different cardiovascular disorders.32,33 Moderate consumption of red wine and some of its compounds (particularly polyphenols) may confer protection in patients with documented cardiovascular disease. 5,6,9,10 Part of this benefit is because of an improvement of endothelial dysfunction through different molecular pathways that include enhanced endothelial nitric oxide production and vasodilatation, improved redox balance and anti-inflammatory mechanisms.34,35 Although circulating biomarkers cannot fully capture the complexity of paracrine regulations in the endothelium, we found that light-to-moderate wine consumption was associated with a dose-dependent reduction in the plasma concentration of a stable precursor of endothelin-1. This highly potent vasoconstrictor peptide, when elevated, is a strong predictor of bad outcome in chronic HF.24,36 Red wine extracts have been shown to inhibit endothelin-1 synthesis by bovine aortic endothelial cells,37 presumably by altering tyrosine–kinase signaling.38 Polyphenols from red wine also blunt the expression of adhesion molecules and inflammatory cytokines related to endothelial dysfunction and atherosclerosis, contributing to a reduction in HF severity.7 Wine consumption, even light, was associated with lower plasma levels of osteoprotegerin and of PTX3 than in patients who did not drink wine. Osteoprotegerin is a cytokine of the tumor necrosis factor receptor superfamily, expressed in vivo by endothelial cells, vascular smooth muscle cells, and osteoblasts. Initially thought to act exclusively on the skeletal and

immune system, more recent evidence suggests that it also hasa proatherogenic role and participates in the pathogenesis of cardiovascular diseases by amplifying the adverse effects of inflammation, hyperlipidemia, endothelial dysfunction, hypertension, and diabetes mellitus.[39,40] PTX3 is rapidly induced in various cell subsets, such as peripheral blood leucocytes, myeloid dendritic cells, and vascular endothelium under the stimulation of inflammatory cytokines. PTX3 shares some similarities with CRP, but differs in terms of structural domain, gene organization, and cellular and tissue sources.[41] In this context, high circulating osteoprotegerin and PTX3 levels might reflect an ongoing injury to endothelial cells, indicating a proinflammatory milieu. Together with the reduction in plasma endothelin concentration, this suggests that light-to-moderatewine consumption is associated with an improvement in endothelial dysfunction in patients with chronic HF. However, the pathophysiologic relevance of an anti-inflammatory action of moderate wine consumption should be seen in the light of the fact that in GISSI-HF we found that circulating inflammatory markers had little if any independent prognostic value[23,27] and that rosuvastatin significantly decreased high-sensitivity C-reactive protein levels without affecting outcomes.[18]

Finally, although statistically significant, the trend between N-terminal pro B-type natriuretic peptide or high-sensitivity cardiac troponin T and red wine consumption was not clear as for other biomarkers. This is consistent with the absence of any independent relation between red wine intake and clinical outcome.

Wine Consumption, QoL, and Depression

The evidences on the benefits of wine consumption are scarce to date, as the medical literature is mainly focused on the unhealthy consequences of alcohol drinking. Moderate wine drinkers reported better lifestyles and metabolic parameters compared with nondrinkers,[42] lower incidence of HF,[3] lower mortality,[43] and a better perceived health[43–45] and psychological functioning.[46] The differences remained statistically significant after adjustment for several variables, and even within populations of the same social class.[43] This is the first time that such an association is reported in patients with chronic HF: in the 1465 patients in the QoL, depression, and cognitive function substudy, depression of moderate-to-high severity was significantly less frequent in patients drinking at least 1 glass of wine a day. The perception of health status, as assessed by Kansas City Cardiomyopathy Questionnaire, was significantly better in the same patients even after full adjustments. Our results are not easily comparable with other studies on general populations of Northern European countries, with different habits toward alcohol consumption and where wine drinking may be associated to a higher social background.[42,43,46] Social class is not a confounder in our population because wine consumption is widespread and only a minority of patients drank

beer or other spirits. The list of other potential confounders may include smoking, exercise, and social networks. However, Poikolainen et al45 reported that despite these adjustments, the associations between wine consumption and perceived health remained, weakening the role of lifestyles. In other studies, a good perception of health was independently associated with lower mortality in patients with HF,19 and depression overall,47 specifically major depression,48 was independently associated with a higher risk of cardiovascular and all-cause mortality. Moderate wine consumption is strongly associated with both favorable prognostic factors. Although we did not observe benefits on mortality or hospitalizations, we neither observed negative effects on health in moderate wine drinkers, highlighting that it is not necessarily a negative habit. Whether it is the wine consumption per se— and not the characteristics of the people who decide to drink wine, to account for the differences in health perception—is not clear. Because of the strength of the association, wine consumption could be a possible indicator of better attitude toward life, and not a behavior to be necessarily blamed in patients with HF.

Some limitations need to be pointed out. The dietary questionnaire used in the GISSI-HF trial did not distinguish between red and white wine, 2 beverages whose content in biologically active compounds may differ, although the differences in the cardiovascular effects of the 2 kinds of wine have been questioned.49 For this reason, data from GISSI-HF cannot be easily compared with other populations with different types and patterns of alcohol consumption. In addition, the design of the clinical trial did not permit any causal relationship but only associations between patient-reported wine consumption and health status, which may be influenced by unreported confounding clinical variables. The patient characteristics were typical of those found in randomized clinical trials because in the general population, patients with HF are older, more often women, and more frequently with preserved LVEF.

Generated by a large and well-documented population of patients with HF, with the support of 2 complementary sets of the soft data on the QoL and circulating biomarkers, our findings do provide a reasonably consistent and comprehensive view of this old problem of cardiology.

Among the various protective or risk factors which characterize HF, wine does not seem to play either a beneficial nor a dangerous role. Across the levels of exposure, wine seems more as descriptive variable which accompanies the more relevant hard determinants of health/risk: a critical clinical condition is a cause of nonexposure, or the expression of a multifactorial exposure to risks, including tobacco; low to moderate consumption could be part of a positive attitude to life consistent with the corresponding estimates of QoL.

References

1. Ruidavets JB, Ducimetière P, Evans A, Montaye M, Haas B, Bingham A, Yarnell J, Amouyel P, Arveiler D, Kee F, Bongard V, Ferrières J. Patterns
of alcohol consumption and ischaemic heart disease in culturally divergent countries: the Prospective Epidemiological Study of Myocardial Infarction (PRIME). *BMJ*. 2010;341:c6077. doi: 10.1136/bmj.c6077.

2. Leong DP, Smyth A, Teo KK, McKee M, Rangarajan S, Pais P, Liu L, Anand SS, Yusuf S; INTERHEART Investigators. Patterns of alcohol consumption and myocardial infarction risk: observations from 52 countries in the INTERHEART case-control study. *Circulation*. 2014;130:390–398.doi:10.1161/CIRCULATIONAHA.113.007627.

3. Gonçalves A, Claggett B, Jhund PS, Rosamond W, Deswal A, Aguilar D, Shah AM, Cheng S, Solomon SD. Alcohol consumption and risk of heart failure: the Atherosclerosis Risk in Communities Study. *Eur Heart J*. 2015;36:939–945. doi: 10.1093/eurheartj/ehu514.

4. American Heart Association Nutrition Committee, Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, Franch HA, Franklin B, Kris-Etherton P, Harris WS, Howard B, Karanja N, Lefevre M, Rudel L, Sacks F, Van Horn L, Winston M, Wylie-Rosett J. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. *Circulation*. 2006;114:82–96.

5. Ronksley PE, Brien SE, Turner BJ, Mukamal KJ, Ghali WA. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. *BMJ*. 2011;342:d671. doi: 10.1136/bmj.d671.

6. Andriantsitohaina R, Auger C, Chataigneau T, Étienne-Selloum N, Li H, Martínez MC, Schini-Kerth VB, Laher I. Molecular mechanisms of the cardiovascular protective effects of polyphenols. *Br J Nutr*. 2012;108:1532–1549. doi: 10.1017/S0007114512003406.

7. Chiva-Blanch G, Urpi-Sarda M, Llorach R, Rotches-Ribalta M, Guillén M, Casas R, Arranz S, Valderas-Martinez P, Portoles O, Corella D, Tinahones F, Lamuela-Raventos RM, Andres-Lacueva C, Estruch R. Differential effects of polyphenols and alcohol of red wine on the expression of adhesion molecules and inflammatory cytokines related to atherosclerosis: a randomized clinical trial. *Am J Clin Nutr*. 2012;95:326–334. doi: 10.3945/ajcn.111.022889.

8. Aguilar D, Skali H, Moyé LA, Lewis EF, Gaziano JM, Rutherford JD, Hartley LH, Randall OS, Geltman EM, Lamas GA, Rouleau JL, Pfeffer MA, Solomon SD. Alcohol consumption and prognosis in patients with left ventricular systolic dysfunction after a myocardial infarction. *J Am Coll Cardiol*. 2004;43:2015–2021. doi: 10.1016/j.jacc.2004.01.042.

9. Chiva-Blanch G, Arranz S, Lamuela-Raventos RM, Estruch R. Effects of wine, alcohol and polyphenols on cardiovascular disease risk factors: evidences from human studies. *Alcohol Alcohol*. 2013;48:270–277. doi:10.1093/alcalc/agt007.

10. Levantesi G, Marfisi R, Mozaffarian D, Franzosi MG, Maggioni A, Nicolosi GL, Schweiger C, Silletta M, Tavazzi L, Tognoni G, Marchioli R. Wine consumption and risk of cardiovascular events after myocardial infarction: results from the GISSI-Prevenzione trial. *Int J Cardiol*. 2013;163:282–287. doi: 10.1016/j.ijcard.2011.06.053.

11. Hansel B, Thomas F, Pannier B, Bean K, Kontush A, Chapman MJ, Guize L, Bruckert E. Relationship between alcohol intake, health and social status and cardiovascular risk factors in the Urban Paris-Ile-de- France Cohort: is the cardioprotective action of alcohol a myth? *Eur J Clin Nutr*. 2010;64:561–568. doi: 10.1038/ejcn.2010.61.

12. Kloner RA, Rezkalla SH. To drink or not to drink? That is the question. *Circulation*. 2007;116:1306–1317. doi: 10.1161/ CIRCULATIONAHA.106.678375.

13. Cooper HA, Exner DV, Domanski MJ. Light-to-moderate alcohol consumption and prognosis in patients with left ventricular systolic dysfunction. *J Am Coll Cardiol*. 2000;35:1753–1759.

14. Petrone AB, Gaziano JM, Djoussé L. Alcohol consumption and risk of death in male physicians with heart failure. *Am J Cardiol*. 2014;114:1065–1068. doi: 10.1016/j.amjcard.2014.07.021.

15. Gargiulo G, Testa G, Cacciatore F, Mazzella F, Galizia G, Della-Morte D, Langellotto A, Pirozzi G, Ferro G, Ferrara N, Rengo F, Abete P. Moderate alcohol consumption predicts long-term mortality in elderly subjects with chronic heart failure. *J Nutr Health Aging*. 2013;17:480– 485. doi: 10.1007/s12603-012-0430-4.

16. Piano MR. Alcohol and heart failure. *J Card Fail*. 2002;8:239–246.

17. GISSI-HF Investigators, Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo- controlled trial. *Lancet*. 2008;372:1223–1230. doi: 10.1016/ S0140-6736(08)61239-8.

18. GISSI-HF Investigators, Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G. Effect of rosuvastatin in patients with chronic heart failure (the GISSIHF trial): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;372:1231–1239. doi: 10.1016/S0140-6736(08)61240-4.

19. Network of Nurses of GISSI-HF, Di Giulio P. Should patients perception of health status be integrated in the prognostic assessment of heart failure patients? A prospective study. *Qual Life Res*. 2014;23:49–56. doi: 10.1007/s11136-013-0468-8.

20. Miani D, Rozbowsky P, Gregori D, Pilotto L, Albanese MC, Fresco C, Fioretti PM. The Kansas City Cardiomyopathy Questionnaire: Italian translation and validation. *Ital Heart J*. 2003;4:620-626.

21. Spertus J, Peterson E, Conard MW, Heidenreich PA, Krumholz HM, Jones P, McCullough PA, Pina I, Tooley J, Weintraub WS, Rumsfeld JS; Cardiovascular Outcomes Research Consortium. Monitoring clinical changes in patients with heart failure: a comparison of methods. *Am Heart J*. 2005;150:707–715. doi: 10.1016/j.ahj.2004.12.010.

22. D'Ath P, Katona P, Mullan E, Evans S, Katona C. Screening, detection and management of depression in elderly primary care attenders. I: the acceptability and performance of the 15 item Geriatric Depression Scale (GDS15) and the development of short versions. *Fam Pract*. 1994;11:260–266.

23. Røysland R, Masson S, Omland T, Milani V, Bjerre M, Flyvbjerg A, Di Tano G, Misuraca G, Maggioni AP, Tognoni G, Tavazzi L, Latini R; GISSI-HF Investigators. Prognostic value of osteoprotegerin in chronic heart failure: the GISSI-HF trial. *Am Heart J*. 2010;160:286–293. doi: 10.1016/j.ahj.2010.05.015.

24. Masson S, Latini R, Carbonieri E, Moretti L, Rossi MG, Ciricugno S, Milani V, Marchioli R, Struck J, Bergmann A, Maggioni AP, Tognoni G, Tavazzi L; GISSI-HF Investigators. The predictive value of stable precursor fragments of vasoactive peptides in patients with chronic heart failure: data from the GISSI-heart failure (GISSI-HF) trial. *Eur J Heart Fail*. 2010;12:338–347. doi: 10.1093/eurjhf/hfp206.

25. Masson S, Anand I, Favero C, Barlera S, Vago T, Bertocchi F, Maggioni AP, Tavazzi L, Tognoni G, Cohn JN, Latini R; Valsartan Heart FailureTrial (Val-HeFT) and Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca–Heart Failure (GISSI-HF) Investigators. Serial measurement of cardiac troponin T using a highly sensitive assay in patients with chronic heart failure: data from 2 large randomized clinical trials. *Circulation*. 2012;125:280–288. doi: 10.1161/CIRCULATIONAHA.111.044149.

26. Masson S, Gori F, Latini R, Milani V, Flyvbjerg A, Frystyk J, Crociati L, Pietri S, Vago T, Barlera S, Maggioni AP, Tognoni G, Tavazzi L, Omland T, Franzosi MG; GISSI-HF Investigators. Adiponectin in chronic heart failure: influence of diabetes and genetic variants. *Eur J Clin Invest*. 2011;41:1330–1338. doi: 10.1111/j.1365-2362.2011.02548.x.

27. Latini R, Gullestad L, Masson S, Nymo SH, Ueland T, Cuccovillo I, Vårdal M, Bottazzi B, Mantovani A, Lucci D, Masuda N, Sudo Y, Wikstrand J, Tognoni G, Aukrust P, Tavazzi L; Investigators of the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) and GISSI-Heart Failure (GISSI-HF) trials. Pentraxin-3 in chronic heart failure: the CORONA and GISSI-HF trials. *Eur J Heart Fail*. 2012;14:992–999. doi: 10.1093/eurjhf/hfs092.

28. Schafer JL. *Analysis of Incomplete Multivariate Data*. London, United Kingdom: Chapman & Hall; 1997.

29. Ghali WA, Quan H, Brant R, van Melle G, Norris CM, Faris PD, Galbraith PD, Knudtson ML; APPROACH (Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease) Investigators. Comparison of 2 methods for calculating adjusted survival curves from proportional hazards models. *JAMA*. 2001;286:1494–1497.

30. Chang IM, Gelman R, Pagano M. Corrected group prognostic curves and summary statistics. *J Chronic Dis*. 1982;35:669–674.

31. Hofmann U, Frantz S. How can we cure a heart "in flame"? A translational view on inflammation in heart failure. *Basic Res Cardiol*. 2013;108:356. doi: 10.1007/s00395-013-0356-y.

32. Brien SE, Ronksley PE, Turner BJ, Mukamal KJ, Ghali WA. Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studies. *BMJ*. 2011;342:d636. doi: 10.1136/bmj.d636.

33. Imhof A, Woodward M, Doering A, Helbecque N, Loewel H, Amouyel P, Lowe GD, Koenig W. Overall alcohol intake, beer, wine, and systemic markers of inflammation in western Europe: results from three MONICA samples (Augsburg, Glasgow, Lille). *Eur Heart J*. 2004;25:2092–2100. doi: 10.1016/j.ehj.2004.09.032.

34. Schmitt CA, Heiss EH, Dirsch VM. Effect of resveratrol on endothelial cell function: Molecular mechanisms. *Biofactors*. 2010;36:342–349. doi: 35. Tsutamoto T, Hisanaga T, Fukai D, Wada A, Maeda Y, Maeda K, Kinoshita M. Prognostic value of plasma soluble intercellular adhesion molecule-1 and endothelin-1 concentration in patients with chronic congestive heart failure. *Am J Cardiol*. 1995;76:803–808. 10.1002/biof.109.

35. Tsutamoto T, Hisanaga T, Fukai D, Wada A, Maeda Y, Maeda K, Kinoshita M. Prognostic value of plasma soluble intercellular adhesion molecule-1 and endothelin-1 concentration in patients with chronic congestive heart failure. *Am J Cardiol*. 1995;76:803–808.

36. Masson S, Latini R, Anand IS, Barlera S, Judd D, Salio M, Perticone F, Perini G, Tognoni G, Cohn JN; Val-HeFT investigators. The prognostic value of big endothelin-1 in more than 2,300 patients with heart failure enrolled in the Valsartan Heart Failure Trial (Val-HeFT). *J Card Fail*. 2006;12:375–380. doi: 10.1016/j.cardfail.2006.02.013.

37. Khan NQ, Lees DM, Douthwaite JA, Carrier MJ, Corder R. Comparison of red wine extract and polyphenol constituents on endothelin-1 synthesis by cultured endothelial cells. *Clin Sci (Lond)*. 2002;103(suppl 48):72S–75S. doi: 10.1042/CS103S072S.

38. Corder R, Douthwaite JA, Lees DM, Khan NQ, Viseu Dos Santos AC, Wood EG, Carrier MJ. Endothelin-1 synthesis reduced by red wine. *Nature*. 2001;414:863–864. doi: 10.1038/414863a.

39. Venuraju SM, Yerramasu A, Corder R, Lahiri A. Osteoprotegerin as a predictor of coronary artery disease and cardiovascular mortality and morbidity. *J Am Coll Cardiol*. 2010;55:2049–2061. doi: 10.1016/j. jacc.2010.03.013.

40. Montagnana M, Lippi G, Danese E, Guidi GC. The role of osteoprotegerin in cardiovascular disease. *Ann Med*. 2013;45:254–264. doi: 10.3109/07853890.2012.727019.

41. Bottazzi B, Doni A, Garlanda C, Mantovani A. An integrated view of humoral innate immunity: pentraxins as a paradigm. *Annu Rev Immunol*.2010;28:157–183. doi: 10.1146/annurev-immunol-030409-101305.

42. Rosell M, De Faire U, Hellénius ML. Low prevalence of the metabolic syndrome in wine drinkers–is it the alcohol beverage or the lifestyle? *Eur J Clin Nutr*. 2003;57:227–234. doi: 10.1038/sj.ejcn.1601548.

43. Strandberg TE, Strandberg AY, Salomaa VV, Pitkälä K, Tilvis RS, Miettinen TA. Alcoholic beverage preference, 29 year mortality, and quality of life in men in old age. *J Gerontol*. 2007; 62A:213–218.

44. Grønbaek M, Mortensen EL, Mygind K, Andersen AT, Becker U, Gluud C, Sørensen TI. Beer, wine, spirits and subjective health. *J Epidemiol Community Health*. 1999;53:721–724.

45. Poikolainen K, Vartiainen E. Wine and good subjective health. *Am J Epidemiol*. 1999;150:47–50.

46. Mortensen EL, Jensen HH, Sanders SA, Reinisch JM. Better psychological functioning and higher social status may largely explain the apparent health benefits of wine: a study of wine and beer drinking in young Danish adults. *Arch Intern Med*. 2001;161:1844–1848.

47. Freedland KE, Carney RM, Rich MW. Effect of depression on prognosis in heart failure. *Heart Fail Clin*. 2011;7:11–21. doi: 10.1016/j. hfc.2010.08.003.

48. Fan H, Yu W, Zhang Q, Cao H, Li J, Wang J, Shao Y, Hu X. Depression after heart failure and risk of cardiovascular and all-cause mortality: a metaanalysis. *Prev Med*. 2014;63:36–42. doi: 10.1016/j.ypmed.2014.03.007.

49. Krenz M, Korthuis RJ. Moderate ethanol ingestion and cardiovascular protection: from epidemiologic associations to cellular mechanisms. *J Mol Cell Cardiol*. 2012;52:93–104. doi: 10.1016/j.yjmcc.2011.10.011.

Table 1: **Baseline characteristics of 6,973 patients enrolled in the GISSI-HF trial, in relation to wine consumption.**

	Daily wine consumption					
	Never N=2,461 (35.3%)	**Sometimes** N=1,325 (19.0%)	**1-2glasses/d** N=2,570 (36.8%)	**≥3glasses/d** N=617 (8.9%)	**Overall** N=6,973 (100%)	**P for trend**
Patients' characteristics						
Age (years)	67 (11)	66 (11)	68 (10)	67 (10)	67 (11)	0.01
Age > 70 years	1060 (43.1)	499 (37.7)	1152 (44.8)	236 (38.3)	2947 (42.3)	0.93
Women	880 (35.8)	332 (25.1)	297 (11.6)	7 (1.1)	1516 (21.7)	<0.0001
Heart disease risk factors						
BMI (kg/m^2)	27 (5)	27 (4)	27 (4)	27 (4)	27 (4)	0.004
SBP (mm Hg)	127 (18)	125 (18)	126 (18)	128 (18)	126 (18)	0.90
DBP (mm Hg)	77 (9)	76 (10)	77 (9)	79 (10)	77 (10)	0.10
Heart rate (beats per min)	73 (14)	72 (14)	72 (14)	73 (15)	73 (14)	0.002
Current smoking	308 (12.5)	181 (13.7)	363 (14.1)	134 (21.7)	986 (14.1)	<0.0001
History of hypertension	1421 (57.7)	698 (52.7)	1377 (53.6)	313 (50.7)	3809 (54.6)	0.0003
NYHA class						<0.0001
II	1439 (58.5)	855 (64.5)	1698 (66.1)	431 (69.9)	4423 (63.4)	
III	929 (37.8)	442 (33.4)	819 (31.9)	175 (28.4)	2365 (33.9)	
IV	93 (3.8)	28 (2.1)	53 (2.1)	11 (1.8)	185 (2.7)	
LVEF (%)	33.3 (8.9)	32.7 (8.3)	32.9 (8.2)	33.5 (8.4)	33.1 (8.5)	0.69
LVEF > 40%	255 (10.4)	112 (8.5)	222 (8.6)	64 (10.4)	653 (9.4)	0.21
Medical history						
Admission for HF in previous year	1319 (53.6)	613 (46.3)	1191 (46.3)	260 (42.1)	3383 (48.5)	<0.0001
Previous AMI	985 (40.0)	599 (45.2)	1100 (42.8)	223 (36.1)	2907 (41.7)	0.98
Previous stroke	135 (5.5)	59 (4.5)	129 (5.0)	22 (3.6)	345 (5.0)	0.12
Diabetes mellitus	805 (32.7)	386 (29.1)	655 (25.5)	127 (20.6)	1973 (28.3)	<0.0001
CABG	382 (15.5)	250 (18.9)	528 (20.5)	110 (17.8)	1270 (18.2)	0.0002

PCI	300 (12.2)	196 (14.8)	310 (12.1)	60 (9.7)	866 (12.4)	0.19
ICD	166 (6.8)	122 (9.2)	172 (6.7)	37 (6.0)	497 (7.1)	0.47
Pacemaker	319 (13.0)	178 (13.4)	324 (12.6)	70 (11.4)	891 (12.8)	0.35
History of atrial fibrillation	462 (18.8)	255 (19.3)	496 (19.3)	111 (18.0)	1324 (19.0)	0.98
Peripheral vascular disease	219 (8.9)	105 (7.9)	220 (8.6)	66 (10.7)	610 (8.8)	0.52
COPD	528 (21.5)	249 (18.8)	578 (22.5)	178 (28.9)	1533 (22.0)	0.002
Neoplasia	79 (3.2)	46 (3.5)	102 (4.0)	29 (4.7)	256 (3.7)	0.048
Cause of heart failure						
Ischemic	1197 (48.6)	709 (53.5)	1282 (49.9)	278 (45.1)	3466 (49.7)	0.53
Dilative	703 (28.6)	349 (26.3)	787 (30.6)	186 (30.2)	2025 (29.0)	0.09
Hypertensive	393 (16.0)	185 (14.0)	369 (14.4)	89 (14.4)	1036 (14.9)	0.13
Other	77 (3.1)	39 (2.9)	50 (2.0)	29 (4.7)	195 (2.8)	0.64
Non-detectable/unknown	91 (3.7)	43 (3.3)	82 (3.2)	35 (5.7)	251 (3.6)	0.42
Physical examination						
Pulmonary rales	715 (29.1)	301 (22.7)	608 (23.7)	145 (23.5)	1769 (25.4)	<0.0001
Third heart sound	655 (26.6)	328 (24.8)	601 (23.4)	153 (24.8)	1737 (24.9)	0.02
Mitral insufficiency	1608 (65.3)	849 (64.1)	1610 (62.7)	343 (55.6)	4410 (63.2)	<0.0001
Aortic stenosis	55 (2.2)	24 (1.8)	55 (2.1)	9 (1.5)	143 (2.1)	0.43
ECG findings						
QRS > 120 ms	824 (33.5)	445 (33.6)	903 (35.1)	207 (33.6)	2379 (34.1)	0.39
Atrial fibrillation	390 (15.9)	189 (14.3)	458 (17.8)	102 (16.5)	1139 (16.3)	0.09
Pathological Q waves	538 (21.9)	325 (24.5)	605 (23.5)	136 (22.0)	1604 (23.0)	0.40
Left ventricular hypertrophy	455 (18.5)	219 (16.5)	537 (20.9)	127 (20.6)	1338 (19.2)	0.02
Laboratory tests						
Fibrinogen (mg/dL)	376 (107)	379 (113)	364 (109)	351 (106)	370 (109)	<0.0001
WBC (/mm^3)	7384 (2158)	7464 (2123)	7291 (2045)	7254 (2134)	7353 (2109)	0.05
Serum creatinine (mg/dL)	1.20 (0.59)	1.20 (0.43)	1.21 (0.43)	1.14 (0.34)	1.20 (0.48)	0.21
eGFR (mL*min^{-1}*1.73m^{-2})	63 (23)	64 (22)	64 (21)	70 (20)	64 (22)	<0.0001
Serum bilirubin (mg/dL)	0.84 (0.64)	0.83 (0.56)	0.84 (0.50)	0.93 (0.91)	0.85 (0.61)	0.02
AST (U/L)	25 (31)	24 (12)	24 (14)	26 (15)	24 (21)	0.92
Hemoglobin (mg/dL)	13.4 (1.7)	13.6 (1.6)	13.9 (1.6)	14.3 (1.5)	13.7 (1.7)	<0.0001

Total cholesterol (mg/dL)	189 (43)	189 (42)	191 (42)	201 (45)	191 (43)	<0.0001
Serum HDL-cholesterol (mg/dL)	46 (12)	46 (13)	48 (13)	51 (15)	47 (13)	<0.0001
Blood glucose (mg/dL)	121 (48)	121 (51)	116 (43)	114 (37)	119 (46)	<0.0001
Medical treatment						
ACE inhibitors	1860 (75.6)	988 (74.6)	2014 (78.4)	511 (82.8)	5373 (77.1)	<0.0001
ARBs	484 (19.7)	291 (22.0)	463 (18.0)	82 (13.3)	1320 (18.9)	0.0008
ACE inhibitors/ARBs	2293 (93.2)	1233 (93.1)	2415 (94.0)	577 (93.5)	6518 (93.5)	0.33
B blockers	1590 (64.6)	906 (68.4)	1635 (63.6)	390 (63.2)	4521 (64.8)	0.26
Spironolactone	1004 (40.8)	534 (40.3)	968 (37.7)	233 (37.8)	2739 (39.3)	0.02
Diuretic drugs	2247 (91.3)	1179 (89.0)	2303 (89.6)	530 (85.9)	6259 (89.8)	0.0005
Digitalis	990 (40.2)	469 (35.4)	930 (36.2)	198 (32.1)	2587 (37.1)	<0.0001
Oral anticoagulant drugs	667 (27.1)	374 (28.2)	793 (30.9)	174 (28.2)	2008 (28.8)	0.02
Aspirin	1165 (47.3)	647 (48.8)	1235 (48.1)	310 (50.2)	3357 (48.1)	0.31
Other antiplatelet agents	285 (11.6)	138 (10.4)	244 (9.5)	49 (7.9)	716 (10.3)	0.002
Nitrates	909 (36.9)	468 (35.3)	905 (35.2)	190 (30.8)	2472 (35.5)	0.01
Calcium-channel blockers	267 (10.9)	133 (10.0)	240 (9.3)	69 (11.2)	709 (10.2)	0.32
Amiodarone	436 (17.7)	270 (20.4)	536 (20.9)	116 (18.8)	1358 (19.5)	0.04
Statin (open)	570 (23.2)	306 (23.1)	560 (21.8)	141 (22.9)	1577 (22.6)	0.37

Continuous variables are reported as mean (SD), discrete variables as numbers (%) of patients for which the variable was present, percentages may not add up to 100 because of missing values or rounding. P for trend <0.05 for differences across categories of wine consumption. ACE indicates angiotensin-converting enzyme; AMI Acute myocardial Infarction; ARB, angiotensin II type 1 receptor blocker; AST, aspartate aminotransferase; BMI, body-mass index; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; DBP/SBP, diastolic/systolic blood pressure; eGFR, estimated glomerular filtration rate; HDL; High Density lipoprotein; HF, heart failure; ICD, implantable cardioverter defibrillator; LFEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; WBC, white blood cells.

Table 2: Clinical outcomes during follow-up by levels of wine consumption

	Daily wine consumption			
	Never **2,461** **(35.3%)**	**Sometimes** **1,325** **(19.0%)**	**1-2 glasses/d** **2,570** **(36.8%)**	**≥3 glasses/d** **617** **(8.9%)**
Causes of death				
All causes	716 (29.1)	350 (26.4)	752 (29.3)	150 (24.3)
Worsening HF	231 (9.4)	126 (9.5)	244 (9.5)	50 (8.1)
Presumed arrhythmic	204 (8.3)	107 (8.1)	224 (8.7)	43 (7.0)
CV death	523 (21.3)	274 (20.7)	572 (22.3)	108 (17.5)
Sudden death	222 (9.0)	121 (9.1)	240 (9.3)	49 (7.9)
Hospitalization				
All causes	1368 (55.6)	775 (58.5)	1492 (58.1)	378 (61.3)
CV reasons	1127 (45.8)	663 (50.0)	1239 (48.2)	292 (47.3)
HF	685 (27.8)	384 (29.0)	739 (28.8)	165 (26.7)
Ventricular arrhythmias	59 (2.4)	53 (4.0)	96 (3.7)	20 (3.2)
Total events				
All cause death or hospitalization for CV causes	1413 (57.4)	781 (58.9)	1489 (57.9)	350 (56.7)
Total MI	85 (3.5)	47 (3.6)	89 (3.5)	15 (2.4)
Total stroke	86 (3.5)	46 (3.5)	75 (2.9)	18 (2.9)
Total HF	718 (29.2)	394 (29.7)	761 (29.6)	170 (27.6)
Total arrhythmias*	255 (10.4)	151 (11.4)	308 (12.0)	60 (9.7)

Data are reported as number and percentage of the 6,973 patients. Total events include both fatal and non-fatal events. CV indicates cardiovascular; HF heart failure; and MI Myocardial Infarction.

Table 3: Cox proportional hazard models for wine consumption and clinical outcomes

	Model	Sometimes 1,325	1-2 glasses/d 2,570	≥3 glasses/d 617	P for trend	Wine x n-3 PUFA interaction	Wine x rosuvastatin interaction
All-cause mortality	Unadjusted	0.89 [0.79-1.02]	1.00 [0.91-1.11]	0.79 [0.66-0.94]	0.18	0.04	
	Fully adjusted	0.91 [0.80-1.03]	0.96 [0.86-1.07]	0.91 [0.76-1.09]	0.31	0.29	
All cause death or hospitalization for CV causes	Unadjusted	1.04 [0.96-1.14]	1.00 [0.93-1.08]	0.93 [0.82-1.04]	0.42	0.22	
	Fully adjusted	1.07 [0.98-1.17]	1.01 [0.94-1.09]	1.04 [0.92-1.18]	0.64	0.30	
Worsening HF	Unadjusted	1.03 [0.91-1.17]	1.03 [0.92-1.14]	0.90 [0.76-1.06]	0.62	0.89	
	Fully adjusted	1.06 [0.94-1.21]	1.08 [0.97-1.21]	1.12 [0.94-1.34]	0.11	0.94	
Sudden death	Unadjusted	1.00 [0.80-1.24]	1.03 [0.86-1.24]	0.83 [0.61-1.14]	0.66	0.53	
	Fully adjusted	0.99 [0.79-1.24]	0.98 [0.81-1.19]	0.90 [0.65-1.24]	0.63	0.79	

Data are shown as hazard ratio and 95% confidence interval in univariate and multivariable Cox proportional hazard models, with patients never drinkers as the reference category.

Covariates for adjustment: age, sex, body mass index, ischemic etiology, NYHA class, admission for HF in the previous year, prior stroke, smoking, history of hypertension, diabetes, ICD, peripheral vascular disease, COPD, peripheral edema, pulmonary congestion, aortic stenosis, left ventricular ejection fraction, heart rate, systolic and diastolic blood pressure, pathological Q waves, atrial fibrillation, left ventricular hypertrophy, hemoglobin, total cholesterol, triglycerides, blood glucose, glomerular filtration rate, serum potassium, serum sodium, total creatine kinase, glycated hemoglobin, digitalis, spironolactone, diuretics, ARBs, β-blockers, oral anticoagulants, antiplatelets, nitrates, amiodarone, antidepressants, n-3 PUFA and statins.

Table 4: Quality of life and depression scale in 1465 patients enrolled in the QDF sub-study

	All 1,465	Wine consumption				
		Never 489 (33.4%)	Sometimes 301 (20.5%)	1-2 glasses/d 554 (37.8%)	≥3 glasses/d 121 (8.3%)	P*
KCCQ						
Good (≥75)	822 (56.1)	225 (46.0)	173 (57.5)	347 (62.6)	77 (63.6)	
Fair (74-50)	413 (28.2)	161 (32.9)	77 (25.6)	140 (25.3)	35 (28.9)	<0.0001
Poor (25-49)	185 (12.6)	74 (15.1)	43 (14.3)	59 (10.6)	9 (7.4)	
Worst (<25)	45 (3.1)	29 (5.9)	8 (2.7)	8 (1.4)	0 (0.0)	
Median [IR]	78.6 [59.9-90.6]	72.4 [52.9-87.5]	80.2 [59.9-89.2]	82.3 [64.8-92.7]	82.3 [70.3-94.8]	<0.0001§
Depression (GDS score)						
None (0-4)	970 (66.2)	290 (59.3)	198 (65.8)	390 (70.4)	92 (76.0)	
Mild (5-8)	310 (21.2)	109 (22.3)	72 (23.9)	106 (19.1)	23 (19.0)	<0.0122
Moderate/severe (≥9)	185 (12.6)	90 (18.4)	31 (10.3)	58 (10.5)	6 (5.0)	
Median [IR]	3 [1-6]	3 [1-7]	3 [1-6]	2 [1-5]	2 [1-4]	<0.002§

GDS indicates Geriatric Depression Scale and KCCQ, Kansas City Cardiomyopathy Questionnaire

*Adjusted for age, sex, body mass index, ischemic causes of HF, NYHA class, admission for HF in the previous year, previous stroke, smoking, history of hypertension, diabetes mellitus, Implantable, cardioverter defibrillator, peripheral vascular disease, chronic obstructive pulmonary disease, peripheral edema, pulmonary congestion, aortic stenosis, left ventricular ejection fraction, heart rate, systolic and diastolic blood pressure, pathological Q waves, atrial fibrillation, left ventricular hypertrophy, hemoglobin, total cholesterol, triglycerides, blood glucose, glomerular filtration rate, serum potassium, serum sodium, total creatine kinase, glycated hemoglobin, digitalis, spironolactone, diuretics, ARBs, β-blockers, oral anticoagulants, antiplatelets, nitrates, amiodarone, antidepressants, polinstured fatty acids and rosuvastatin.

§ median test
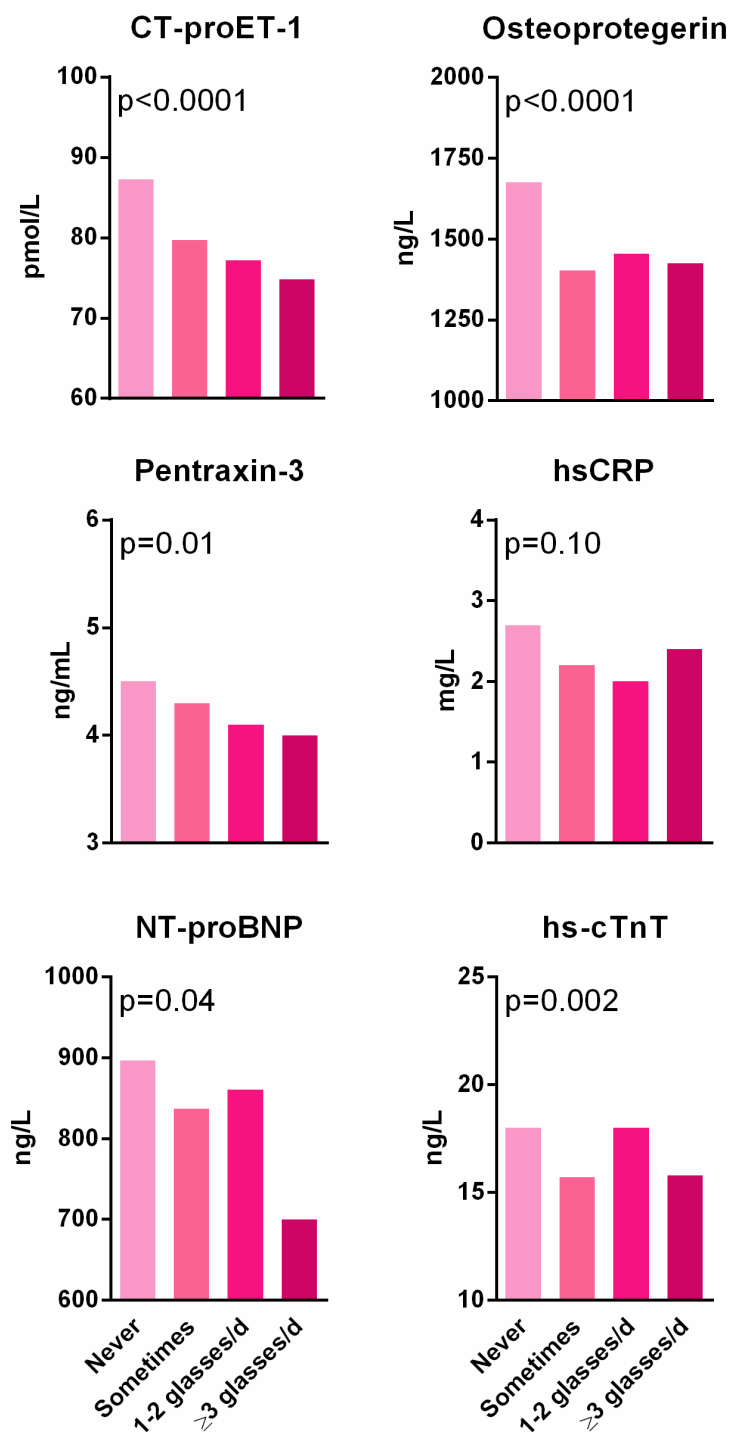
Figure 2. Median (Q1-Q3)plasma concentrations of selected circulating biomarkers in relation to wine consumption in 1235 patients with chronic heart failure from the Gruppo Italiano per lo Studio della Sopravvivenza per l'Insufficienza Cardiaca-Heart Failure study. P values adjusted for age, sex and NYHA class. Multiple regression model on the ranks of the biomarkers adjusted for age, sex and NYHA functional class. CT-proET-1, C-terminal proendothelin-1; hs-cTnT, high-sensitivity

cardiac troponin T; hsCRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal proB-type natriuretic peptide.

A Total mortality

Pts (Events)	0	180	360	540	720	900	1080	1260	1440
Never	2461 (111)	2336 (86)	2246 (99)	2139 (77)	2055 (94)	1957 (74)	1867 (62)	1536 (52)	1176 (61)
Sometimes	1325 (47)	1277 (42)	1235 (44)	1189 (49)	1139 (40)	1098 (38)	1043 (31)	843 (25)	625 (34)
1-2 g/d	2570 (89)	2474 (104)	2369 (87)	2277 (110)	2159 (93)	2065 (67)	1968 (79)	1592 (55)	1181 (68)
≥ 3 g/d	617 (18)	599 (14)	585 (14)	570 (13)	555 (18)	535 (20)	515 (23)	418 (13)	305 (17)

Legend:
- Never 716/2461 (29.1%)
- Sometimes 350/1325 (26.4%)
- 1-2 glasses/d 752/2570 (29.3%)
- ≥ 3 glasses/d 150/617 (24.3)

B Total mortality or admission for CV reasons

Pts (Events)	0	180	360	540	720	900	1080	1260	1440
Never	2461 (441)	2009 (228)	1777 (186)	1583 (137)	1441 (122)	1316 (107)	1196 (90)	934 (54)	684 (48)
Sometimes	1325 (248)	1076 (126)	950 (111)	838 (84)	753 (56)	696 (49)	637 (42)	490 (33)	348 (32)
1-2 g/d	2570 (443)	2121 (247)	1873 (190)	1679 (155)	1519 (145)	1374 (103)	1252 (88)	978 (69)	688 (49)
≥ 3 g/d	617 (89)	528 (36)	492 (57)	434 (38)	394 (36)	357 (33)	324 (25)	256 (17)	180 (19)

Legend:
- Never 1413/2461 (57.4%)
- Sometimes 781/1325 (58.9%)
- 1-2 glasses/d 1489/2570 (57.9%)
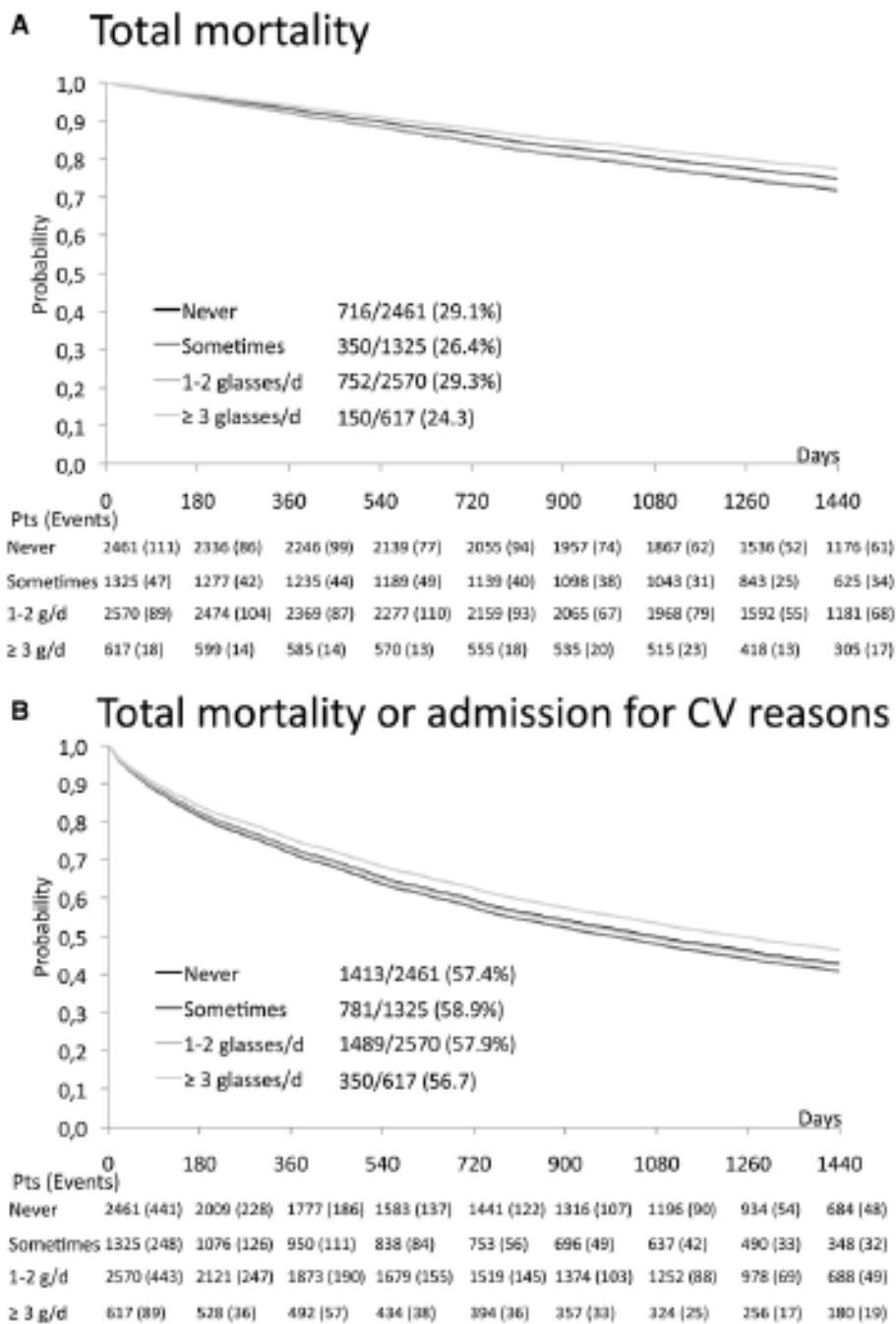- ≥ 3 glasses/d 350/617 (56.7)

Figure 1. Adjustment survival curves for (A) all-cause mortality, (B) all-cause mortality or hospitalization for cardiovascular (CV) reasons by 4 categories of wine consumption. The variables used for adjustment are listed below table 3.