IL SOGGETTO AD ALTO RISCHIO CARDIOVASCOLARE
XVIII GIORNATA STUDIO SISA SEZ. REG. LOMBARDA
MILANO - Four Points by Sheraton 24-26 OTTOBRE 2019

XIII CONGRESSO NAZIONALE SITeCS
26 Ottobre 2019

# Lp(a) e rischio cardiovascolare

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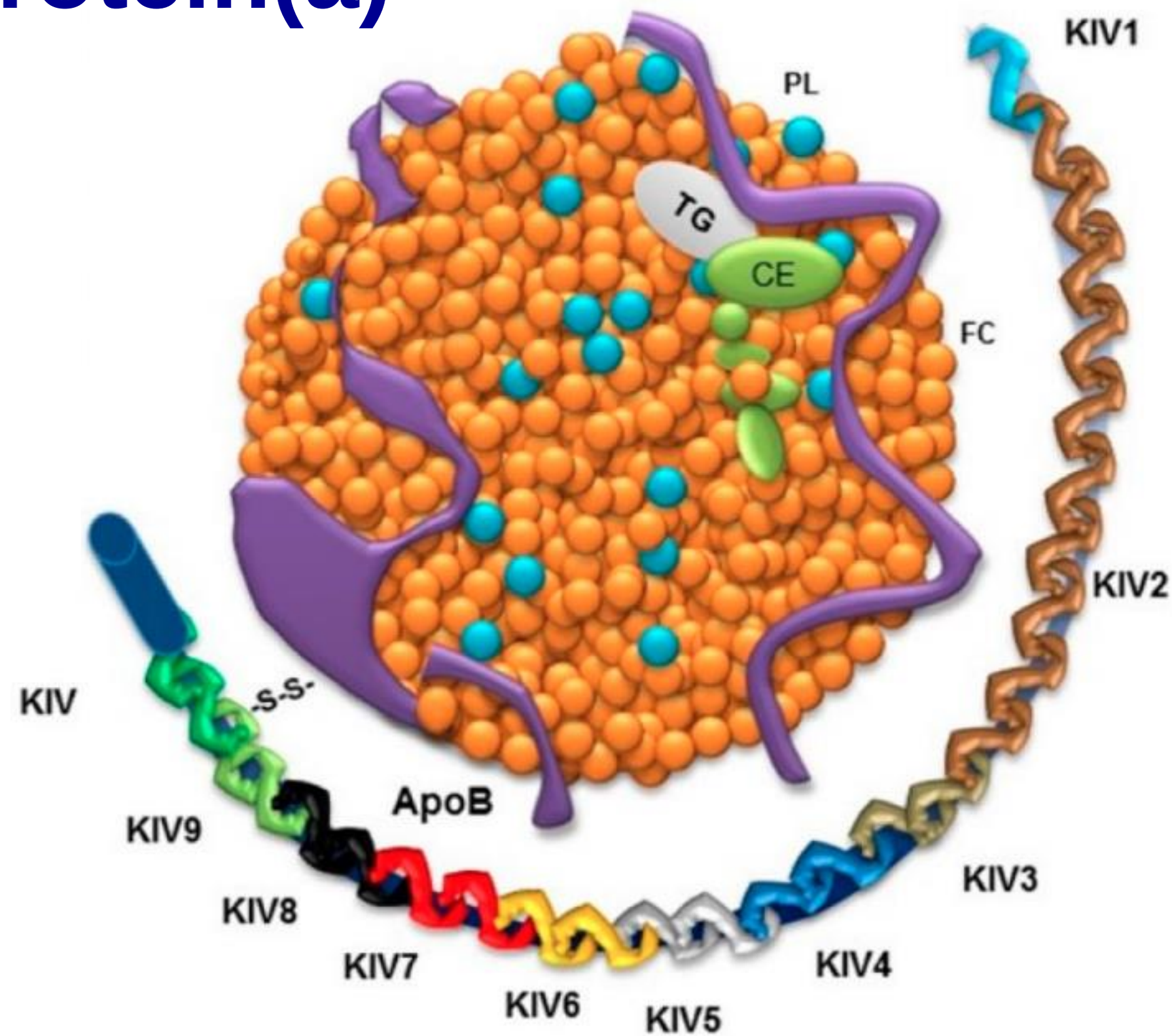
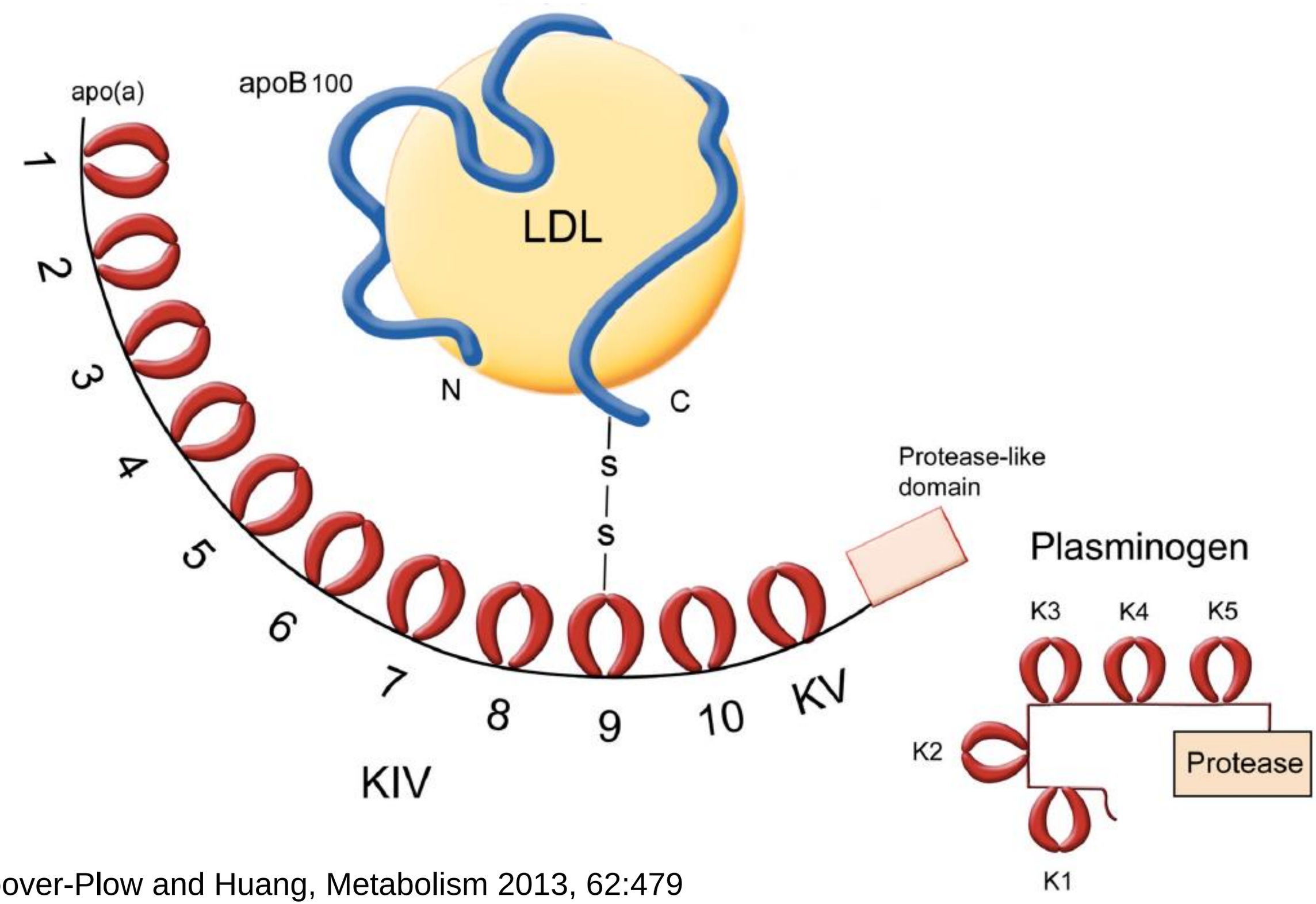
# Lipoprotein(a)

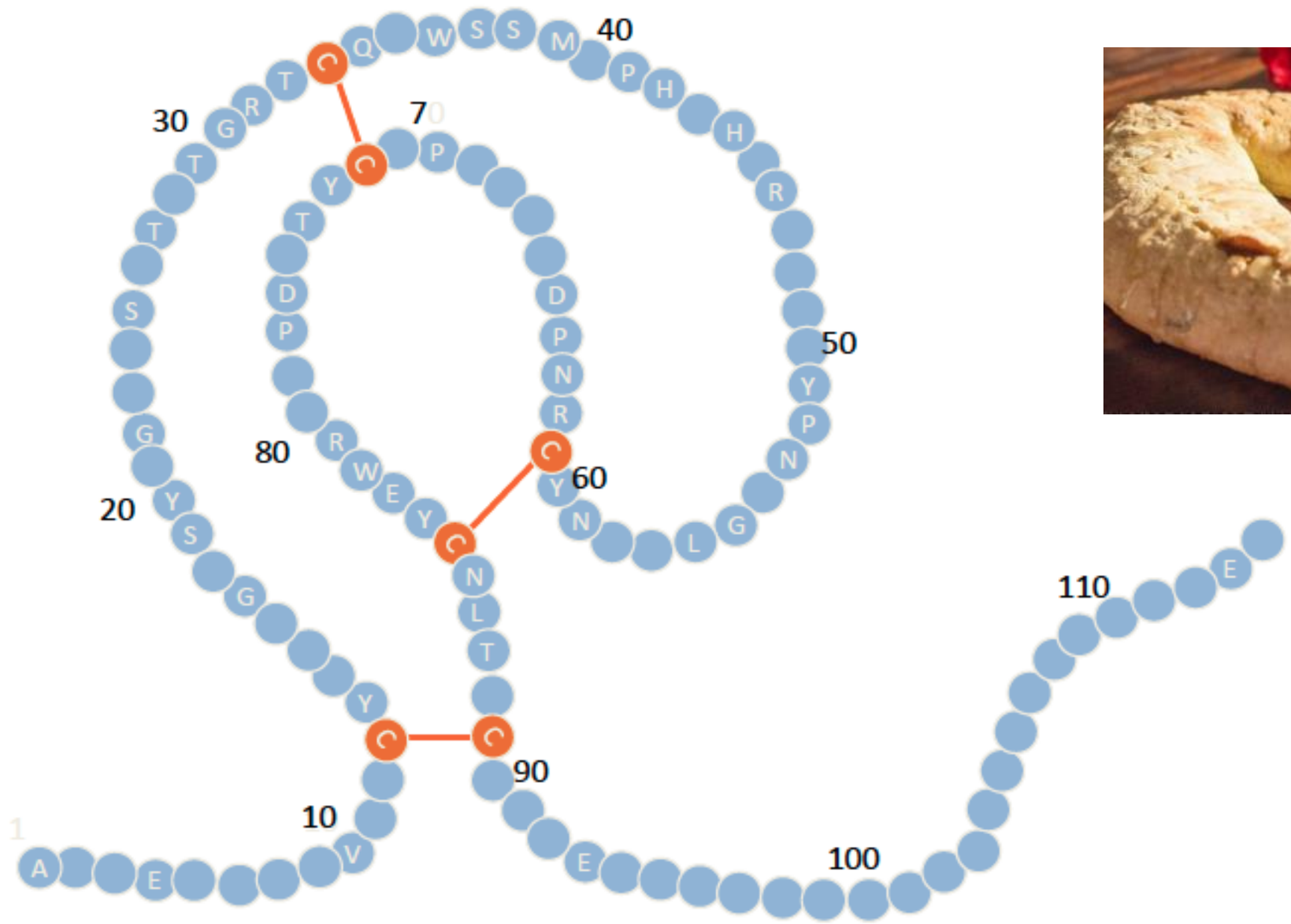


# Lipoprotein(a) structure



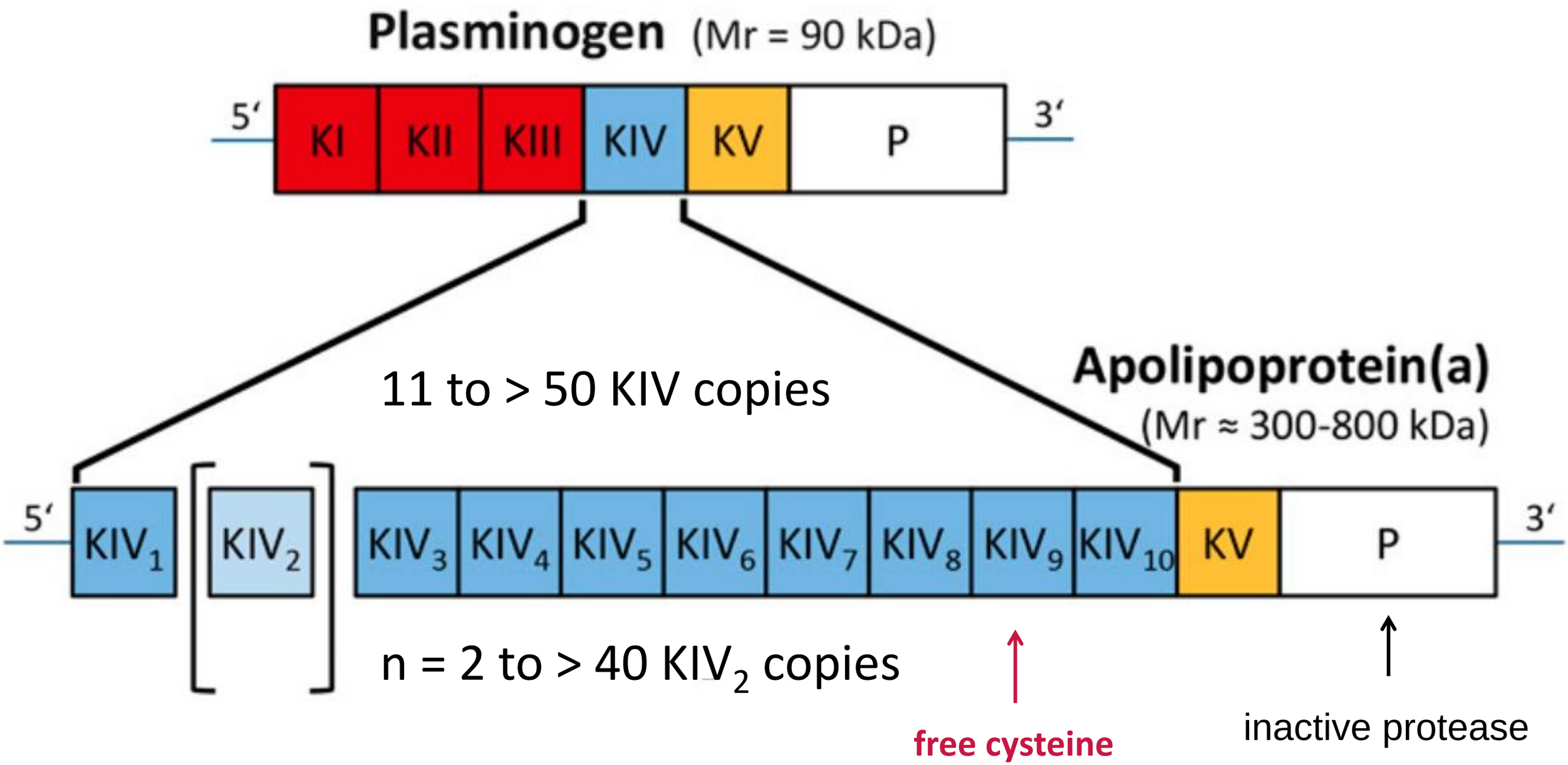

Hoover-Plow and Huang, Metabolism 2013, 62:479

# Typical Kringle structure

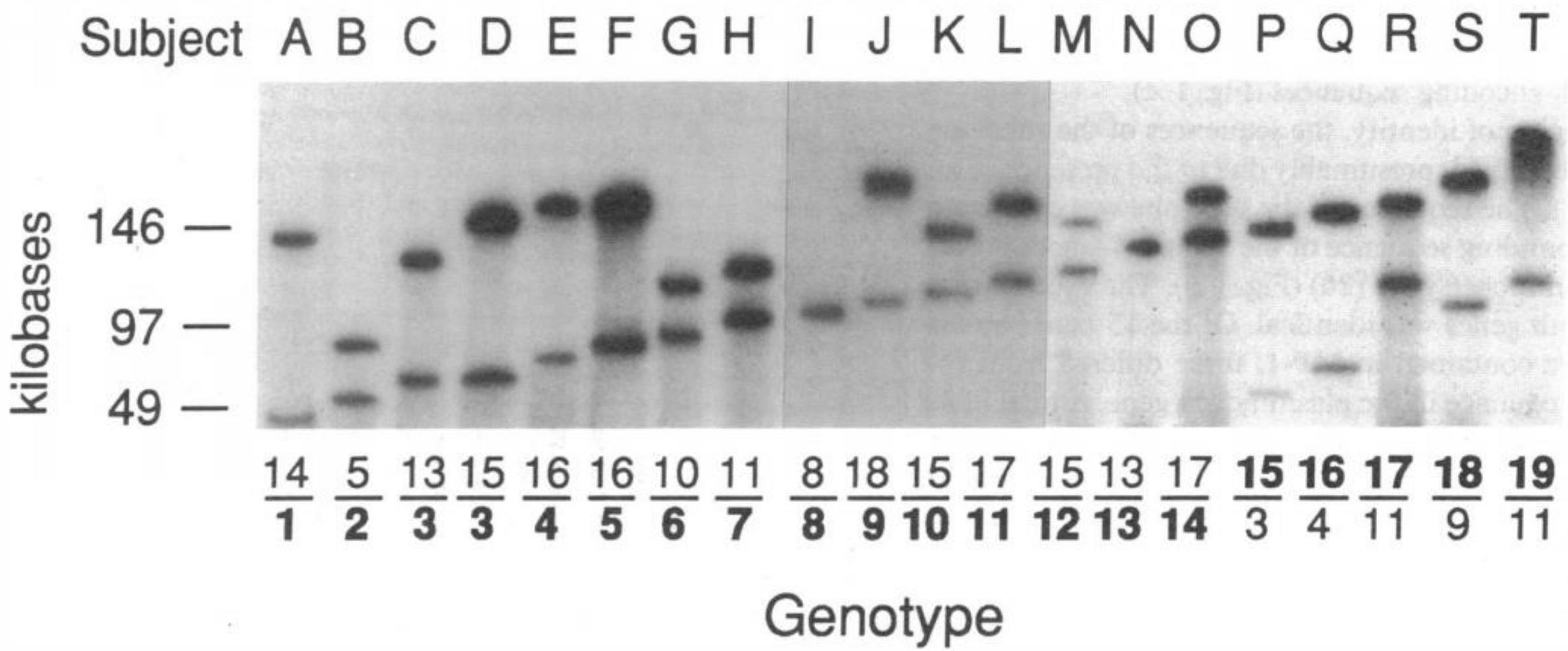


C = cysteine

# Plasminogen and apolipoprotein(a)



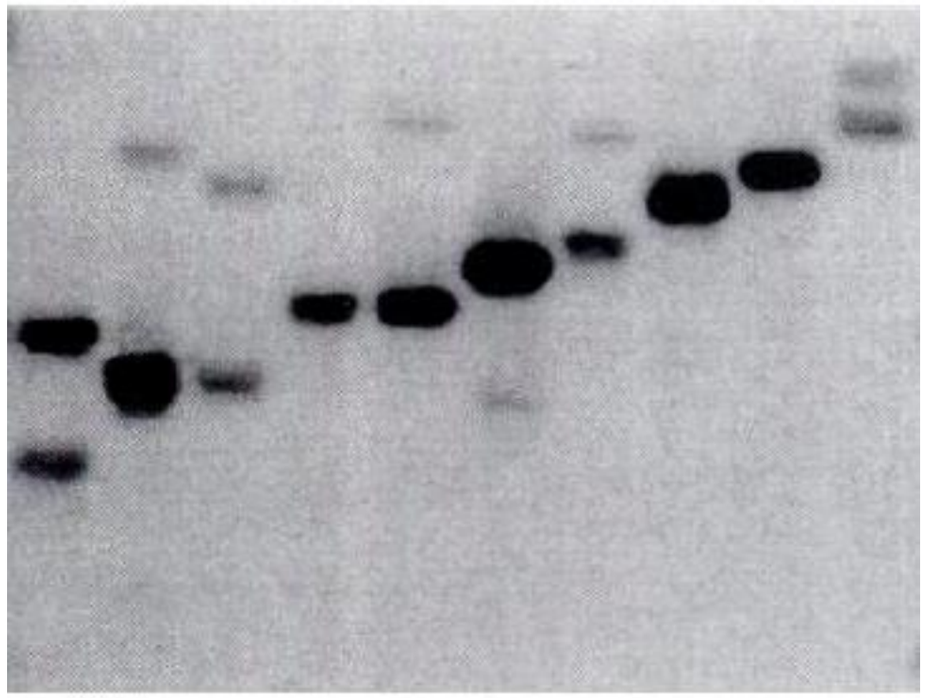
# Genomic blot of apo(a) gene by pulsed-field gel electrophoresis




Lackner et al., J Clin Invest 1991, 87:2077

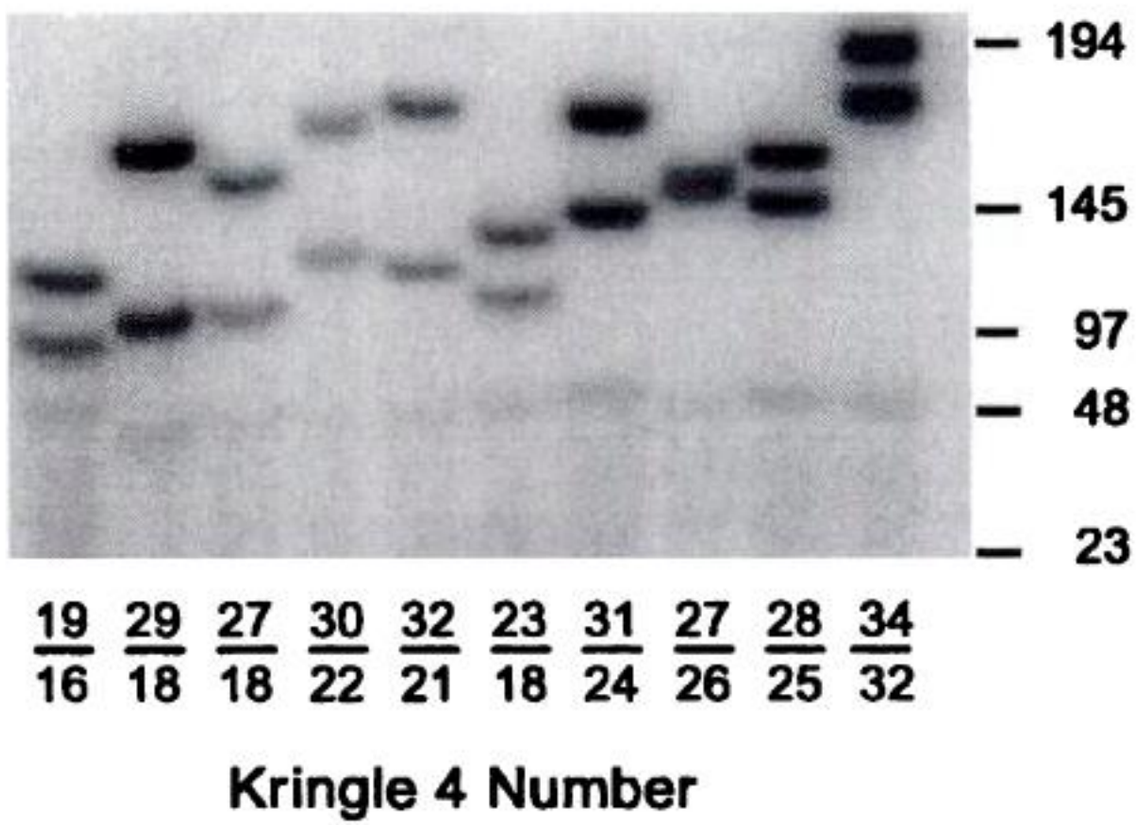
# Size heterogeneity of apo(a) gene and protein

apo(a) immunoblot
(plasma)



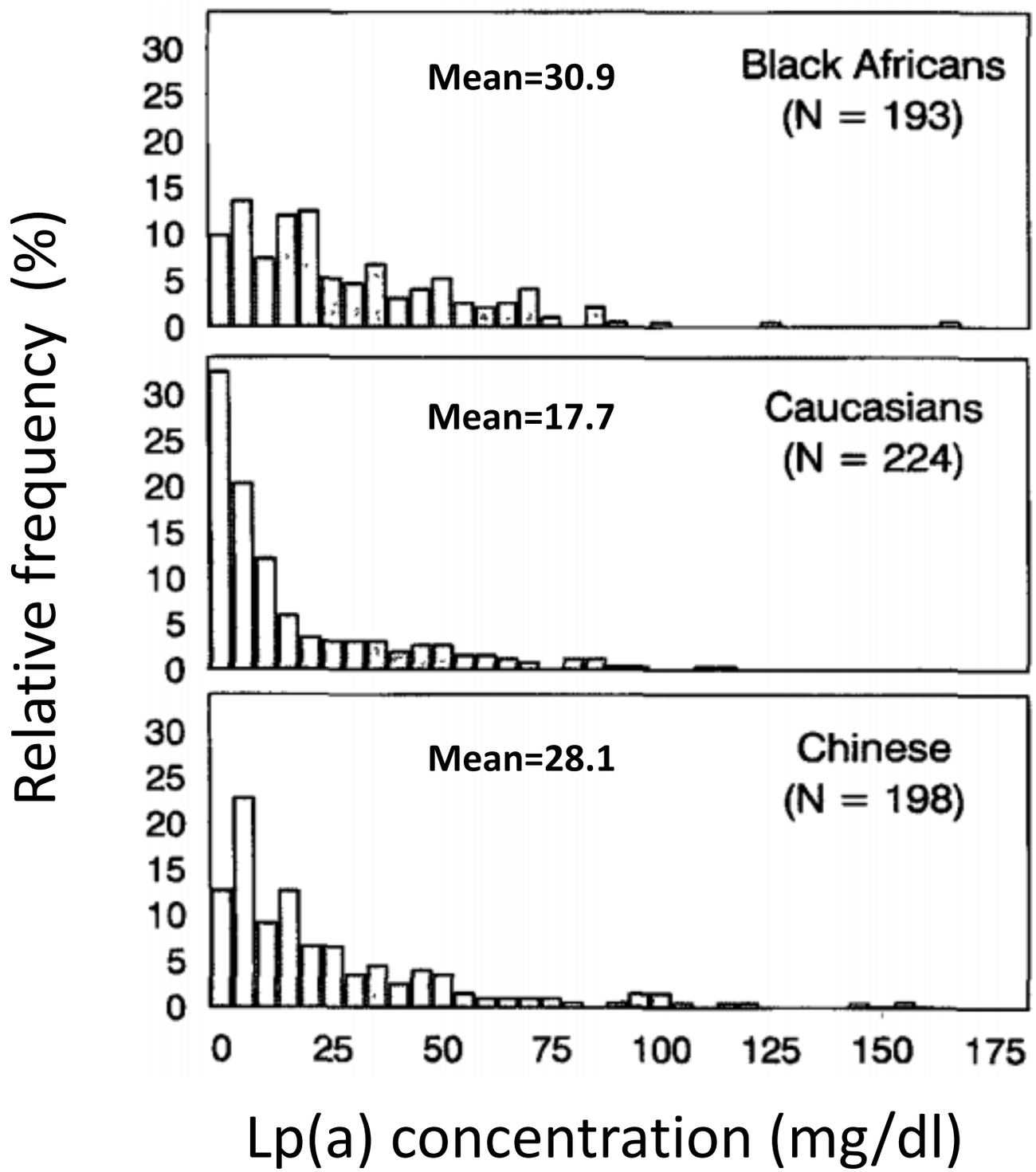
**300-800 kDa**

apo(a) genomic blot



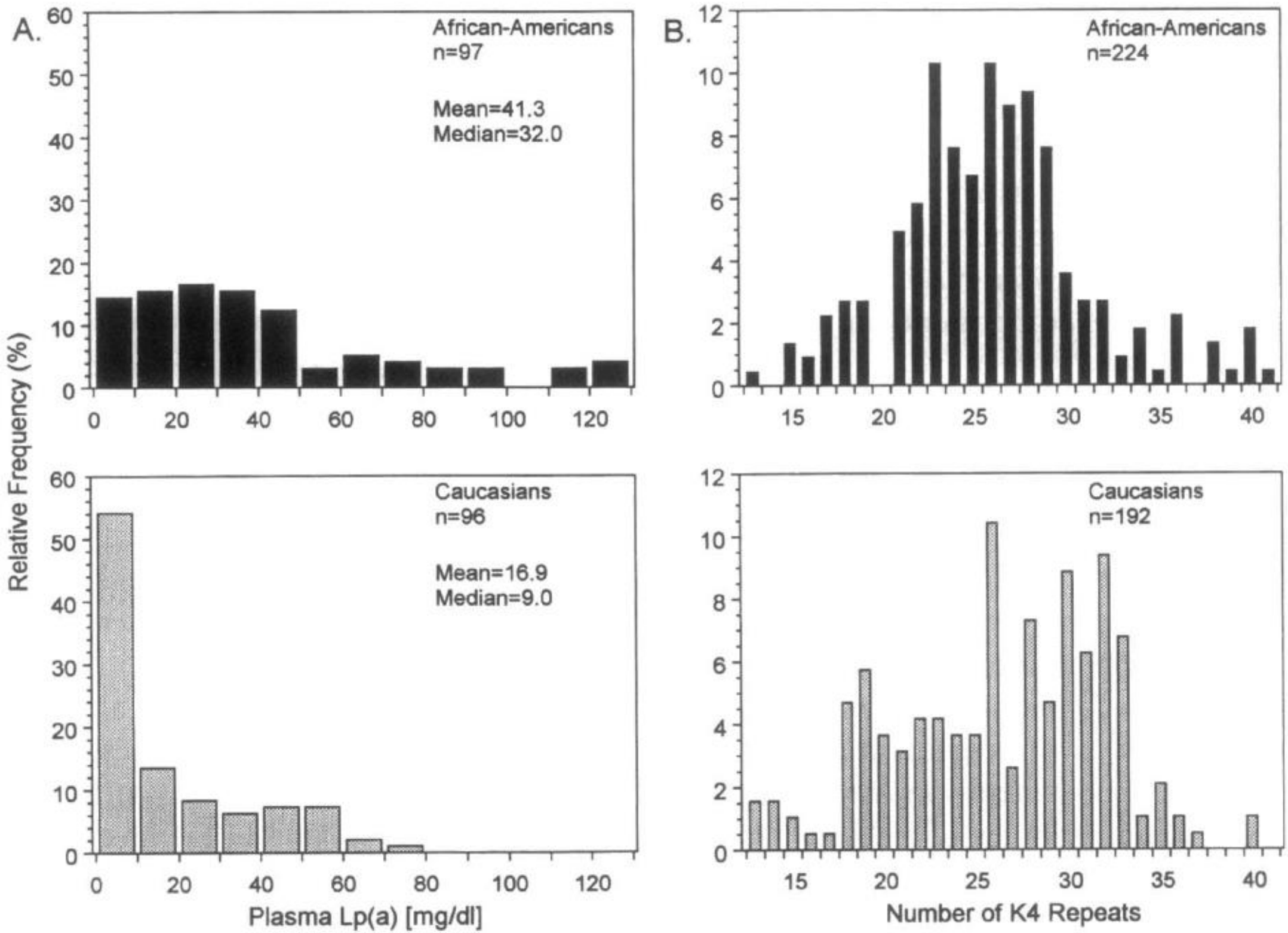

Marcovina et al., Clin Chem 1996, 42:436

# Distribution of Lp(a) concentrations in three populations



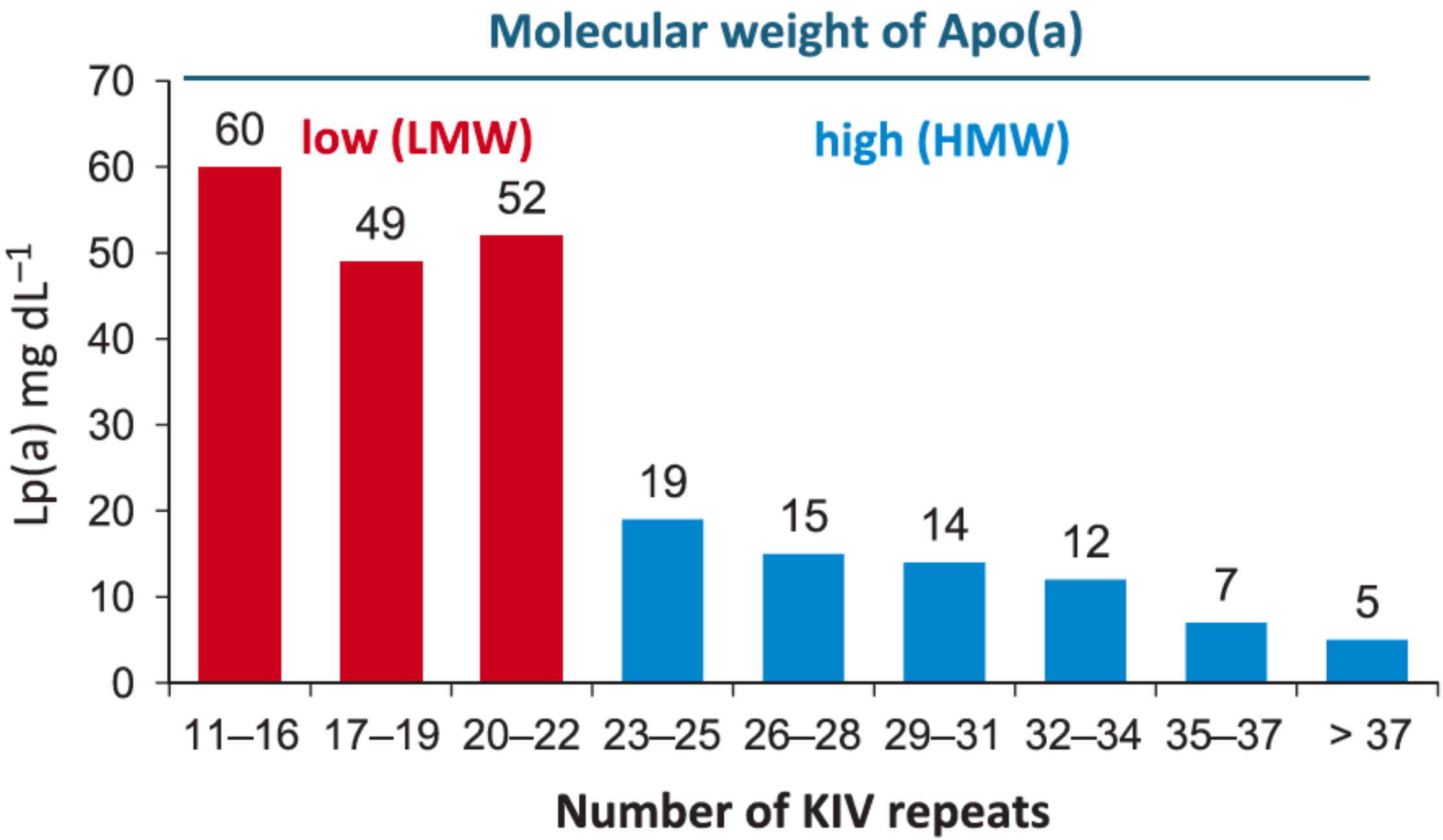

Kraft et al., Eur J Hum Genet 1996, 4:74

# Distribution of plasma Lp(a) levels and number of K4 repeats



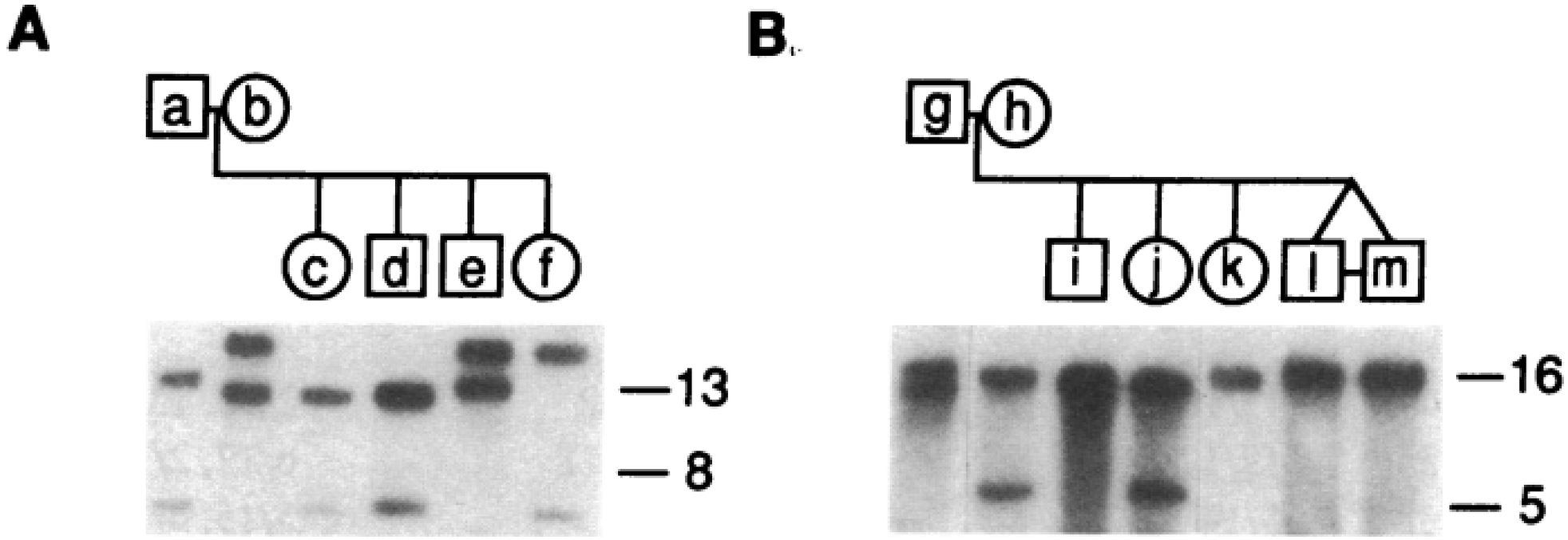

Mooser et al., Am J Hum Genet 1997, 61:402

# Mean Lp(a) concentrations stratified by the number of KIV repeats




Kronenberg et al., J Intern Med 2013, 273:6

# Genomic blot and Lp(a) levels of two unrelated families with the same apo(a) size allele

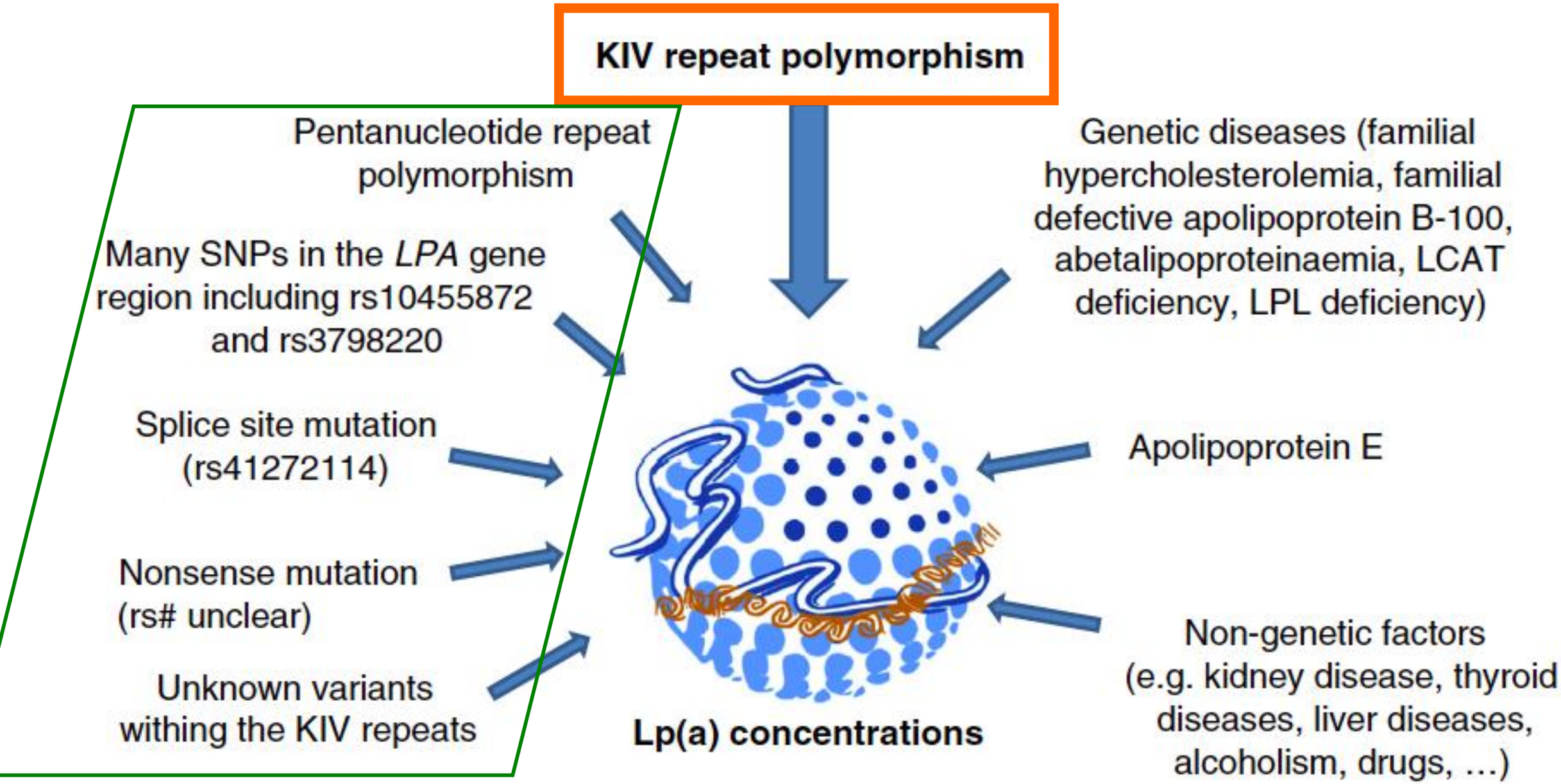



| Apo(a) Genotype | 14/6 | 17/13 | 13/6 | 13/6 | 17/14 | 17/6 |
|---|---|---|---|---|---|---|
| Lp(a) (mg/dl) | 6 | 15 | 7 | 5 | 2 | 3 |

| | 17/15 | 16/6 | 16/15 | 15/6 | 16/15 | 17/16 | 17/16 |
|---|---|---|---|---|---|---|---|
| | 4 | 51 | 5 | 51 | 9 | 5 | 3 |

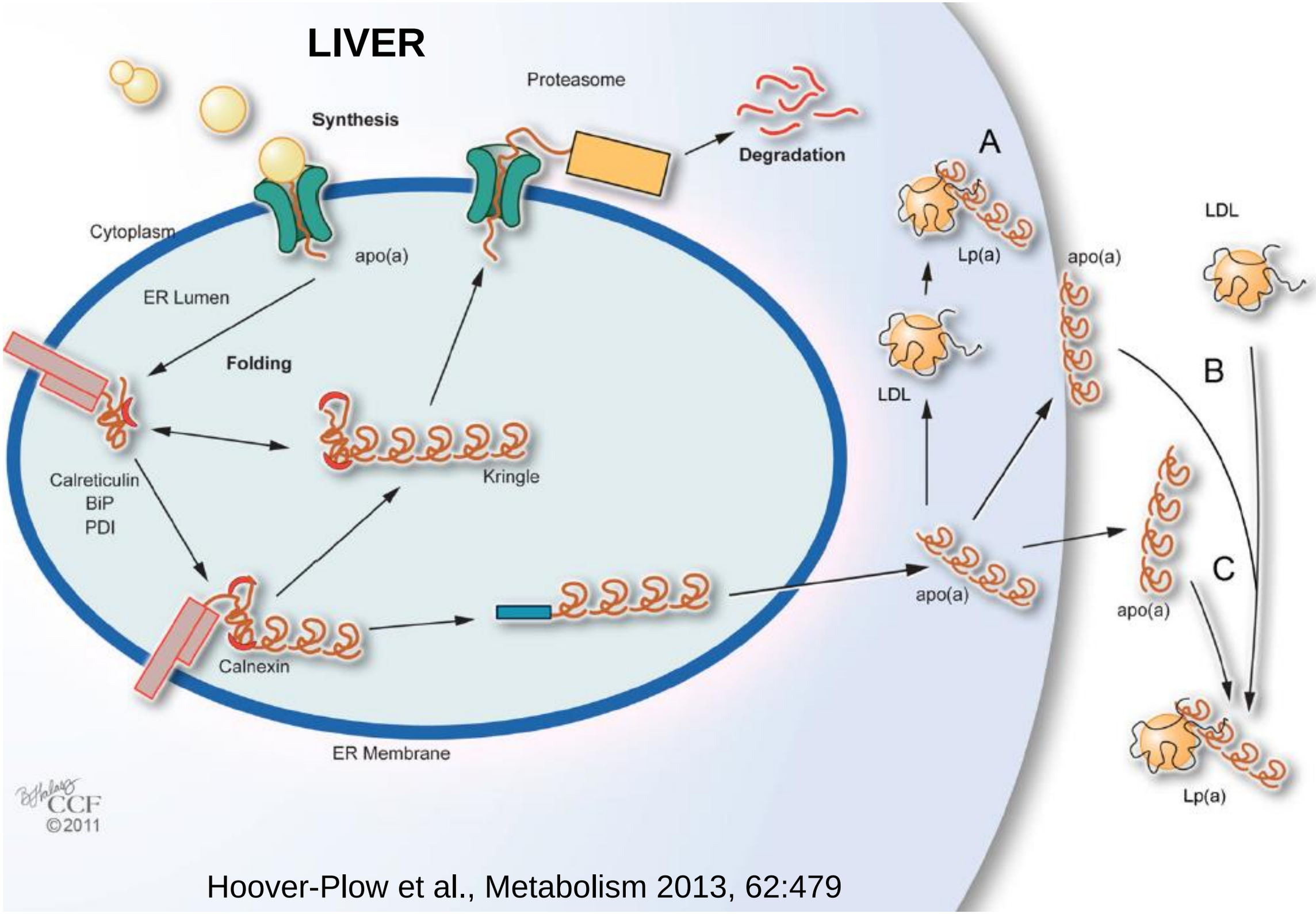
Boerwinkle et al., J Clin Invest 1992, 90:52

# Variations at the apo(a) gene locus account for 90% of Lp(a) levels



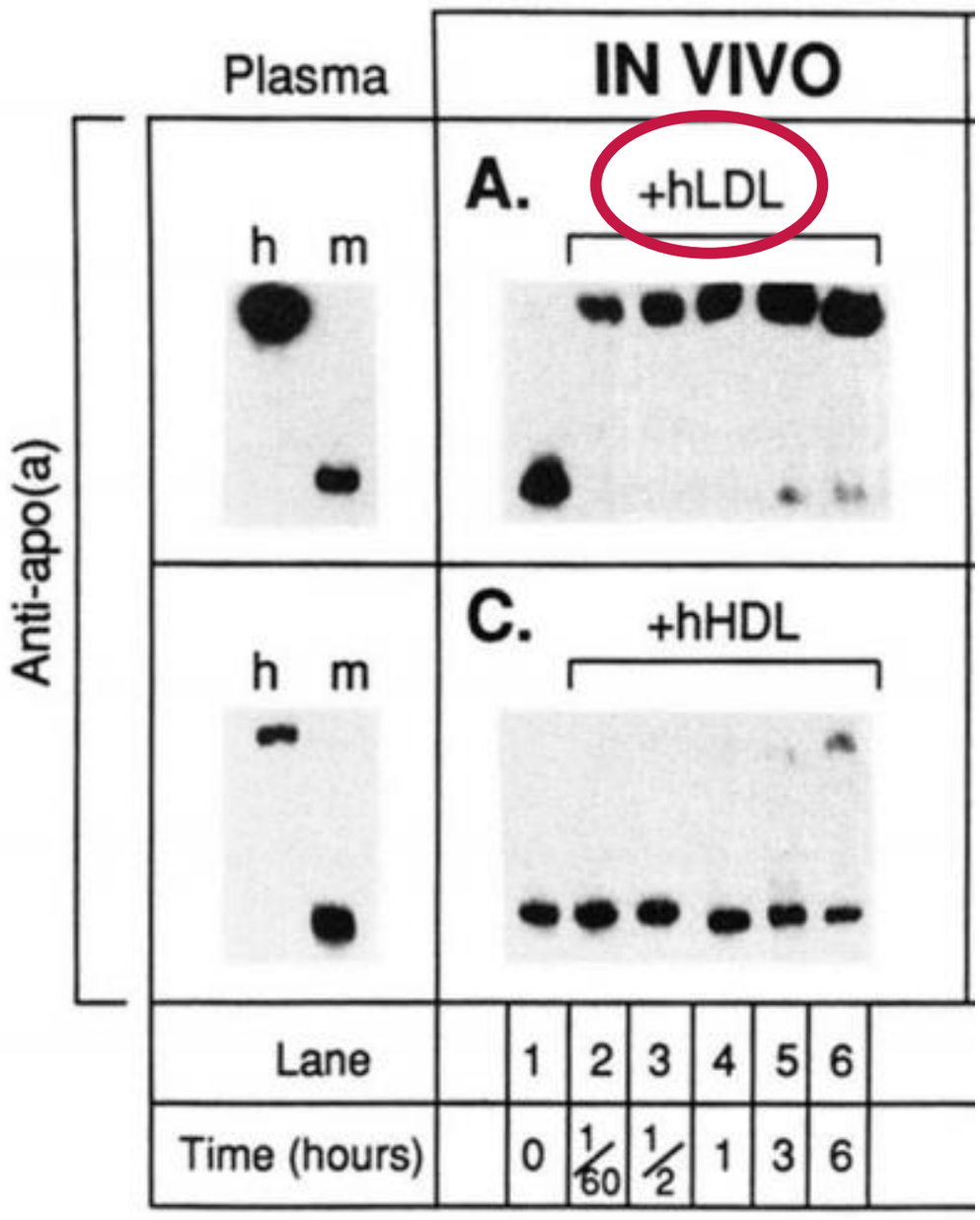

Kronenberg et al., Cardiovascular Drugs Ther 2016, 30:87

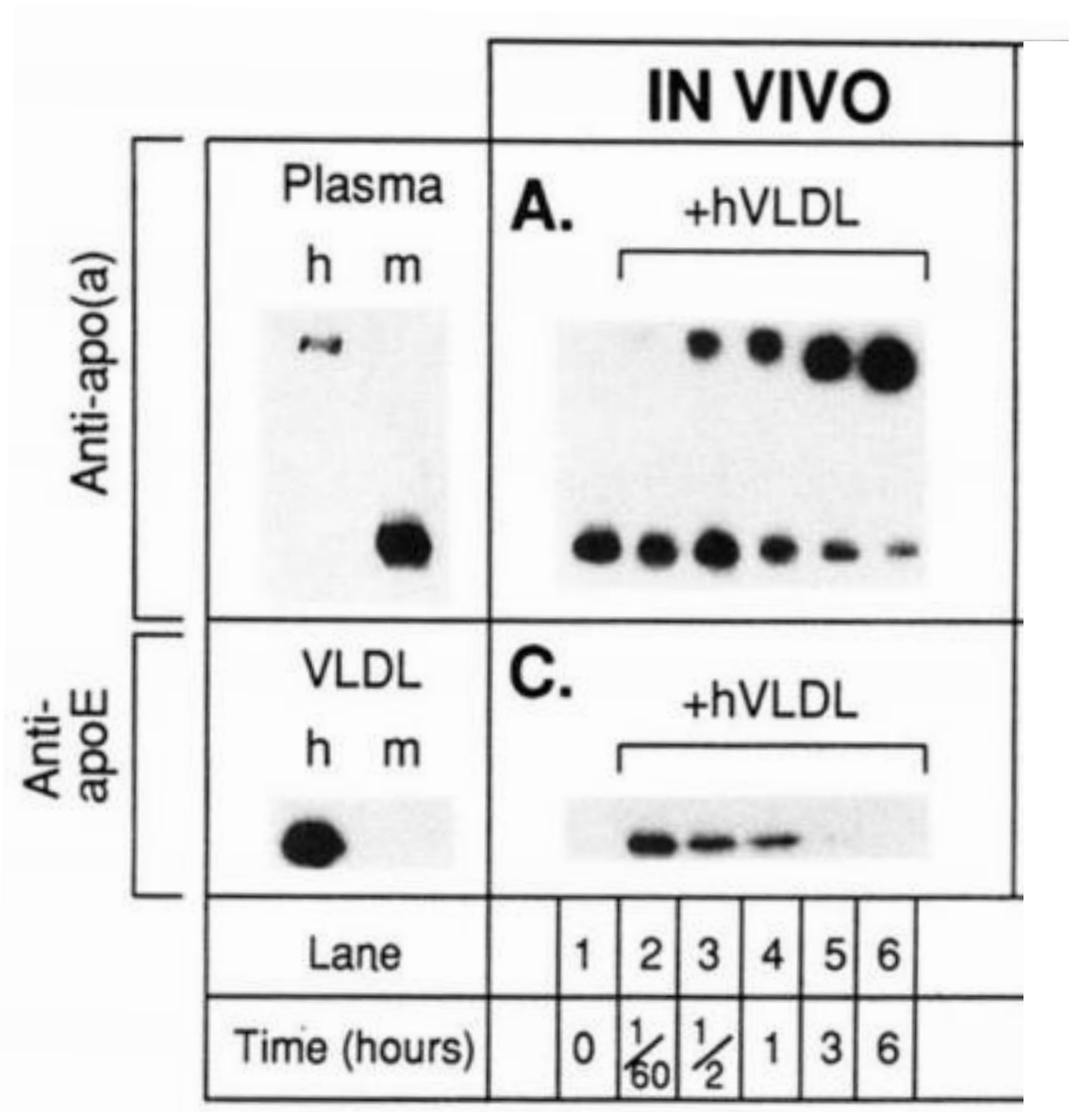
# Lp(a) synthesis/assembly




Hoover-Plow et al., Metabolism 2013, 62:479

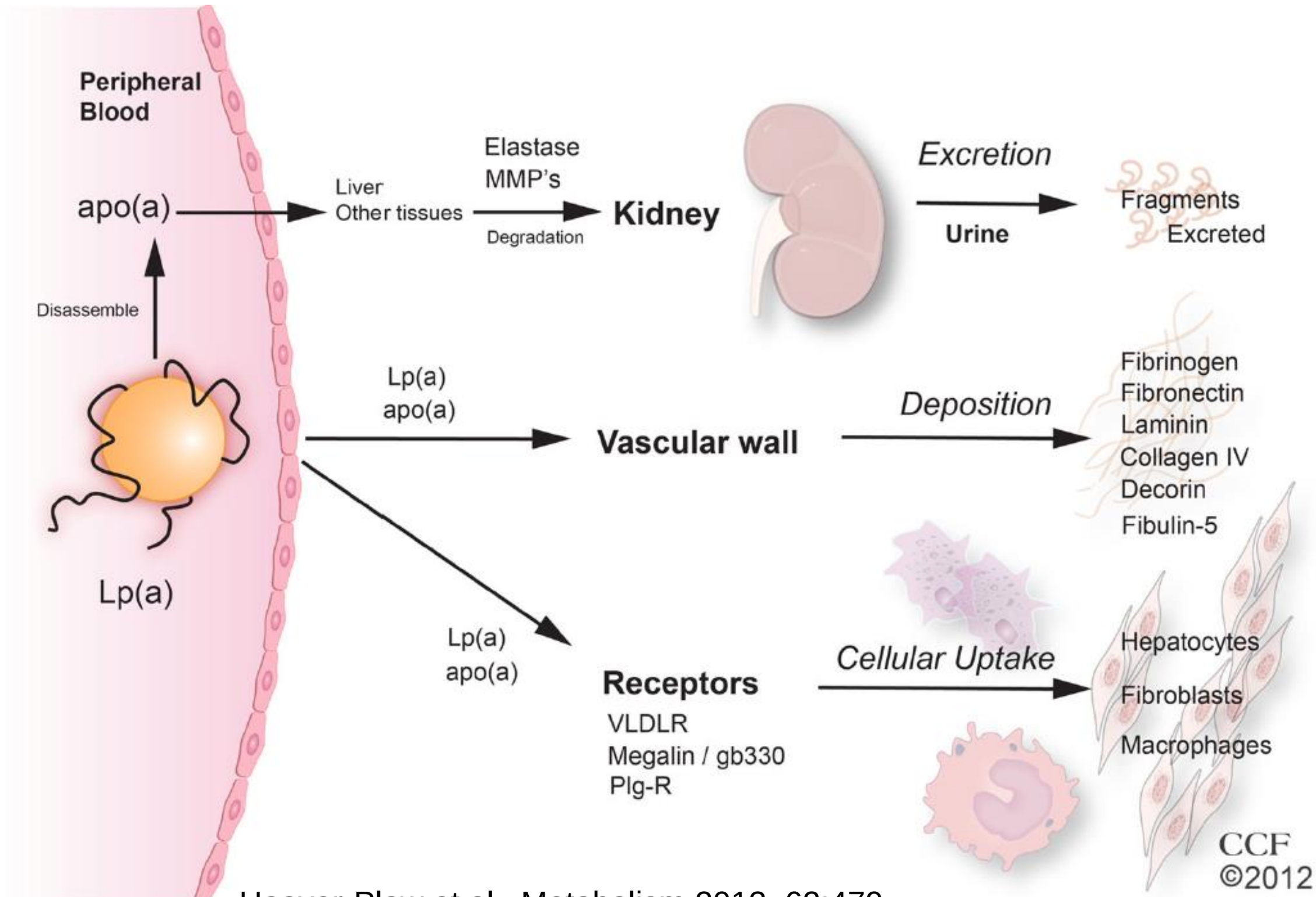
# Lp(a) synthesis/assembly



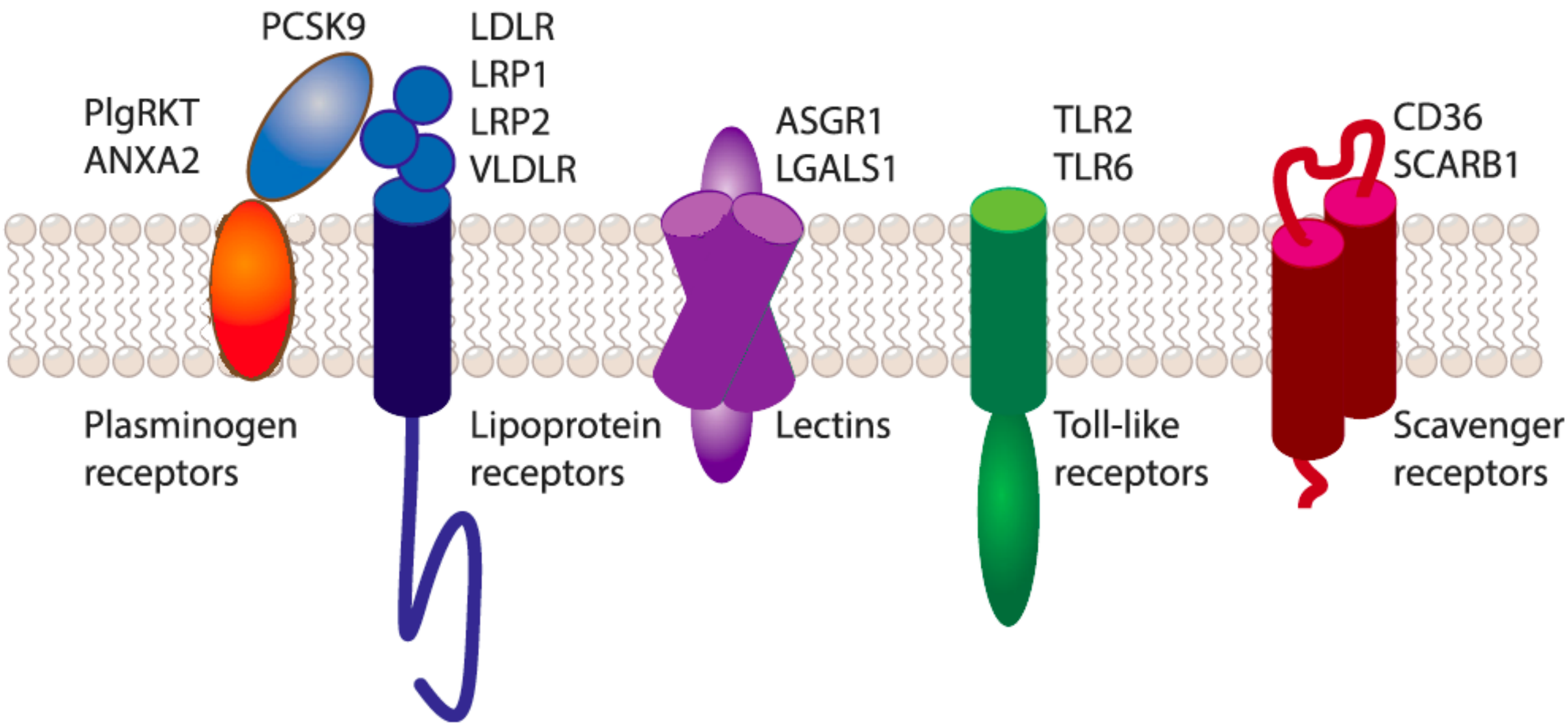

Chiesa et al., J Biol Chem 1992, 267:24369

# Lp(a)/apo(a) catabolism



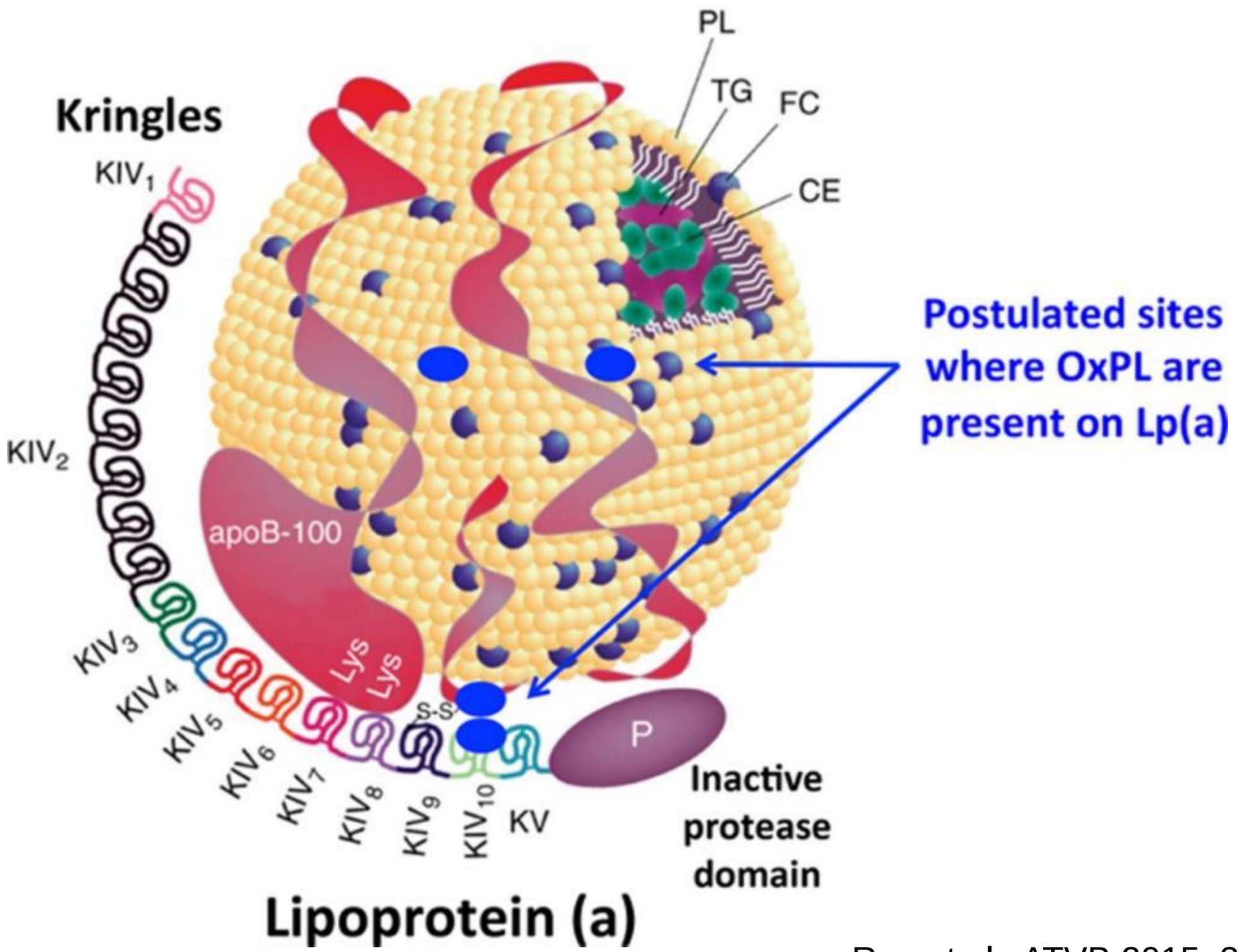

Hoover-Plow et al., Metabolism 2013, 62:479

# Possible receptors implicated in Lp(a) catabolism



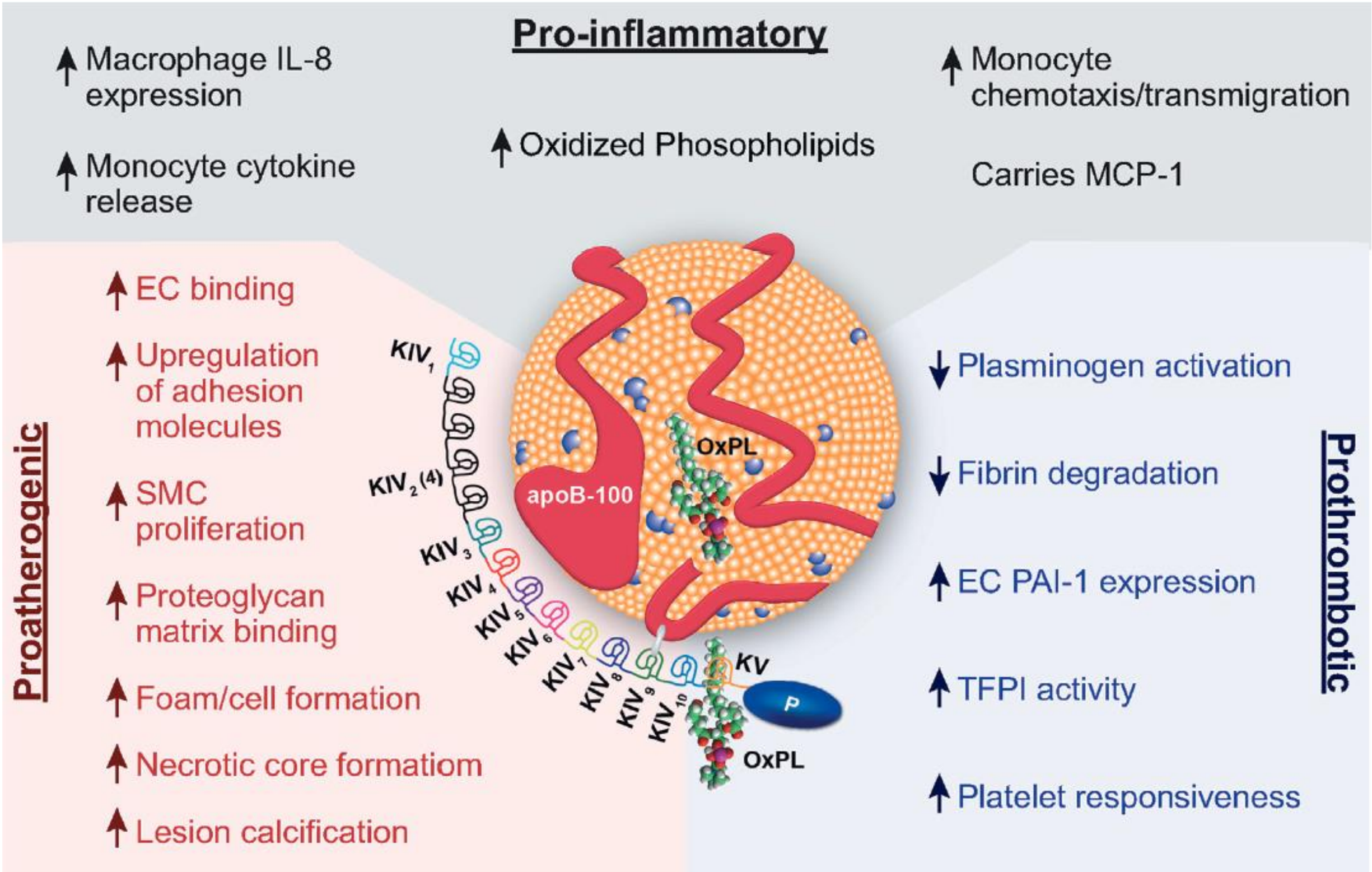

McCormick et al., Pathology 2019, 51:155

# Lp(a) and OxPL



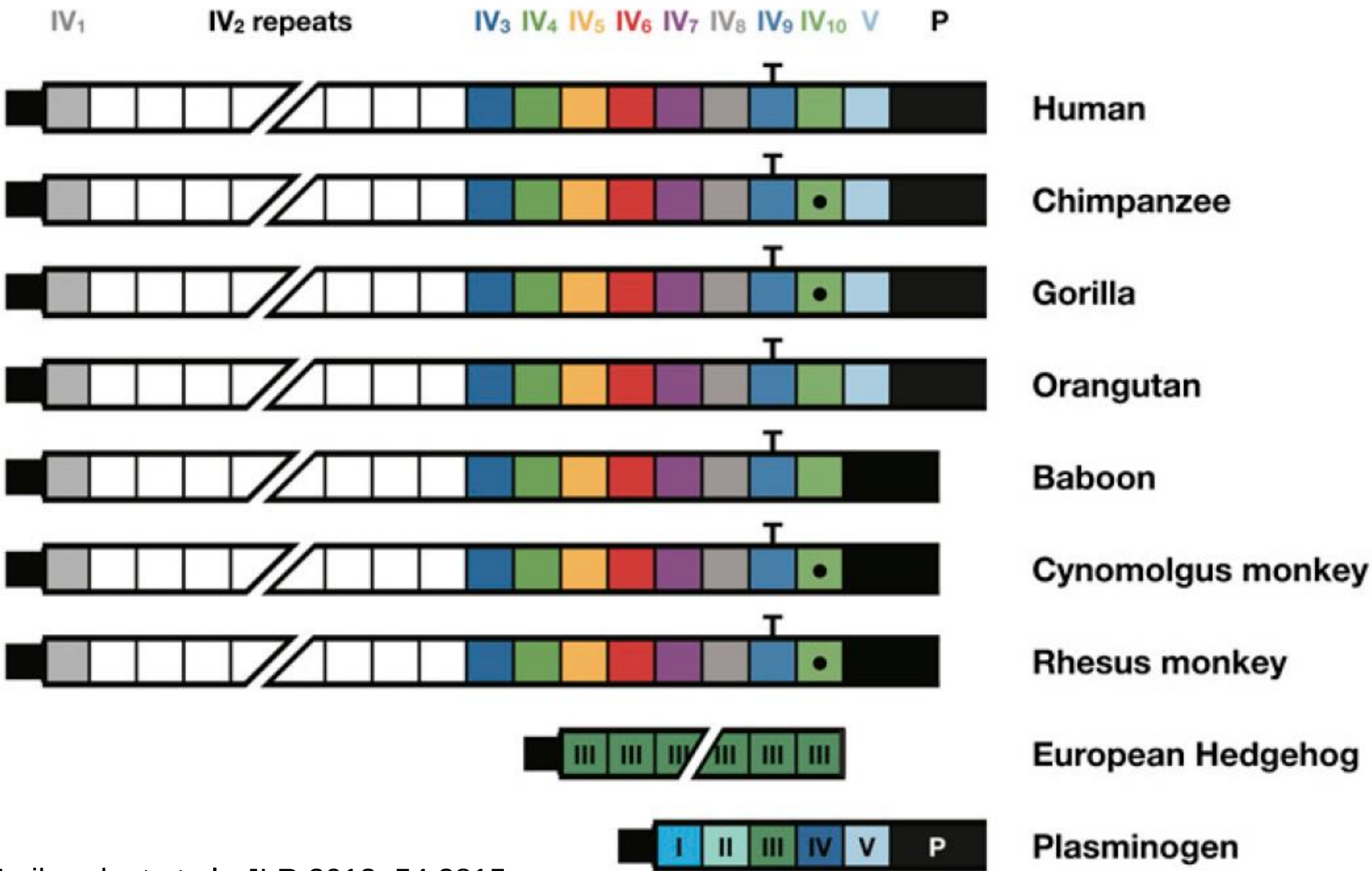

Rao et al., ATVB 2015, 35:1704

# Pathogenic mechanisms of Lp(a)




Tsimikas, JACC 2017, 69:692

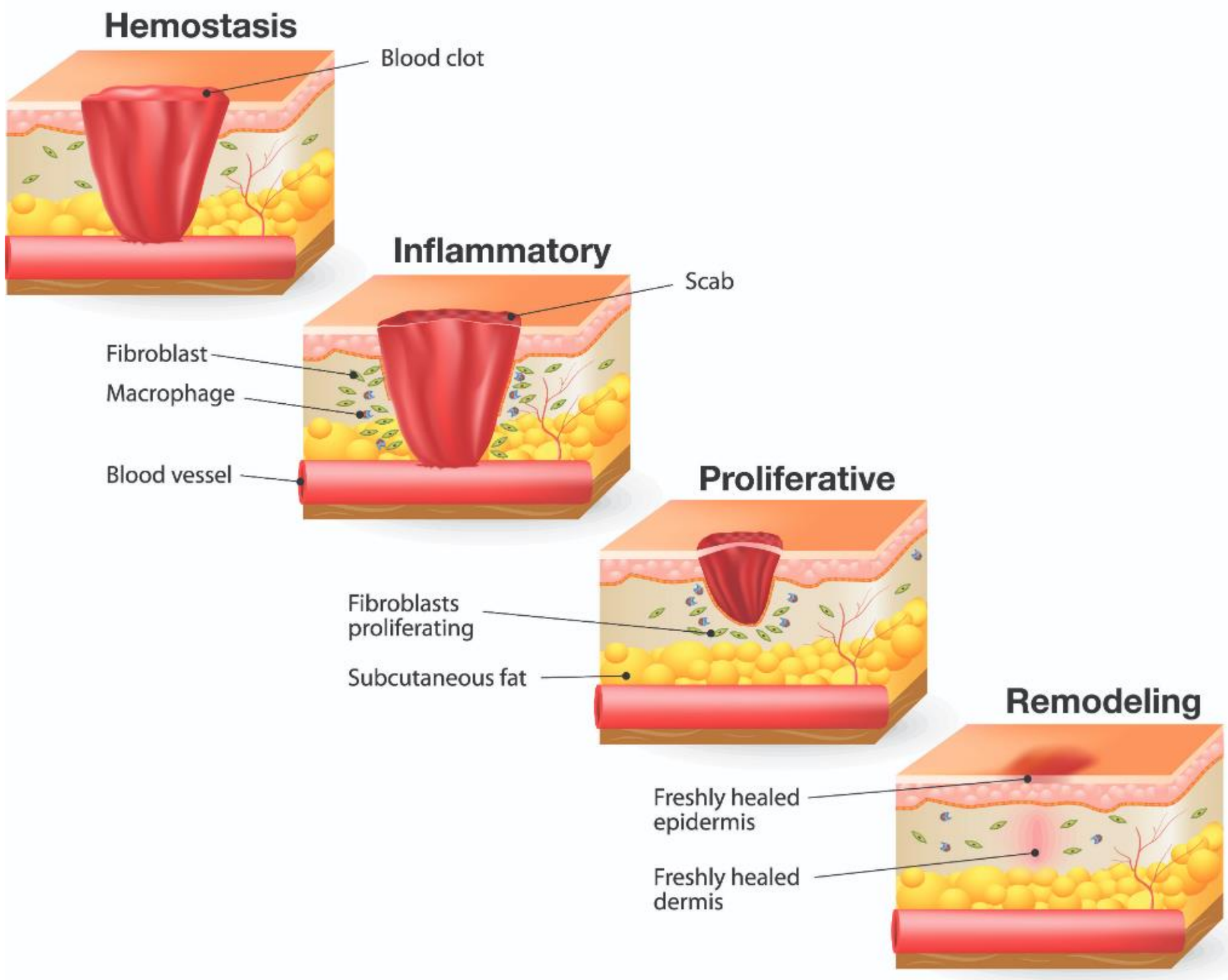
# Species differences in apo(a)



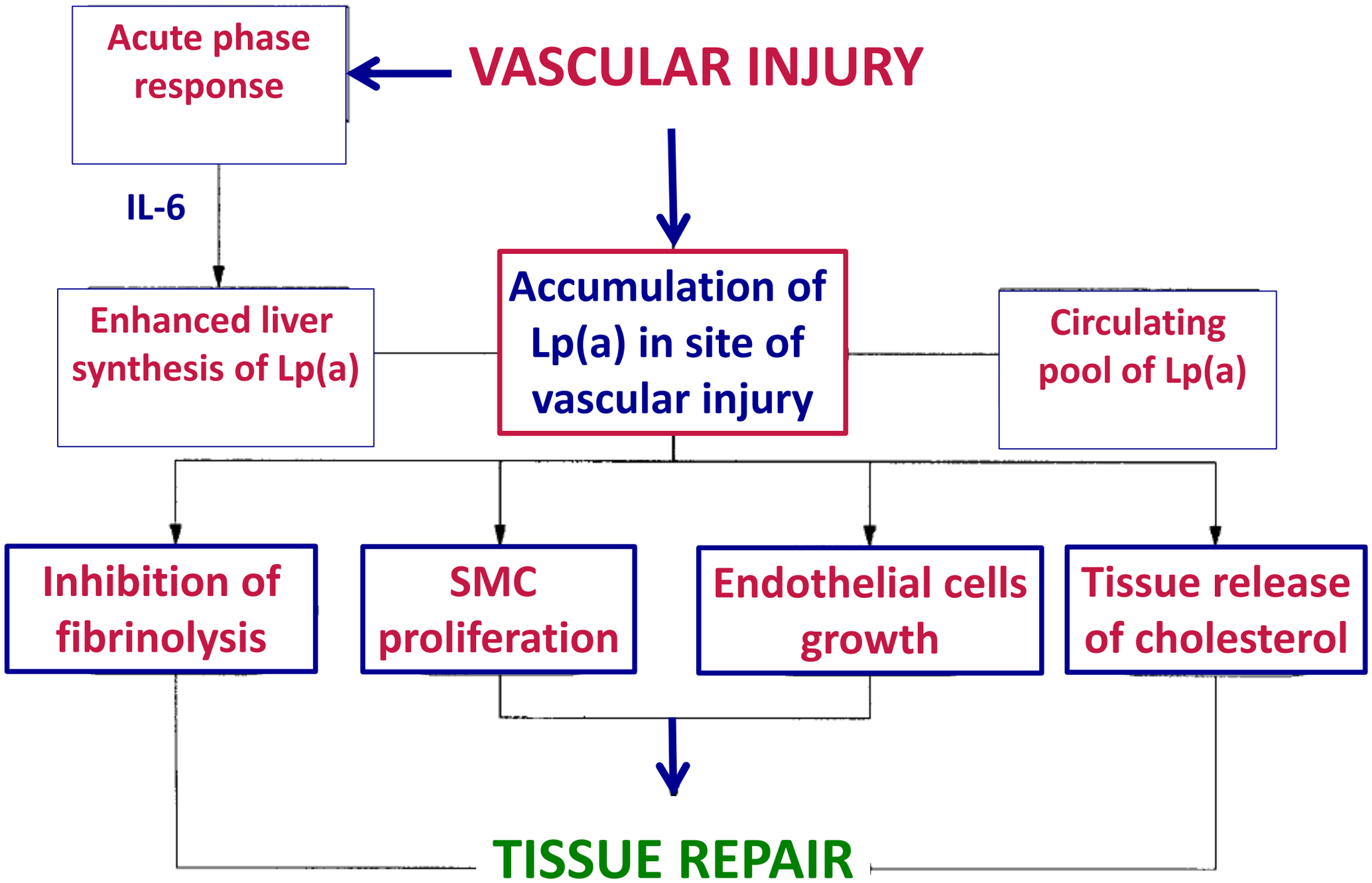

Leibundgut et al., JLR 2013, 54:2815

# Does Lp(a) have a physiological role?

## Possible role in wound healing



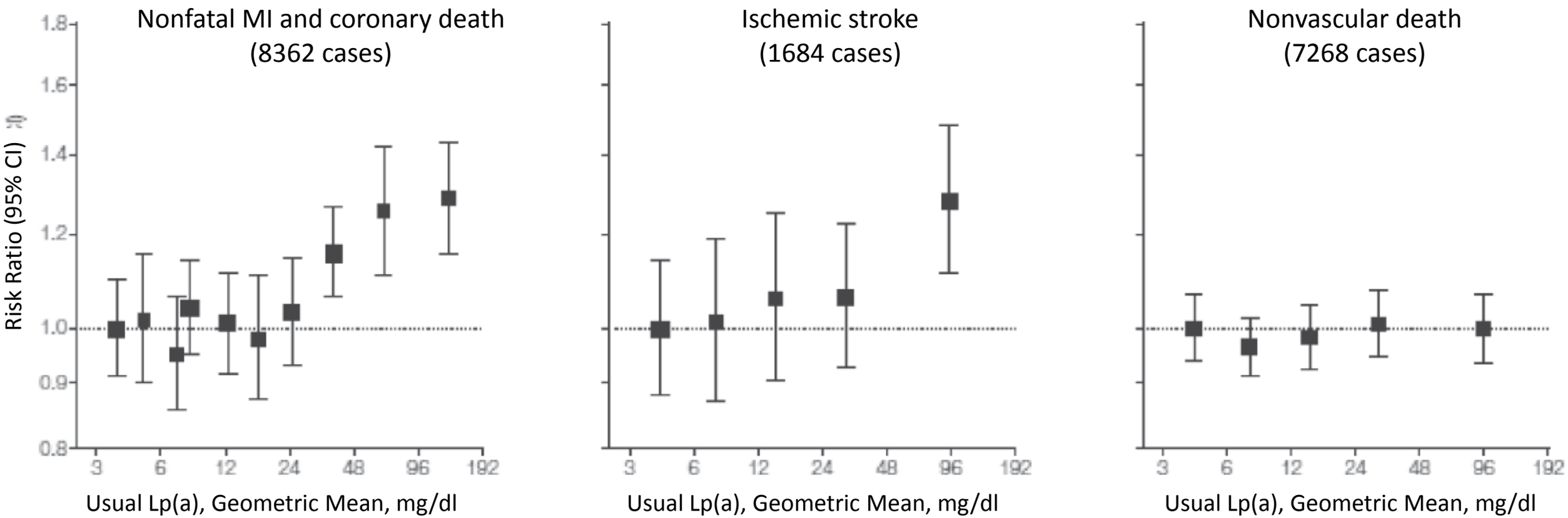
# Lp(a) and wound healing




*modified from* Lippi et al., Q J Med 2000, 93:75

# Lp(a) levels and risk of major vascular and non vascular outcomes

36 long-term prospective studies published between 1970 and 2009
(126,634 individuals, adjustment for established risk factors)

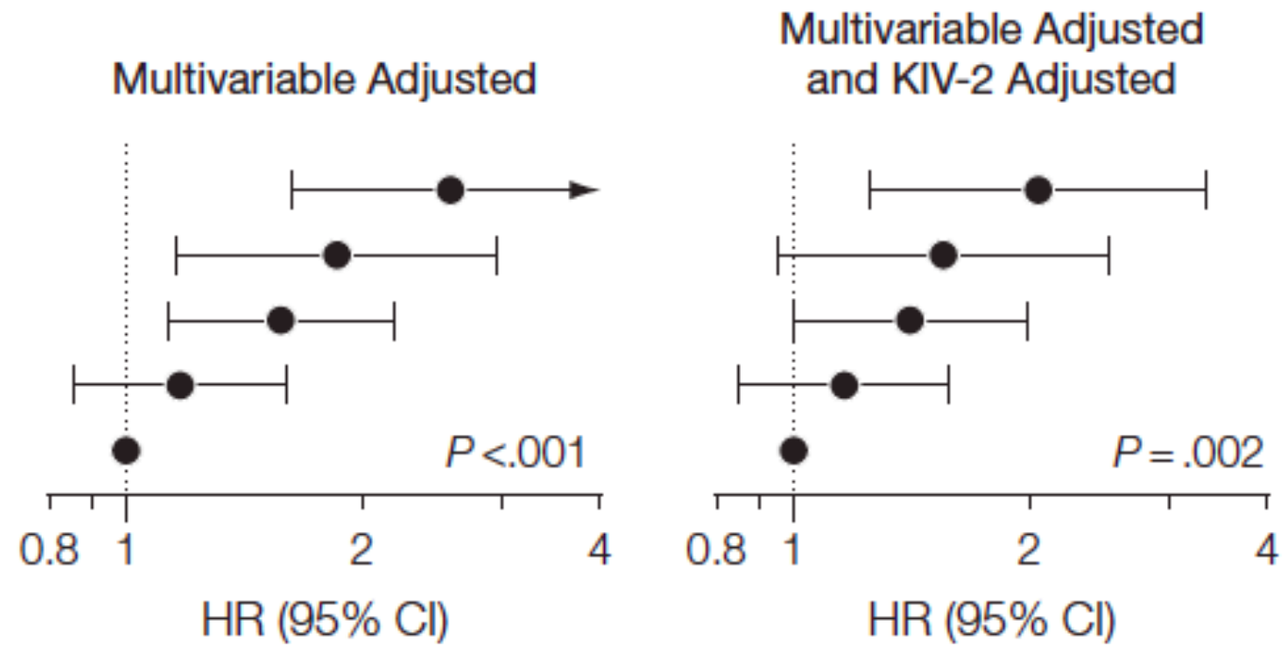



JAMA 2009, 302:412

# Risk of MI by extreme levels of Lp(a) in the general population

40,486 white individuals of Danish descent

| Lipoprotein(a) Percentile | Lipoprotein(a) mg/dL | Participants, No. | Events, No. |
|---|---|---|---|
| >95th | >117 | 376 | 46 |
| 90th-95th | 77-117 | 450 | 46 |
| 67th-89th | 30-76 | 1731 | 155 |
| 22nd-66th | 5-29 | 3385 | 241 |
| <22nd [Reference] | <5 | 1582 | 104 |




Hazard ratios (HRs) were multivariable adjusted for age, sex, total cholesterol (corrected for the lipoprotein[a] contribution), triglycerides, body mass index, hypertension, diabetes mellitus, smoking, and use of lipid-lowering therapy and for women also for menopause and hormone therapy or for all of these variables as well as kringle IV type 2 (KIV-2) genotype. *P* values are test for trend of hazard ratios where lipoprotein(a) groups with increasing levels were coded 1, 2, 3, 4, and 5. Values are from the 1991-1994 examination of the Copenhagen City Heart Study with up to 16 years of follow-up (n=7524). Controls used in the Copenhagen Ischemic Heart Disease Study (n=1200) were excluded from analysis. CI indicates confidence interval.

Kamstrup et al., JAMA 2009, 301:2331

# Lp(a) levels and CV outcomes in African Americans and Caucasians

**African Americans**

| Incident Events | HR (95% CI); Number of Events | | | | | p for linear trend |
|---|---|---|---|---|---|---|
| | Quintile 1 0.1–≤6.1 mg/dl | Quintile 2 >6.1–≤10.3 mg/dl | Quintile 3 >10.3–≤15.8 mg/dl | Quintile 4 >15.8–≤24 mg/dl | Quintile 5 >24 mg/dl | |
| CVD | Reference; 122 | 1.008 (0.78–1.31); 115 | 1.21 (0.95–1.55); 142 | 1.10 (0.85–1.41); 131 | 1.35 (1.06–1.74); 166 | 0.0004 |
| CHD | Reference; 87 | 1.03 (0.76–1.39); 82 | 1.24 (0.92–1.66); 104 | 1.07 (0.79–1.44); 93 | 1.27 (0.94–1.71); 115 | 0.009 |
| Ischemic strokes | Reference; 49 | 0.95 (0.63–1.43); 45 | 1.21 (0.82–1.78); 57 | 1.09 (0.73–1.63); 53 | 1.60 (1.10–2.34); 79 | 0.0004 |

**Caucasians**

| Incident Events | HR (95% CI); Number of Events | | | | | p for linear trend |
|---|---|---|---|---|---|---|
| | Quintile 1 0.1–≤1.5 mg/dl | Quintile 2 >1.5–≤3.1 mg/dl | Quintile 3 >3.1–≤6.0 mg/dl | Quintile 4 >6.0–≤13.5 mg/dl | Quintile 5 >13.5 mg/dl | |
| CVD | Reference; 383 | 0.94 (0.81– 1.09); 327 | 1.01 (0.87–1.17); 339 | 1.05 (0.90–1.22); 363 | 1.27 (1.10–1.47); 409 | 0.001 |
| CHD | Reference; 330 | 0.91 (0.78–1.08); 274 | 0.99 (0.84–1.16); 285 | 1.09 (0.93–1.28); 322 | 1.28 (1.10–1.50); 353 | 0.002 |
| Ischemic strokes | Reference; 77 | 1.03 (0.74–1.44); 72 | 1.17 (0.85–1.62); 81 | 0.87 (0.62–1.23); 64 | 1.27 (0.92–1.76); 86 | 0.25 |

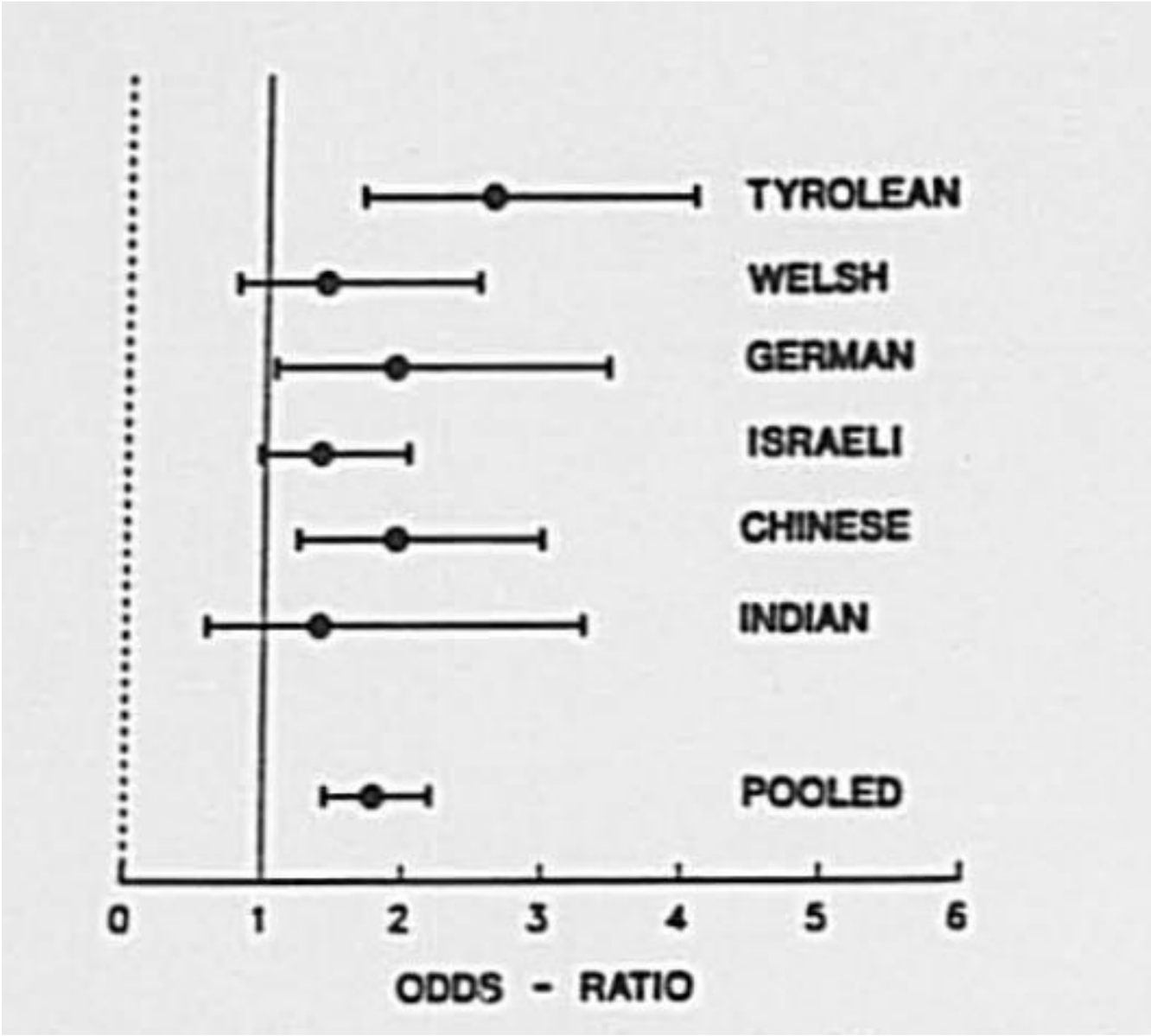
*Adjusted for age, gender, smoking, systolic blood pressure, antihypertensive medication use, diabetes, LDL-C, HDL-C, and triglycerides.

HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; CHD, coronary heart disease.

Virani et al., Circulation 2012, 125:241

# First genetic study on Lp(a) using Mendelian randomization

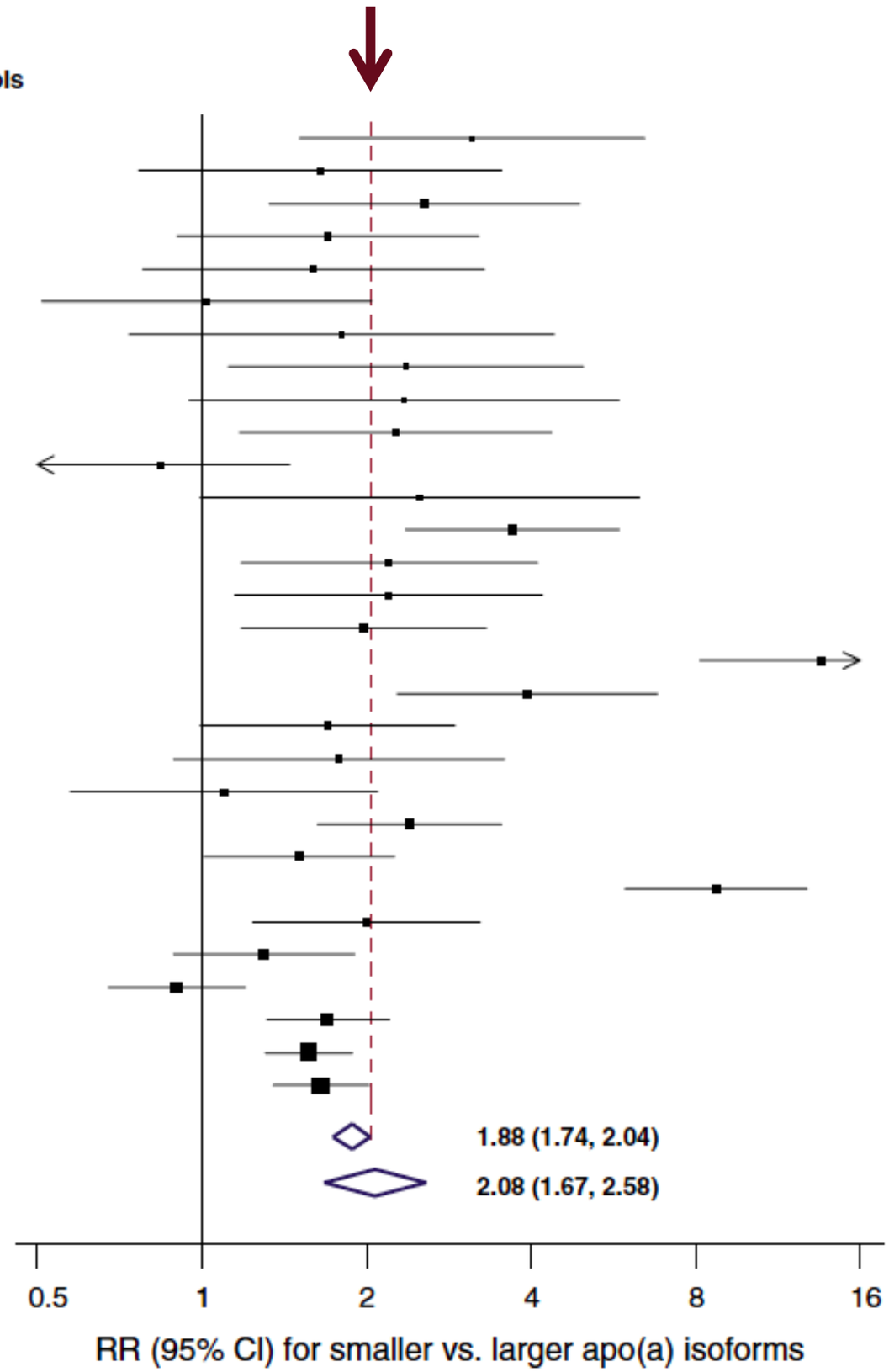
Odds ratios for subjects with small isoforms from six populations to be in the group of CHD patients




Sandholzer, Arterioscler Thromb 1992, 12:1214

# Small apo(a) isoforms double the CHD risk

| Author | Comparison† | Degree of adjustment | No. of cases | No. of controls |
|---|---|---|---|---|
| Kraft, 1996 | KIV ≤ 20 vs. >20 | + | 69 | 69 |
| Klausen, 1997 | Migration speed | ++ | 74 | 190 |
| Emanuele, 2004 | KIV ≤ 25 vs. >25 | + | 83 | 94 |
| Parlavecchia, 1994 | Migration speed | + | 83 | 96 |
| Martin, 2002 | KIV ≤ 25 vs. >25 | +++ | 91 | 99 |
| Simo, 2001 | KIV <22 vs. ≥ 22 | + | 95 | 95 |
| Geethanjali, 2002 | Migration speed | + | 104 | 104 |
| Qin, 1995 | Migration speed | + | 105 | 102 |
| Zelkovic, 2009 | KIV ≤ 22 vs. > 22 | +++ | 109 | 102 |
| Calmarza, 2004 | Migration speed | + | 111 | 99 |
| Akanji, 2000 | Migration speed | + | 128 | 140 |
| Katsouras, 2001 | KIV ≤ 26 vs. > 26 | + | 131 | 33 |
| Gazzaruso, 1997 | Molecular weight | + | 142 | 264 |
| Sandholzer, 1991 | Migration speed | + | 162 | 210 |
| Sandholzer, 1991 | Migration speed | + | 193 | 189 |
| Rifai, 2004 | KIV ≤ 22 vs. > 22 | ++ | 195 | 195 |
| Gazzaruso, 2001 | Molecular weight | + | 201 | 358 |
| Emanuele, 2004 | KIV ≤ 25 vs. > 25 | + | 210 | 105 |
| Gambhir, 2008 | KIV ≤ 22 vs. > 22 | + | 220 | 160 |
| Zorio, 2006 | Migration speed | ++ | 222 | 199 |
| Kalina, 2001 | KIV ≤ 22 vs. > 22 | +++ | 263 | 97 |
| Bigot, 1997 | Migration speed | + | 267 | 259 |
| Paultre, 2000 | KIV < 22 vs. ≥ 22 | + | 289 | 283 |
| Gazzaruso, 1999 | Molecular weight | + | 335 | 370 |
| Emanuele, 2003 | Molecular weight | + | 337 | 103 |
| Kark, 1993 | Migration speed | + | 365 | 397 |
| Abe, 1992 | Migration speed | + | 470 | 465 |
| Brazier, 1999 | KIV ≤ 27 vs. > 27 | + | 481 | 519 |
| Holmer, 2003 | KIV ≤ 22 vs. > 22 | + | 834 | 1548 |
| Sandholzer, 1992 | Migration speed | + | 1013 | 1570 |
| **Overall (fixed-effect)** | | | **7382** | **8514** |
| **Overall (random-effects)** | | | | |

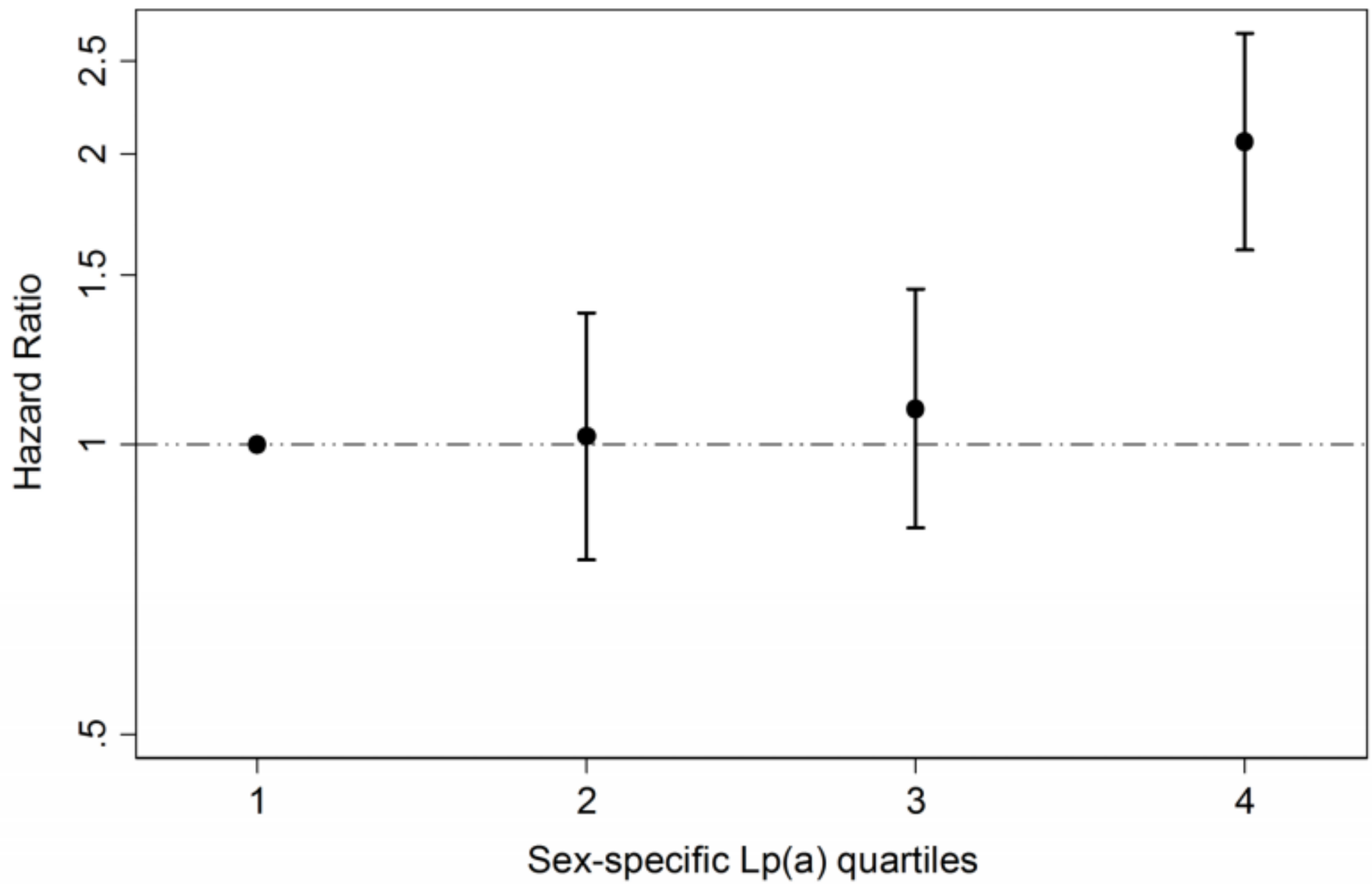



Erqou, JACC 2010, 55:692

# Lp(a) levels and risk of peripheral artery disease (PAD)

EPIC Norfolk prospective population study, 18,720 individuals

| Characteristic | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | P value |
|---|---|---|---|---|---|
| Mean Lp(a) level ,mg/dl | 4.1(1.1) | 8.5(1.5) | 17.3(4.3) | 54.7(24.9) | <0.001 |
| Lp(a) range, mg/dl | 0.1-6.2 | 5.9-11.7 | 11.2-27.9 | 26.6-175.0 | |

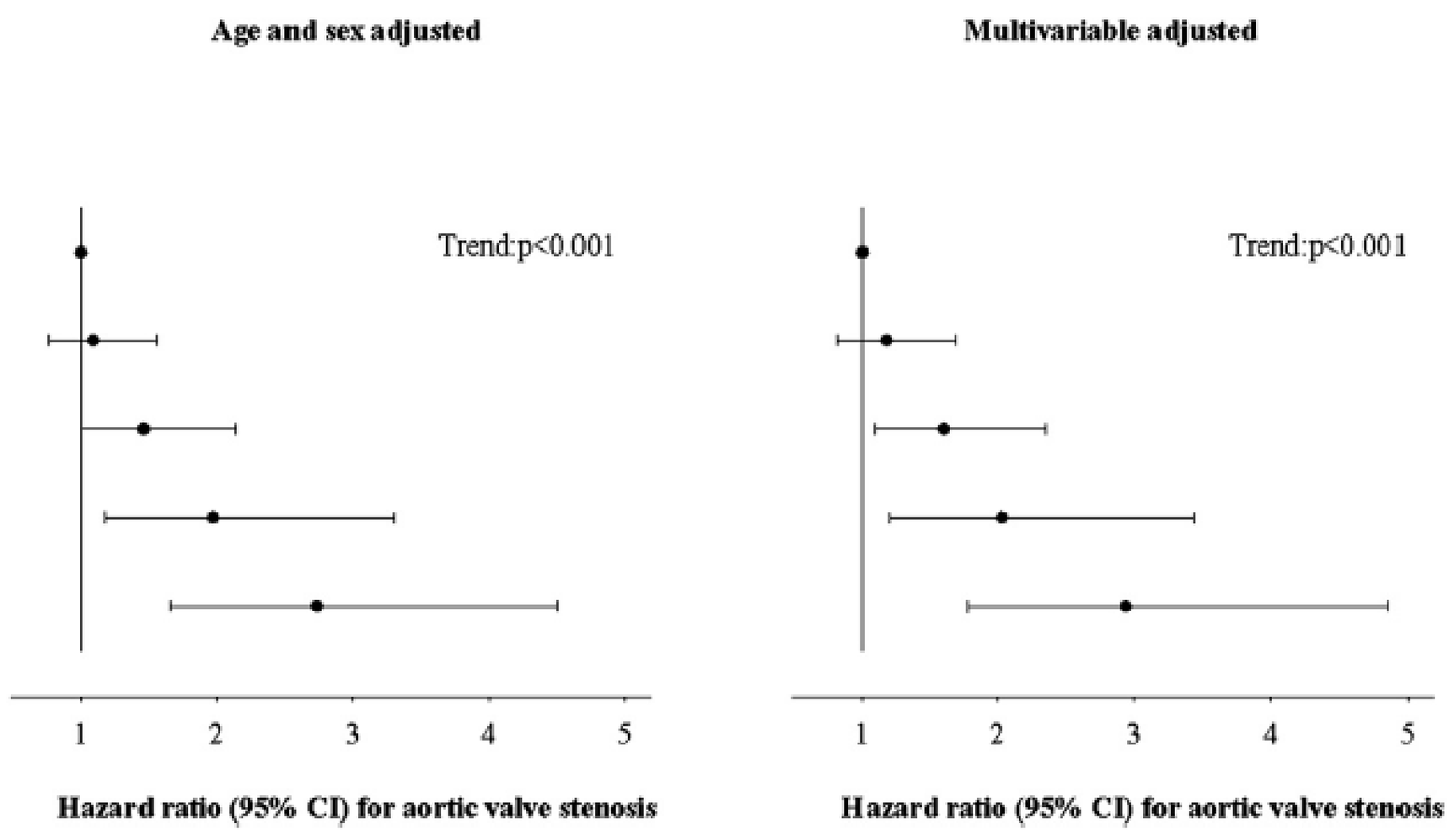



Gurdasani, ATVB 2012, 32:3058

# Risk of aortic valve stenosis as function of Lp(a) levels

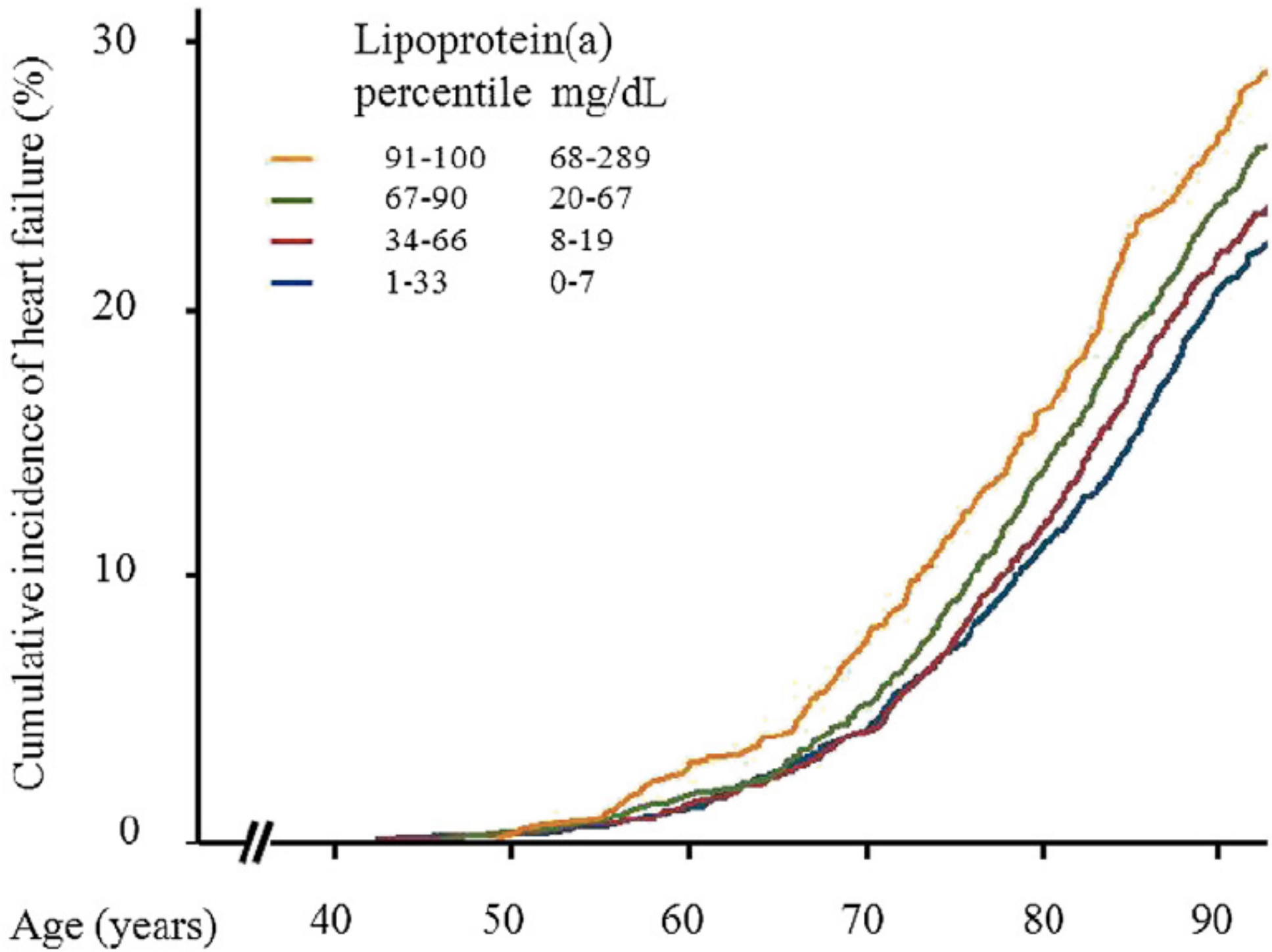
77,680 participants (Copenhagen City Heart Study + Copenhagen General Population Study).

| Lipoprotein(a) percentile | mg/dL | Participants N | Events N |
|---|---|---|---|
| <22 | 3(2-4) | 6123 | 53 |
| 22-66 | 11(7-17) | 13053 | 127 |
| 67-89 | 40(30-51) | 6677 | 87 |
| 90-95 | 80(63-95) | 1728 | 27 |
| >95 | 124(104-148) | 1435 | 30 |



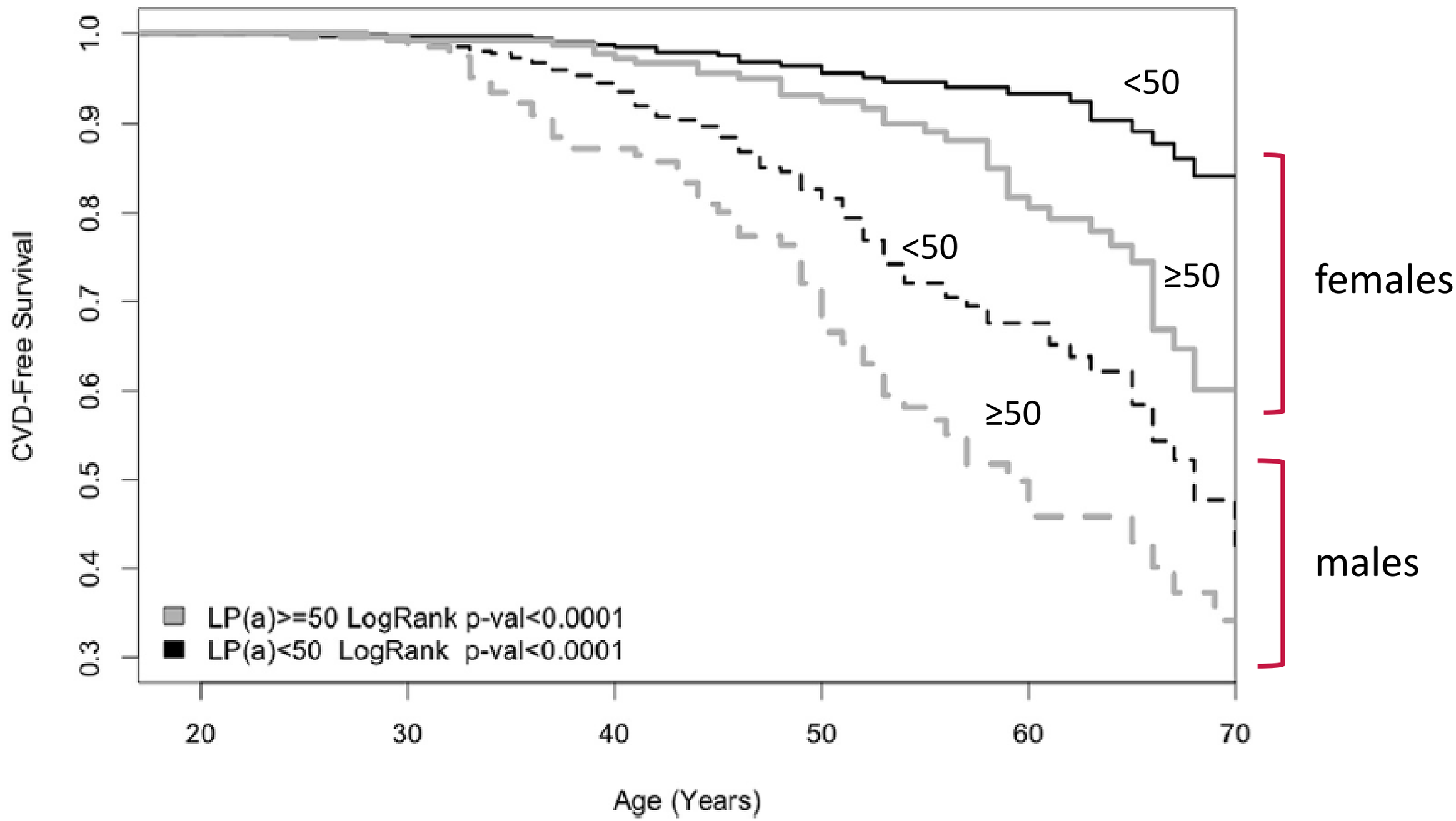

Kamstrup, JACC 2014, 63:470

# Cumulative incidence of heart failure by Lp(a) percentiles (but mediated by MI and AVS)




Kamstrup et al., JACC 2016, 4:78

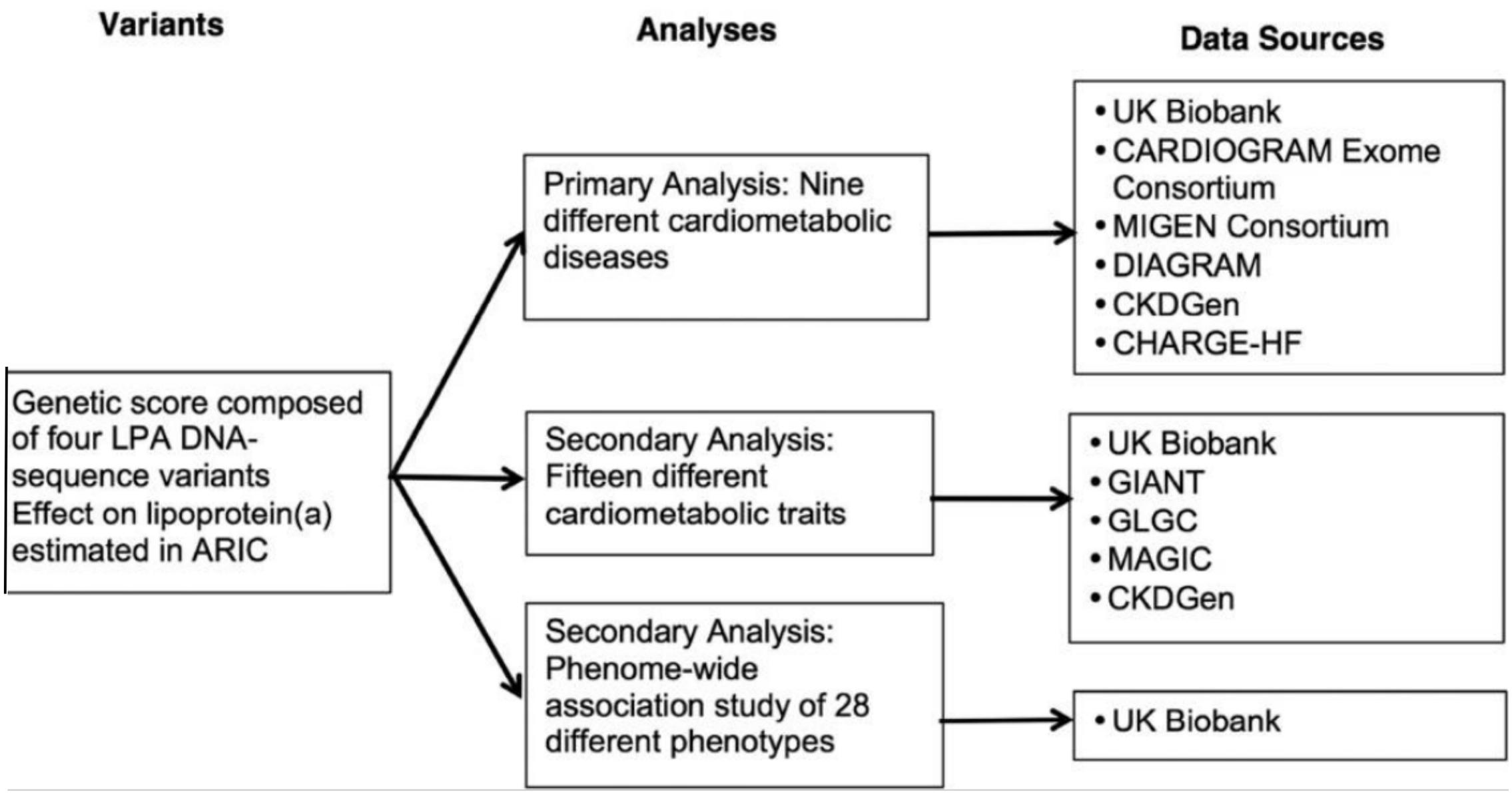
# High Lp(a) levels increase CVD risk in FH patients




Gencer, Eur Heart J 2017, 38:1553

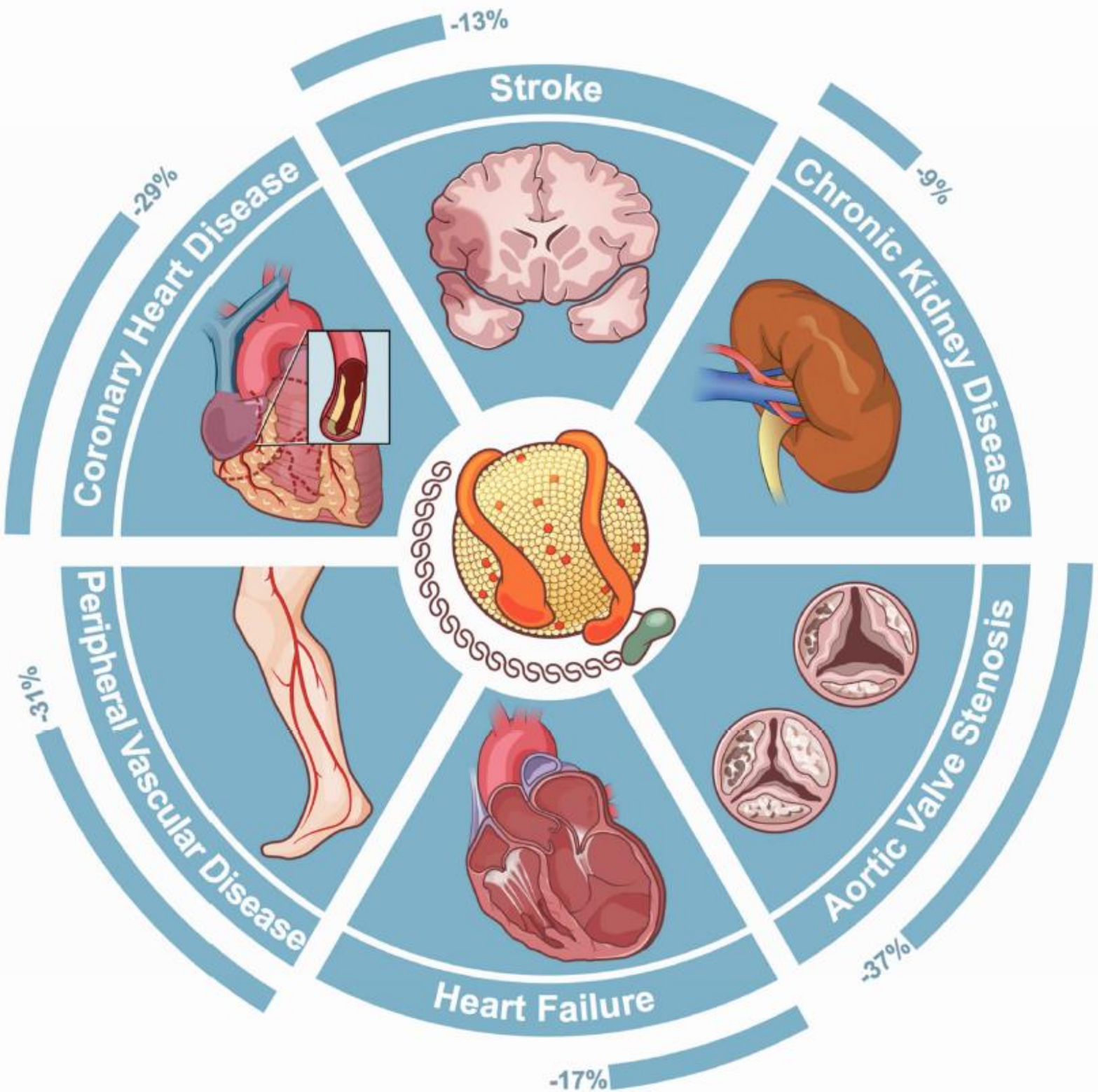
# Phenotypic characterization of genetically lowered human lipoprotein(a) levels

**METHODS—**We leveraged genetic variants at the *LPA* gene from 3 data sources: individual-level data from 112,338 participants in the UK Biobank; summary association results from large-scale genome-wide association studies; and *LPA* gene sequencing results from cases with and controls free of CHD.



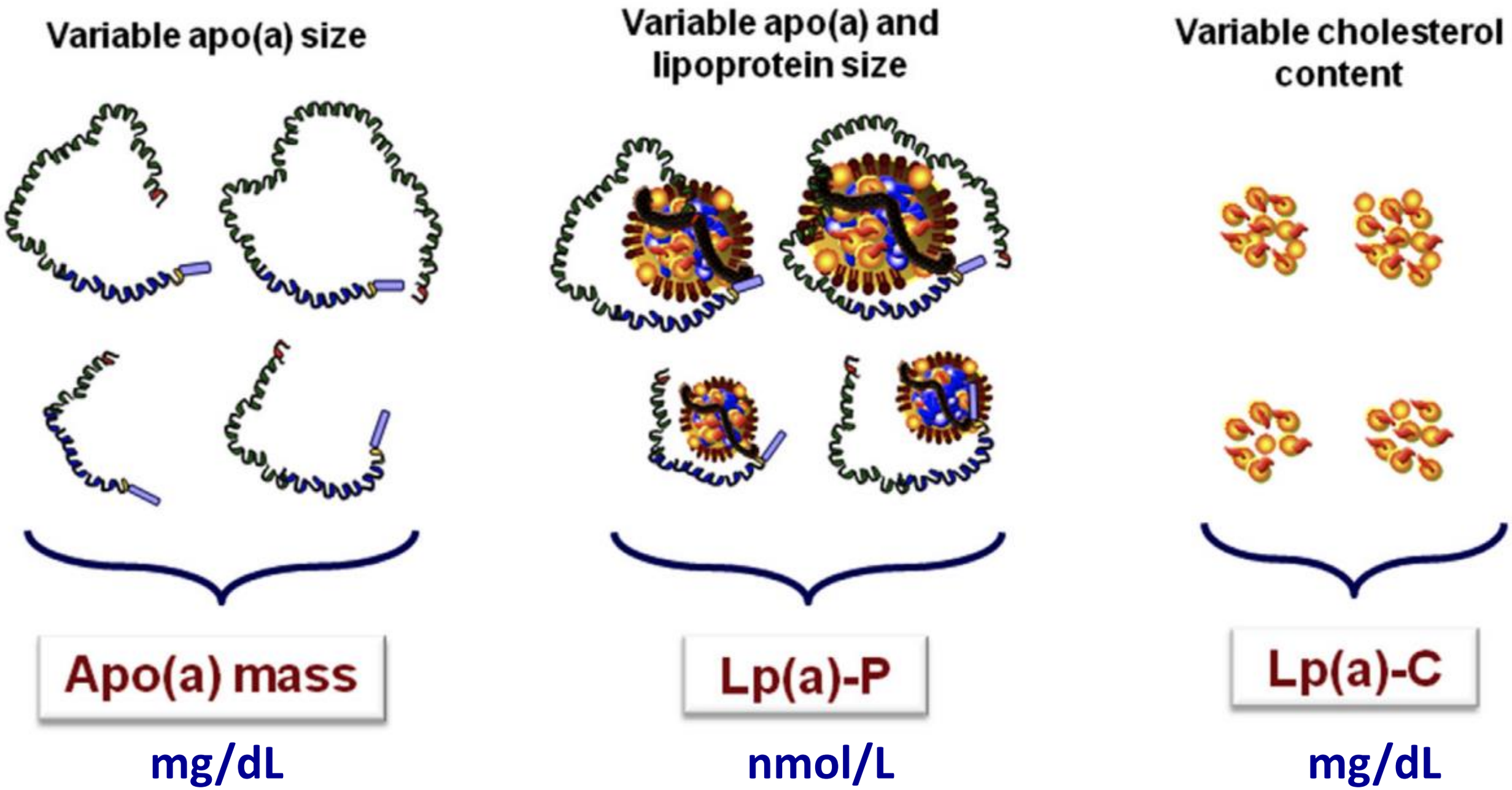

Emdin et al., JACC 2016, 68:2761

# Impact of genetically mediated Lp(a) reduction (1SD) on disease risk




Emdin et al., JACC 2016, 68:2761

# Lp(a) quantification: a complex issue




McConnell et al., J Clin Lipidol 2014, 8:550