

References:

Clinical studies in man showing Hp type predicts risk of CVD and renal disease

1. Levy AP, Roguin A, Marsh S, Nakhoul FM, Herer P, Hochberg I, Skorecki K. Haptoglobin phenotype and vascular complications in diabetes (Research Letter). *New Eng J Med* 2000; 343: 969-970.
2. Levy AP, Hochberg I, Jablonski K, Resnick H, Best L, Lee ET, Howard BV. Haptoglobin phenotype and the risk of cardiovascular disease in individuals with diabetes: The Strong Heart Study. *J Am Coll Card* 2002; 40: 1984-1990.
3. Roguin A, Koch W, Kastrati A, Aronson D, Schomig A, Levy AP. Haptoglobin genotype is predictive of major adverse cardiac events in the one year period after PTCA in individuals with diabetes. *Diabetes Care* 2003, 26: 2628-31.
4. Suleiman M, Aronson D, Asleh R, Kapelovich MR, Roguin A, Meisel SR, Shochat M, Suleiman A, Reisner SA, Markiewicz W, Hammerman H, Lotan R, Levy NS, Levy AP. Haptoglobin polymorphism predicts 30-day mortality and heart failure in patients with diabetes and acute myocardial infarction. *Diabetes* 2005; 54: 2802-2806.
5. Simpson M, Snell-Bergeon JK, Kinney GL, Lache O, Miller-Lotan R, Anbinder Y, Rewers M, Levy AP. Haptoglobin genotype predicts development of coronary artery calcification in a prospective cohort of patients with Type I Diabetes Mellitus. *Cardiovascular Diabetology*. 2012, 10:99.
6. Cahill LE, Levy AP, Chiuve SE, Jensen MK, Wang H, Shara NW, Blum S, Howard BV, Pai JK, Mukamal KJ, Rexrode KM, Rimm EB. Haptoglobin genotype is a consistent marker of coronary heart disease risk among individuals with elevated hemoglobin A1c. *J Am Coll Card* 2012, 61:728-37.
7. Cahill LE, Jensen MK, Chasman DI, Hazra A, Levy AP, Rimm EB. Currently available versions of genome wide association studies cannot be used to query the common Haptoglobin copy number variant (Letter). *J Am Coll Card* 2013, 62:860-861.
8. Orchard TJ, Sun W, Cleary P, Lachin JM, McGee P, Patterson AD, Raskin P, Anbinder Y, Levy AP. Haptoglobin genotype and the rate of function decline in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study. *Diabetes* 2013; 62:3218-3223.
9. Costacou T, Ferrell RE, and Orchard TJ. Haptoglobin genotype: a determinant of cardiovascular complication risk in type I diabetes. *Diabetes* 57:1702-1706, 2008.
10. Adams JN, Cox AJ, Freedman BI, Langefeld CD, Carr J, Bowden DW. Genetic analysis of Haptoglobin polymorphisms with cardiovascular disease and type 2 diabetes in the diabetes heart study. *Card Diab* 12: 31, 2013.

Clinical studies in man showing vitamin E prevents CVD and improves HDL function in Hp 2-2 Diabetic individuals:

11. Levy AP, Gerstein H, Lotan R, Ratner R, McQueen M, Lonn E, Pogue J. The effect of vitamin E supplementation on cardiovascular risk in diabetic individuals with different haptoglobin phenotypes. *Diabetes Care* 2004;27: 2767.
12. Milman U, Blum S, Shapira C, Aronson D, Miller-Lotan R, Anbinder Y, Alsheik J, Bennett L, Kostenko M, Landau M, Keidar S, Levy Y, Khemlin A, Radan A, Levy AP. Vitamin E supplementation reduces cardiovascular events in a subgroup of middle-aged individuals with both Type 2 Diabetes Mellitus and the Haptoglobin 2-2 genotype: a prospective, double-blinded clinical trial. *Art Thromb Vasc Biol* 2008; 28: 341-347.
13. Blum S, Milman U, Shapira C, Miller-Lotan R, Bennett L, Kostenko M, Landau M, Keidar S, Levy Y, Khemlin A, Radan A, Levy AP. Dual Therapy with statins and antioxidants is superior to statins alone in decreasing the risk of cardiovascular disease in a subgroup of middle-aged individuals with both Diabetes Mellitus and the Haptoglobin 2-2 genotype. *Art Thromb Vasc Biol* 2008; 28:e18-e20.
14. Asleh R, Blum S, Kalet-Litman S, Alsheik J, Miller-Lotan R, Asaf R, Rock W, Aviram M, Milman U, Shapira C, Abassi Z, Levy AP. Correction of HDL dysfunction in individuals with Diabetes and the Haptoglobin 2-2 genotype. *Diabetes* 2008; 57: 2794-2800.
15. Blum S, Vardi M, Brown JB, Russell A, Milman U, Shapira C, Levy NS, Miller-Lotan R, Asleh R, Levy AP. Vitamin E reduces cardiovascular disease in individuals with Diabetes Mellitus and the Haptoglobin 2-2 genotype. *Pharmacogenomics* 2010; 11:675-684.
16. Blum S, Vardi M, Levy NS, Miller-Lotan R, Levy AP. The effect of vitamin E supplementation on cardiovascular risk in diabetic individuals with different Haptoglobin phenotypes. *Atherosclerosis*. 2010; 211:25-27.
17. Asleh R, Levy AP, Blum S. Cholesterol efflux, capacity and atherosclerosis (letter to the editor). *N Engl J Med* 2011; 364:1473.
18. Farbstein D, Blum S, Pollak M, Asaf R, Viener HL, Lache O, Asleh R, Miller-Lotan R, Barkay I, Star M, Schwartz A, Kalet-Litman S, Ozeri D, Vaya J, Tavori H, Vardi M, Laor A, Bucher SE, Anbinder Y, Moskovich D, Abbas N, Perry N, Levy AP. Vitamin E therapy results in a reduction in HDL function in individuals with Diabetes and the Haptoglobin 2-1 genotype. *Atherosclerosis* 2011; 219: 240-4.

Mechanistic studies for why Hp 2-2 is inferior antioxidant and produces susceptibility to diabetic vascular disease (preclinical and clinical data)

19. Frank M, Lache O, Enav B, Szafrank T, Levy NS, Ricklis RM, Levy AP. Structure/function analysis of the anti-oxidant properties of haptoglobin. *Blood* 2001; 98: 3693-3698.
20. Asleh R, Marsh S, Shiltruck M, Binah O, Guetta J, Lejbkowitz F, Enav B, Shehadeh N, Kanter Y, Lache O, Cohen O, Levy NS, Levy AP. Genetically determined heterogeneity in hemoglobin scavenging and susceptibility to diabetic cardiovascular disease. *Circ Res* 2003; 92: 1193-1200.
21. Asleh R, Guetta J, Kalet-Litman S, Miller-Lotan R, Levy AP. Haptoglobin genotype and diabetes dependent differences in iron mediated oxidative stress in vitro and in vivo. *Circ Res* 2005; 96: 435-441.
22. Asleh R, Miller-Lotan R, Aviram M, Hayek T, Yulish M, Levy JE, Miller B, Blum S, Milman U, Shapira C, Levy AP. Haptoglobin Genotype is a Regulator of Reverse Cholesterol Transport in Diabetes In Vitro and In Vivo. *Circ Res* 2006; 99: 1419-1425.
23. Levy AP, Levy JE, Kalet-Litman S, Miller-Lotan R, Levy NS, Asaf R, Guetta J, Yang C, Purushothaman KR, Fuster V, Moreno PR. Haptoglobin genotype is a determinant of iron, lipid peroxidation and macrophage accumulation in the atherosclerotic plaque. *Arteriosclerosis Thromb Vasc Biol* 2007; 27: 134-140.
24. Blum S, Asaf R, Guetta J, Miller-Lotan R, Asleh R, Kremer R, Levy NS, Berger FG, Fu X, Zhang R, Hazen SL, Levy AP. Haptoglobin genotype determines myocardial infarct size in diabetic mice. *J Am Coll Card* 2007; 49:82-87.
25. Levy AP, Purosothaman KR, Levy NS, Purosothaman M, Strauss M, Asleh R, Marsh S, Cohen O, Moestrup SK, Moller HJ, Zias EA, Benhayon D, Fuster V, Moreno PR. Downregulation of the hemoglobin scavenger receptor in individuals with diabetes and the Hp 2-2 genotype: implications for the response to intraplaque hemorrhage and plaque vulnerability. *Circ Res* 2007; 101:106-110.

26. Moreno PR, Purushothaman KR, Purushothaman M, Muntner P, Levy NS, Fuster V, Fallon JT, Lento P, Winterstern A, Levy AP. Haptoglobin genotype is a major determinant of the amount of iron in the human atherosclerotic plaque. *J Am Coll Card.* 2008; 52: 1049-1051.
27. Nakhoul FM, Miller-Lotan R, Awad H, Asleh R, Jad K, Nakhoul N, Asaf R, Abu-Seleh N, Levy AP. Pharmacogenomic effect of vitamin E on kidney structure and function in transgenic mice with the Haptoglobin 2-2 genotype and diabetes mellitus. *Am J Phys* 2009; 296: F830-838.
28. Asleh R, Levy AP. Divergent effects of α -tocopherol and vitamin C on the generation of dysfunctional HDL associated with Diabetes and the Hp 2-2 genotype. *Antioxidant and redox signaling.* 2010; 12:209-217.
29. Kalet-Littman S, Moreno PR, Levy AP. The Haptoglobin 2-2 genotype is associated with increased redox active hemoglobin derived iron in the atherosclerotic plaque. *Atherosclerosis.* 2010; 209:28-31.
30. K-Raman P, Purushothaman M, Levy AP, Lento PA, Evrand S, Kovacic JC, Briley-Saebo K, Tsimikas S, Witztum J, Krishnan P, Kini A, Fayad ZA, Fuster V, Sharma SK, Moreno PR. Increased expression of oxidation-specific epitopes and apoptosis are Haptoglobin genotype dependent: implications for plaque progression in human atherosclerosis. *J Am Coll Card* 2012; 60:112-119.
31. Asleh R, Nakhoul FM, Miller-Lotan R, Awad H, Farbstein D, Levy NS, Nakhoul N, Iancu TC, Manov I, Laue M, Traber MG, Lebold KM, Levy AP. Poor lysosomal membrane integrity in proximal tubule cells of Haptoglobin 2-2 genotype mice with Diabetes Mellitus. *Free Rad Biol Med* 2012, 53:779-786.
32. Asleh R, Ward J, Levy NS, Safuri S, Aronson D, Levy AP. Haptoglobin genotype dependent differences in macrophage lysosomal oxidative injury. *J Biol Chem* 2014; 289: 16313-16325.

Reviews of mechanistic and clinical data:

33. Levy AP. Application of pharmacogenomics in the prevention of diabetic cardiovascular disease: mechanistic basis and clinical evidence for utilization of the haptoglobin genotype in determining benefit from antioxidant therapy. *Pharmacology and Therapeutics* 2006; 112; 501-512.
34. Levy AP, Blum S. Pharmacogenomics in the prevention of Diabetic CVD: utilization of the haptoglobin genotype in determining benefit from vitamin E. *Exp Rev Card* 2007; 5: 1105-1111.
35. Blum S, Milman U, Shapira C, Levy AP. Pharmacogenomic application of the Haptoglobin genotype in the Prevention of Diabetic Cardiovascular Disease. *Pharmacogenomics* 2008; 9: 989-991.
36. Schwartz A, Blum S, Asleh R, Pollak M, Levy AP. Pharmacogenomic application of the Haptoglobin genotype in the treatment of HDL dysfunction. *Pharmacogenomics and Personalized Medicine.* 2009; 2:1-8.
37. Levy AP. Modification of HDL structure and function in individuals with Diabetes and the Haptoglobin 2-2 genotype with Vitamin E. *Future Lipidology.* 2009; 4:5-8.
38. Farbstein D, Levy AP. HDL dysfunction in diabetes-causes and possible treatments. *Expert Reviews Cardiovascular Therapy* 2012; 10:353-361
39. Costacou T, Levy AP. Haptoglobin genotype and its role in Diabetic Cardiovascular Disease. *J Cardiovasc Transl Res* 2012; 5:428-435.
40. Vardi M, Blum S, Levy AP. Haptoglobin genotype and cardiovascular outcomes in diabetes mellitus-natural history of disease and the effect of vitamin E treatment. Meta-analysis of the medical literature. *Eur J Int Med* 2012; 23:628-632.
41. Goldenstein H, Levy NS, Lipener T, Levy AP. Expert Reviews in Cardiology. Patient selection in Vitamin E treatment in Diabetes Mellitus. 2013; 11:319-26.
42. Vardi M, Levy NS, Levy AP. Vitamin E in the prevention of cardiovascular disease-the importance of proper patient selection. *J Lipid Research* 2013; 54:2307-2314.

Description of the ELISA-accuracy and comparison against other methods

43. Levy NS, Vardi M, Blum S, Miller-Lotan R, Ainbinder Y, Cleary P, Paterson AD, Bharaj B, Snell Bergeon JK, Rewers MJ, Lache O, Levy AP. An enzyme linked immunosorbent assay (ELISA) for the determination of the human Haptoglobin phenotype. *Clin Chem Lab Med* 2013; 51:1615-1622.