DOI: 10.4149/BLL_2017_072

Bratisl Med J 2017; 118 (5)
292 – 298

CLINICAL STUDY

Red or white wine consumption effect on atherosclerosis in healthy individuals (In Vino Veritas study).

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ABSTRACT
AIMS: Consumption of wine has a protective effect on cardiovascular diseases. Data from prospective, long-term, head-to-head comparisons of effects of different drinks on markers of atherosclerosis have been insufficient.
METHODS AND RESULTS: In Vino Veritas (IVV) study is long-term, prospective, multi-centre, randomized trial comparing effects of red and white wine on atherosclerosis. 157 healthy subjects were randomized to white or red wine consumption for one year. We did not find increase in HDL-cholesterol in the whole group (1.66±0.58 vs 1.62±0.49, p=0.180) or difference between both groups (1.60±0.53 vs 1.64±0.46, p=0.634). At 12 months there was reduction of LDL-cholesterol in both groups, but with no difference between the groups (3.37±0.75 vs 3.60±1.10, p=0.134); there was no difference between the groups in total cholesterol, CRP, fasting blood glucose and liver function tests. Both groups had comparable differences from baseline in levels of parameters of oxidative stress.
CONCLUSION: We did not find any clinically relevant differences in the lipid profile, CRP, fasting blood glucose and other markers of atherosclerosis, between long-term consumption of red and white wine. Moreover, we were unable to confirm the hypothesis that wine drinking is associated with an elevation of HDL *(Tab. 7, Fig. 1, Ref. 30)*. Text in PDF *www.elis.sk.*
KEY WORDS: red wine, white wine, atherosclerosis, HDL-cholesterol, French paradox.

Introduction

The observation of the so-called "French paradox" by Renaud and Lorgeril in 1992 (1) started an enormous effort to discover the mechanisms behind the beneficial effect of wine drinking on cardiovascular prognosis. Since the early '90s, a number of experimental and clinical studies have been published, describing the protective effect of red wine on different pathways of the pathogenesis of atherosclerosis. Antioxidants, flavonoids and polyphenols became the first substances contained in red wine with proven beneficial effects in various diseases, such as inhibition of LDL oxidation or attenuation of ischemia-reperfusion injury (2). However, several experimental studies have also shown that alcohol itself may have a protective impact (2) and these observations were confirmed by data from large population-based studies and registries, showing cardiovascular benefits of drinking alcohol, regardless of type of beverage, with similar benefits shown for red and white wines, beer and even liquors (3, 4). It has been shown in animal experiments and *in vitro* studies that there are major differences in basic characteristics between red and white wines. However, prospective data from long-term, head-to-head comparisons of the effects of red and white wines on markers of atherosclerosis are missing (5).

Methods

Objective

The objective of the IVV trial is to compare the long-term effects of regular red and white wine drinking on the biomarkers of atherosclerosis.

Study overview

This is a prospective, multicentre, randomized, comparative study in healthy individuals with mild to moderate risk of cardiovascular disease. The study protocol, information for patient, and informed consent were reviewed and approved by a multicentre ethics committee as well as by local ethics committees in each institution before study initiation.

Eligible individuals were randomized to one of two arms: regular drinking of red wine (RW; Pinot Noir, 2008, Moravia,

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Registration of clinical trials: The clinical trial was registered in *ISRCTN registry*
Registration Number: ISRCTN54359610; DOI 10.1186/ISRCTN54359610

Funding: This work was supported by an unrestricted grant support from Vino e Cuore, Ltd. The company provided all bottles of wine for the study.

Tab. 1. Chemical analysis of the selected white wine and red wine.

	Chardonnay-Pinot 2008	Pinot Noir 2008
Polyphenols	269	1974
Flavanols	11.9	11.9
Antioxidant activity	42.9	579.6
Catechin	4.07	143.81
Epicatechin	1.25	78.11
Trans-resveratrol	0.44	2.97
Trans-piceid	0.17	1.97
Cis-resveratrol	0.69	5.63
Cis-piceid	0.66	8.79
Trans-piceatannol	0.05	0.85
Trans-astringin	0.04	0.36
Rutin	0	3.37
Myricetin	0	0.55
Quercetin	0	0.10
Tyrosol	24.01	13.38
Anthocyans	0	71.20

Data are expressed in mg/L. Both wines were grown and produced by the Gala winery (Moravia, Czech Republic).

Tab. 2. Baseline characteristics of patients according to type of wine.

N (%)/Mean (SD)	Total	White wine	Red wine	p[1]
N	146	74	72	
Female	85 (58.2%)	42 (56.8%)	43 (59.7%)	0.716
Male	61 (41.8%)	32 (43.2%)	29 (40.3%)	
Age	49.3 (11.2)	48.7 (11.5)	49.9 (10.9)	0.499
Height	173 (9)	173 (10)	172 (8)	0.769
Weight	78 (15)	78 (16)	78 (14)	0.897
BMI	26.2 (3.6)	26.1 (3.8)	26.2 (3.5)	0.900
Waist	88 (12)	88 (12)	89 (11)	0.439
Hips	103 (9)	102 (9)	104 (9)	0.184

[1] statistical significance of difference between wine tested by ML Chi square test for category parameters and by independent t-test for continuous parameters

Czech Republic) or white wine (WW; Chardonnay-Pinot, 2008, Moravia, Czech Republic). Women with a body weight of less than 70 kg received 0.2 litres per day, women over 70 kg and men 0.3 litres per day. The chemical specifications of the respective wines are shown in Table 1. Participants were followed on an intention-to-treat basis.

Study endpoints

The primary endpoint is the level of HDL-cholesterol.

The secondary endpoints are levels of other markers associated with the progression of atherosclerosis (total- and LDL-cholesterol, triglycerides, oxidized LDL, C-reactive protein, advanced oxidation protein product, myeloperoxidase, interleukin 6, interleukin 18, matrix metalloproteinases, glutathione s-transferase, monocyte chemoattractant protein 1, soluble CD40L, fatty acid binding protein, Lp-PLA_2).

Study population

157 asymptomatic individuals with mild to moderate risk of cardiovascular disease according to the HeartScore (6) and without a known acute or chronic inflammatory disease nor liver or renal disease were enlisted to the study. The baseline physical characteristics are shown in Table 2.

Randomization and follow-up

Eligible individuals willing to participate in the IVV study were (after the signing of informed consent) randomized into one of the two arms. Red or white wine was supplied in bottles directly to the participants' homes in the respective amount. Each participant also obtained a workbook with instructions to make notes about daily consumption of the study wine as well as other alcoholic beverages. Blood samples for the measurement of the laboratory endpoint and safety parameters were obtained at a randomization visit and then after one, six, and twelve months. All visits included a physical examination and assessment of cardiovascular events and other medical history since the last visit. At twelve months, after the final visit, the wine supply was stopped. Participants were required to return the corks from the wine bottles to confirm that they had drunk the wine rather than sold it. During the study period no specific restrictions and recommendations were made with respect to diet, lifestyle or possible diagnostic or therapeutic procedures.

Safety assessment

Liver enzymes (alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase, alkaline phosphatase) were investigated during every visit. If any of the parameters exceeded threefold (>3x) the upper limit of normal range (ULN), an unscheduled safety visit was performed. If any of the liver enzymes remained >3x ULN for 14 days, wine consumption was to be stopped.

Statistical methods

Standard descriptive statistics were applied in the analysis: absolute and relative frequencies for categorical variables and mean supplemented by standard deviation for continuous variables. The statistical significance of differences between groups of patients was computed using maximum likelihood chi-square test for categorical variables, independent t-test for continuous variables with two categories and analysis of variance (ANOVA) for three groups of patients; logarithmic transformation was applied when necessary. The change of parameters in time was tested by paired t-test.

The level of statistical significance was set at a = 0.05. IBM SPSS 21 for Windows (Release 21.0.0, IBM Corporation 2012) was adopted in all analyses.

Results

Both groups were comparable in baseline physical characteristics (Tab. 2). The groups also did not differ in the baseline blood pressure values, liver function tests, fasting blood glucose level, and lipid parameters with the exception of total cholesterol, which was significantly higher in the RW group (Tab. 3).

11 of 157 study participants (7 %) did not finish the 1-year follow up. 146 patients completed the study with complete records. Nobody had to stop wine consumption due to significant liver enzyme elevation.

The level of HDL significantly decreased at 6 months in the WW group in comparison with the baseline value (Tab. 4). How-

Tab. 3.Value of measured parameters at randomization (enrolment) according to type of wine.

Mean (SD)	Total	White wine	Red wine	p[1]
N	146	74	72	
SBP	130 (15)	129 (15)	130 (16)	0.619
DBP	82 (11)	81 (10)	83 (12)	0.444
HF	72 (11)	72 (11)	73 (11)	0.786
Primary endpoint				
HDL	1.66 (0.58)	1.66 (0.66)	1.65 (0.50)	0.912
Secondary endpoint				
LDL	3.73 (0.90)	3.61 (0.80)	3.85 (0.98)	0.098
CRP[+]	2.68 (3.54)	2.27 (2.28)	3.09 (4.46)	0.435
TG[+]	1.63 (0.95)	1.65 (1.11)	1.61 (0.77)	0.624
TC	6.06 (1.08)	5.88 (1.01)	6.24 (1.11)	**0.040**
q CH/HDLc	3.43 (1.69)	3.35 (1.86)	3.51 (1.52)	0.564
Glucose[+]	5.48 (1.10)	5.49 (0.86)	5.47 (1.31)	0.686
Liver function[+]				
ALT	0.48 (0.24)	0.49 (0.26)	0.46 (0.21)	0.537
AST	0.43 (0.17)	0.42 (0.14)	0.45 (0.20)	0.511
ALP	1.28 (0.42)	1.30 (0.45)	1.26 (0.39)	0.868
GGT	0.47 (0.32)	0.45 (0.28)	0.48 (0.35)	0.499
Bilirubin	11.2 (5.4)	11.8 (5.5)	10.6 (5.2)	0.182
Additional markers[+]				
Lp-PLA2 (ng/ml)	281 (116)	285 (102)	276 (129)	0.322
Copeptin (pmol/l)	8.19 (4.83)	7.64 (4.45)	8.76 (5.16)	0.236

[1] statistical significance of difference between wines tested by independent t-test
[+] parameters were logarithmically transformed (ln (x)) before testing

Tab. 4. Change in endpoints at 6 and 12 months from enrolment according to wine.

Mean (SD)	Total	White wine	Red wine	p[1]
N	146	74	72	
HDL				
At enrolment	1.66 (0.58)	1.66 (0.66)	1.65 (0.50)	0.912
At 6 months	1.58 (0.48)	1.54 (0.52)	1.62 (0.43)	0.317
Difference 1	-0.09 (0.34)	-0.14 (0.41)	-0.04 (0.26)	0.074
p[2]	**0.002**	**0.005**	0.231	
At 12 months	1.62 (0.49)	1.60 (0.53)	1.64 (0.46)	0.634
Difference 2	-0.04 (0.36)	-0.07 (0.42)	-0.01 (0.29)	0.362
p[2]	0.180	0.171	0.718	
TG[+]				
At enrolment	1.63 (0.95)	1.65 (1.11)	1.61 (0.77)	0.767
At 6 months	1.61 (1.02)	1.62 (1.10)	1.59 (0.93)	0.852
Difference 1	-0.01 (0.82)	0.00 (0.93)	-0.02 (0.70)	0.923
p[2]	0.422	0.903	0.289	
At 12 months	1.61 (1.01)	1.59 (0.99)	1.64 (1.04)	0.759
Difference 2	-0.02 (0.91)	-0.06 (0.85)	0.03 (0.97)	0.559
p[2]	0.530	0.750	0.572	
LDL				
At enrolment	3.73 (0.90)	3.61 (0.80)	3.85 (0.98)	0.098
At 6 months	3.40 (0.87)	3.23 (0.78)	3.58 (0.93)	**0.016**
Difference 1	-0.33 (0.71)	-0.39 (0.74)	-0.27 (0.68)	0.345
p[2]	**<0.001**	**<0.001**	**0.001**	
At 12 months	3.48 (0.94)	3.37 (0.75)	3.60 (1.10)	0.134
Difference 2	-0.24 (0.73)	-0.24 (0.68)	-0.24 (0.78)	0.982
p[2]	**<0.001**	**0.003**	**0.013**	
TC				
At enrolment	6.06 (1.08)	5.88 (1.01)	6.24 (1.11)	**0.040**
At 6 months	5.74 (0.98)	5.57 (0.88)	5.91 (1.05)	**0.035**
Difference 1	-0.33 (0.99)	-0.32 (1.13)	-0.33 (0.82)	0.957
p[2]	**<0.001**	**0.017**	**0.001**	
At 12 months	5.84 (1.02)	5.69 (0.82)	5.99 (1.18)	0.085
Difference 2	-0.21 (0.87)	-0.18 (0.93)	-0.24 (0.82)	0.684
p[2]	**0.004**	0.096	**0.016**	

[1] statistical significance of difference between wines tested by independent t-test, [2] statistical significance of difference between two points in time tested by dependent t-test, [+] parameters were logarithmically transformed (ln (x)) before testing, Difference 1 = Value at 6 months – Value at enrolment, Difference 2 = Value at 12 months – Value at enrolment

ever, there was only a trend to lower HDL level in the WW group in the intergroup analysis at 6 months and no difference was observed in HDL levels at 12 months in both intra- and intergroup analyses (Tab. 4).

The levels of TG were comparable between groups during the study.

On the other hand, we found significant reduction in LDL in both groups at 6 and 12 months compared with the baseline. The LDL level was significantly lower at 6 months in the WW group, however, it was not different at 12 months and the differences from baseline were comparable between the groups (Tab. 4).

Similarly, we observed a significant reduction of TC in both groups at 6 months; at 12 months this effect reached statistical significance only in the RW group, however, the differences from baseline were again comparable (Tab. 4).

The level of CRP was significantly higher at 12 months in the WW group in comparison to the baseline value, however, no differences were found in the intergroup analysis (Tab. 5). Fasting blood glucose levels were significantly reduced in both groups at 6 months; at 12 months we observed only a trend towards lower glucose levels in comparison with baseline values in the RW group; no differences were found in glucose levels in the intergroup comparison at 6 or 12 months (Tab. 5).

The Lp-PLA_2 levels at 12 months were significantly lower in the RW group both in comparison with the WW group and in comparison with baseline values (Tab. 6, Fig. 1). However, in the WW group we also found a trend to reduced Lp-PLA_2 values in comparison to baseline levels and both groups had comparable differences from baseline (Tab. 6, Fig. 1). We also demonstrated a trend towards copeptin level reduction in the RW group at 12 months in comparison with the baseline value but no differences were detected in the intergroup analysis (Tab. 6, Fig. 1).

We did not detect any differences in the levels of ALT, GGT or bilirubin (Tab. 7). Only a trend towards lower AST level was found in the WW group at 12 months in comparison with baseline values, with no difference in the intergroup analysis (Tab. 7). The levels of ALP were significantly reduced in both groups at 6 and at 12 months, this effect was comparable in the intergroup analyses (Tab. 7).

No clinically relevant differences were found in any other parameters. No clinically relevant differences were found in any of the measured parameters after adjusting for gender and age.

Discussion

There is a large body of evidence that the Mediterranean diet and light to moderate alcohol consumption, in particular red wine, are associated with less cardiovascular diseases and an improved lipid profile (7). However, it is still not clear whether alcohol per

Tab. 5. Change in measured parameters at 6 and 12 months from enrolment according to wine.

Mean (SD)	Total	White wine	Red wine	p[1]
N	146	74	72	
CRP[+]				
At enrolment	2.68 (3.54)	2.27 (2.28)	3.09 (4.46)	0.435
At 6 months	2.98 (5.41)	2.55 (4.68)	3.41 (6.05)	0.181
Difference 1	0.28 (5.62)	0.24 (4.29)	0.32 (6.70)	0.932
p[2]	0.885	0.571	0.559	
At 12 months	3.04 (4.03)	2.61 (2.54)	3.49 (5.12)	0.711
Difference 2	0.39 (4.53)	0.37 (3.08)	0.40 (5.68)	0.966
p[2]	**0.012**	**0.045**	0.138	
Glucose[+]				
At enrolment	5.48 (1.10)	5.49 (0.86)	5.47 (1.31)	0.686
At 6 months	5.16 (0.75)	5.23 (0.71)	5.08 (0.78)	0.199
Difference 1	-0.30 (0.94)	-0.26 (0.88)	-0.35 (1.01)	0.585
p[2]	**<0.001**	**0.027**	**0.007**	
At 12 months	5.29 (0.85)	5.39 (0.84)	5.19 (0.86)	0.113
Difference 2	-0.17 (0.96)	-0.09 (0.98)	-0.25 (0.94)	0.322
p[2]	0.061	0.443	0.058	

[1] statistical significance of difference between wines tested by independent t-test, [2] statistical significance of difference between two points in time tested by dependent t-test, [+] parameters were logarithmically transformed (ln (x)) before testing, Difference 1 = Value at 6 months – Value at enrolment, Difference 2 = Value at 12 months – Value at enrolment

Tab. 6. Change in parameters of oxidative stress at 6 and 12 months from enrolment according to type of wine.

Mean (SD)	Total	White wine	Red wine	p[1]
N	146	74	72	
Lp-PLA2 - 1 (ng/ml)				
At enrolment	281 (116)	285 (102)	276 (129)	0.322
At 12 months	248 (60)	259 (62)	236 (57)	**0.021**
Difference 2	-29.83 (112.60)	-26.12 (103.60)	-33.71 (121.89)	0.686
p[2]	**0.004**	0.072	**0.027**	
Copeptin -1 (pmol/l)				
At enrolment	8.19 (4.83)	7.64 (4.45)	8.76 (5.16)	0.236
At 12 months	7.63 (5.52)	7.52 (4.20)	7.75 (6.65)	0.765
Difference 2	-0.51 (6.05)	-0.12 (4.98)	-0.93 (7.00)	0.421
p[2]	0.241	0.995	0.083	

[1] statistical significance of difference between wines tested by independent t-test, [2] statistical significance of difference between two points in time tested by dependent t-test, All parameters were logarithmically transformed (ln (x)) before testing, Difference 1 = Value at 6 months – Value at enrolment, Difference 2 = Value at 12 months – Value at enrolment

Tab. 7. Change in parameters of liver function at 6 and 12 months from enrolment according to wine.

Mean (SD)	Total	White wine	Red wine	p[1]
N	146	74	72	
AST				
At enrolment	0.43 (0.17)	0.42 (0.14)	0.45 (0.20)	0.511
At 6 months	0.42 (0.15)	0.41 (0.13)	0.43 (0.17)	0.479
Difference 1	-0.01 (0.12)	-0.01 (0.10)	-0.02 (0.14)	0.545
p[2]	0.510	0.642	0.642	
At 12 months	0.41 (0.26)	0.39 (0.15)	0.43 (0.33)	0.501
Difference 2	-0.02 (0.24)	-0.03 (0.12)	-0.02 (0.32)	0.819
p[2]	**0.024**	0.056	0.178	
ALP				
At enrolment	1.28 (0.42)	1.30 (0.45)	1.26 (0.39)	0.868
At 6 months	1.05 (0.30)	1.07 (0.32)	1.04 (0.28)	0.723
Difference 1	-0.22 (0.26)	-0.24 (0.29)	-0.21 (0.23)	0.404
p[2]	**<0.001**	**<0.001**	**<0.001**	
At 12 months	1.05 (0.28)	1.04 (0.30)	1.05 (0.26)	0.689
Difference 2	-0.23 (0.27)	-0.26 (0.28)	-0.20 (0.26)	0.196
p[2]	**<0.001**	**<0.001**	**<0.001**	
ALT				
At enrolment	0.48 (0.24)	0.49 (0.26)	0.46 (0.21)	0.537
At 6 months	0.49 (0.23)	0.52 (0.24)	0.46 (0.22)	0.074
Difference 1	0.01 (0.21)	0.03 (0.21)	0.00 (0.20)	0.410
p[2]	0.152	0.063	0.902	
At 12 months	0.48 (0.26)	0.51 (0.29)	0.45 (0.21)	0.185
Difference 2	0.01 (0.21)	0.02 (0.21)	-0.01 (0.21)	0.426
p[2]	0.533	0.362	0.927	
GGT				
At enrolment	0.47 (0.32)	0.45 (0.28)	0.48 (0.35)	0.499
At 6 months	0.48 (0.38)	0.51 (0.47)	0.46 (0.26)	0.977
Difference 1	0.03 (0.24)	0.06 (0.30)	0.00 (0.17)	0.153
p[2]	0.341	0.283	0.856	
At 12 months	0.46 (0.28)	0.47 (0.28)	0.46 (0.29)	0.917
Difference 2	0.01 (0.15)	0.02 (0.15)	0.01 (0.14)	0.638
p[2]	0.234	0.180	0.839	
Bilirubin				
At enrolment	11.2 (5.4)	11.8 (5.5)	10.6 (5.2)	0.182
At 6 months	11.2 (5.8)	11.5 (6.0)	10.9 (5.6)	0.649
Difference 1	0.02 (4.93)	-0.20 (5.27)	0.25 (4.57)	0.602
p[2]	0.707	0.577	0.893	
At 12 months	11.3 (5.1)	12.0 (5.5)	10.6 (4.5)	0.139
Difference 2	0.19 (4.58)	0.31 (5.06)	0.06 (4.03)	0.753
p[2]	0.300	0.457	0.474	

[1] statistical significance of difference between wines tested by independent t-test, [2] statistical significance of difference between two points in time tested by dependent t-test, All parameters were logarithmically transformed (ln (x)) before testing, Difference 1 = Value at 6 months – Value at enrolment, Difference 2 = Value at 12 months – Value at enrolment

se or other components of alcoholic beverages protect against heart disease (8). A number of studies demonstrated that alcohol per se exhibits a protective effect (3, 9). On the other hand, several authors described cardio-protective properties of other components, particularly flavonoids (10).

Currently there are conflicting results regarding the comparison of the effects of red and white wines on different clinically relevant endpoints in experimental as well as in small clinical studies (11–13). It is well known that there are major differences in basic characteristics between red and white wines. Red wine exhibits a higher antioxidant capacity and, according to several studies, a protective effect against LDL-oxidation when compared with white wine (14). Rosenkranz et al (15) and Sparwel et al (16) have shown attenuation of platelet-derived growth factor receptor (PDGFR) signalling (an important pathogenic mechanism in the development of atherosclerosis) in rat and human vascular smooth muscle cells (VSMCs) induced by red wine, whereas white wine had no effect. On the other hand, Munday et al (11) did not find any differences between red and white wine in serum lipoprotein profile and fatty streak formation in the C57BL/6 mouse atherosclerosis model. López et al (17) observed a similar reduction in superoxide production and an increase in expression and activity of NO-synthase (iNOS) by dealcoholized red and white wines in a rat model, while up-regulation of cyclo-oxygenase-2 (COX-2) was detected only in the red wine group. Moreover, Auger et al (18) described that both red wine and polyphenols-enriched white wine prevent early atherosclerosis in hamsters.

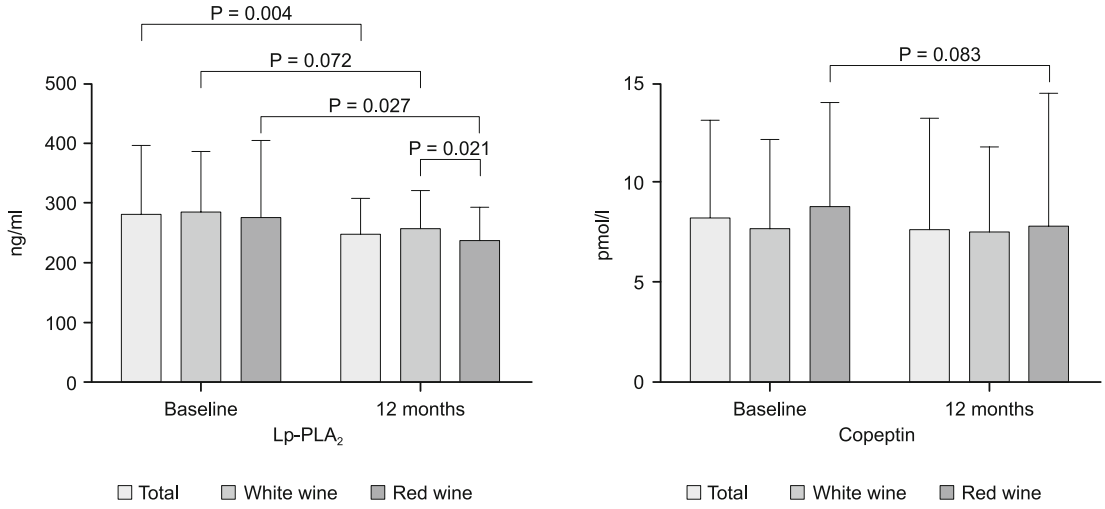

Fig. 1. Change in Lp-PLA2 and copeptin at 12 months from enrolment according to type of wine

Regarding the effects on atherosclerosis, there is only limited evidence from prospective head-to-head comparisons of different alcoholic beverages in human subjects; the published studies were focused mostly on the acute effects of drinking. Tousoulis et al (19) observed reactive hyperaemia after beer and red wine consumption that was not detected after white wine, whiskey or water in healthy young individuals. A reduction in urinary prostaglandin PGF2α-III as a marker of oxidative stress was expressed more after red wine than after white wine in a study on healthy subjects by Pignatelli et al (20). Pace-Asciak et al (21) did not find any advantage in red wine over white wine in preventing platelet aggregation in healthy males. A similar increase in total antioxidant capacity as a result of red or white wine consumption was described by Pinzani et al (22).

Williams et al. (12) did not observe any significant difference in the acute effects of red and white wine drinking on blood pressure, heart rate, plasma lipids, levels of interleukin-6 (IL-6), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) in males with angiographic evidence of coronary artery disease (CAD). Moreover, a comparable acute improvement of endothelial function after red and white wine drinking was reported by Whelan et al (13) in subjects with proven CAD. Blann et al (23) described an increase in beta-thromboglobulin levels after red wine, whereas white wine had no effect.

Until now, the longest exposure to red and white wines in a prospective trial was examined by Sacanella et al (24) in their four-week study; in a group of thirty-six healthy females they found a stronger anti-inflammatory effect of red wine compared with white wine consumption.

To the best of our knowledge, the IVV trial is the first long-term, randomized, prospective study focused on the comparison of the effects of regular white and red wine drinking on several markers of atherosclerosis. Despite there being significant differences in the composition of the red and white wine used in this study (e.g. resveratrol concentration or antioxidant capacity) (Tab. 1), we are unable to demonstrate any clinically important differences in the effects of both wines on monitored parameters. We cannot, therefore, confirm our primary hypothesis that red wine consumption is associated with higher levels of HDL in comparison with white wine. In the IVV trial we compared the effects of consumption of red wine with a high concentration of flavonoids and other antioxidants and white wine with a low concentration of these components and we were unable to find any clinically important differences in biomarkers of atherosclerosis.

It has been repeatedly shown that wine drinking is associated with several changes in lipid profile. The data in the literature are almost consistent in showing that wine consumption decreases the levels of LDL while it increases the levels of HDL (8, 25, 26).

In concordance with these literature data, we observed a highly significant and lasting effect of wine consumption on LDL reduction that was observed in both 6-month and 12-month blood samples. Contrary to the previously published studies, however, we found a transient and weak reduction of HDL after 6 months of white wine consumption. This effect was no more detectable after 12 months. Neither white wine nor red wine drinking was associated with an increase of HDL levels. We can speculate that the inability to demonstrate any elevation of HDL levels in our study could be at least partially caused by the different design of the IVV trial in comparison with the previously published studies: whereas the IVV trial was a prospective and long-term intervention, the literature evidence for an increase of HDL after wine consumption comes mostly from retrospective or small and short-term prospective studies. Moreover, abstinence from alcohol was not required for subject enrolment in our study and therefore the baseline HDL levels could be already elevated as a result of previous drinking; however, in that case we would not expect further reduction of LDL.

We also found a significant elevation in CRP levels at the 12-month follow-up in the WW group and in the total study population. There are conflicting literature data on the effects of wine consumption on inflammatory markers. Our results are in contra-

diction with the results from retrospective studies (27). On the other hand, an increase in plasma pro-inflammatory cytokines consistent with our results has been described in a small prospective trial (12). Current evidence on the effects of alcohol consumption on blood glucose levels has also produced inconsistent data. Our observation of transient significant fasting blood glucose reduction is consistent with several previously published studies (28).

Unaffected liver function tests (levels of gama-glutamyltransferase, aspartate-aminotransferase, and alanine-aminotransferase) in our study may demonstrate the liver safety of long-term moderate wine consumption. A reduction of alkaline phosphatase activity as a result of alcohol drinking observed in our study was already previously described by several authors (29). Our results showing decreased Lp-PLA_2 levels after 12 months of wine consumption confirm prospectively the results of previous retrospective studies (30). We also did not find any differences in copeptin levels and we, therefore, demonstrated for the first time that copeptin levels are not influenced by wine drinking.

Our study has several limitations. Possible biases may be caused by the limited size of the study population. The eligible subjects for study participation were also not required to abstain from alcohol consumption before enrolment. Furthermore, although all participants were strongly encouraged to restrict their alcohol consumption to the study wine and to comply with the recommended doses, the occasional drinking of more alcohol or other alcoholic beverages was not strictly forbidden and was not being assessed as a protocol violation. The reason for this approach was to reflect real life conditions as much as possible in the IVV trial.

Conclusion

In this prospective, randomized trial we did not find any clinically relevant differences in the lipid profile, CRP, fasting blood glucose, other markers of atherosclerosis i.e. Lp-PLA_2 or copeptin, and liver function tests, between long-term consumption of red and white wine. Moreover, we were unable to confirm the hypothesis, mostly from retrospective studies, that wine drinking is associated with an elevation of HDL.

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Received February 21, 2017.
Accepted March 15, 2017.