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Comparing Predictions of Atherothrombotic Disease Risk in Women versus Men

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ABSTRACT

INTRODUCTION

The prediction of the population at risk of atherothrombotic disease (ATD) in women is important because ATD is the leading cause of morbidity and mortality in women. This article presents a novel means of such prediction. The three chief risk factors for ATD in women are cigarette smoking, dyslipidemia, and hypertension.

MATERIALS AND METHOD

Chart review.

RESULTS

ATD prediction in women is similar to the prediction of ATD in men, provided that one uses a ratio between low-density lipoprotein cholesterol (LDL-c) and high-density lipoprotein cholesterol (HDL-c) and combines the three chief ATD risk factors into a single predictive tool. The lipid ratio used by the author is the Cholesterol Retention Fraction (CRF, defined as [LDL-HDL]/LDL). The CRF is plotted on a graph combined with systolic blood pressure (SBP). The data from the ATD population is plotted on this graph and a threshold line can be determined, separating the mainstream of ATD patients from a few outliers. The average age of ATD onset for each patient is assessed, as is the average age of multiple system disease and average age of death. Men and women follow the same pattern. This same graph can be divided into 48 CRF-SBP cohorts and the average age of ATD onset determined for each cohort. Using this approach, the average age of ATD onset can be determined for each cohort, reveling which cohorts are associated with early onset ATD, middle-age onset of ATD, and old-age onset of ATD. Finally, Kaplan-Meier curves can be developed for the CRF. In each analysis, women follow a pattern similar to that of men.

CONCLUSION

The prediction of the population at risk of ATD in women is virtually the same as for men when lipid ratios are used.

KEYWORDS

Atherothrombotic disease; Mortality; Hypertension; Diabetes

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INTRODUCTION

Atherothrombotic disease (ATD) is the leading cause of morbidity and mortality in the western world [1]. It is possible to predict the population at risk of ATD with high accuracy [2]. The major ATD risk factors are cigarette smoking, dyslipidemia, and hypertension, with some contribution from the very high blood glucose levels of uncontrolled diabetes [3]. To maximize numbers in the prior publication [2] due to risk stratification by cigarette smoking status, men and women were combined. This publication involved 870 with full lipid data, known cigarette smoking status, and systolic blood pressure measurements. (An additional male patient had full lipid data and systolic blood pressure measurement, but his cigarette smoking status is unknown to the author). Moreover, a number of patients who will be discussed in this paper had their lipid determinations done prior to 1978 and hence had only total cholesterol [CT] and triglycerides [TG] available, though they did have systolic blood pressure (SBP) measurements and their cigarette smoking status was known. In this presentation, the author will separate out the male from the female ATD cohorts, comparing and contrasting them to determine any differences in ATD risk factors and to align such differences with clinical ATD presentations. To the author's knowledge, this is the first integrated report, as previous reports discussing ATD and women tended to present clinical ATD symptoms and outcomes, with general discussion of cigarette smoking, dyslipidemia, and hypertension presented as independent risk factors [4-19].

MATERIALS AND METHOD

The Bowling Green Study of the Primary and Secondary Prevention of Atherothrombotic Disease (shortened to BGS) was established by the author, its principal investigator, on 4 November, 1974 in Bowling Green, the count seat of Wood County, in northwest Ohio. The evolution of the BGS has been described in various previous publications [2,20,21]. In brief, Wood County is a mostly rural county with its chief city being its county seat in Bowling Green, in which is located Bowling Green State University. Its population at last census was about 120,000, with the large majority being of European descent and the largest minority being of Latin-American descent. African-Americans and Asian-Americans are not present in large numbers. The author's practice of family medicine includes members of both genders and all ages, from newborns to the very old.

The BGS goal was the accurate prediction of the population at risk of ATD. The author wished to use a targeted approach rather than a "herd" approach. To achieve this goal, the author knew that he would have to set up and age-sex register of the various ATD risk factors, which were included in the author's general population data base. To this end, the author measured blood pressure, height and weight each and every time a given patient attended his clinic. (In adults, heights were only measured on the initial visit). Cigarette smoking status was not routinely determined in the General Population until 1983, though it was routinely determined in ATD patients beginning in 1981. Up until that time, cigarette smoking was simply another ATD risk factor. Lipid profiles were obtained whenever practical, as were two hours postprandial blood glucose levels. The author has presented data to document the relative importance of each of the various major ATD risk factors and has previously published this data [3].

Lipid profiles obtained prior to 1 January 1978 involved only CT and TG. High-density lipoprotein cholesterol (HDL-c) became available in the author's local hospital laboratory on 1 January,

1978, and with it the ability to calculate low-density lipoprotein cholesterol (LDL-c) according to the Friedewald formula [22]. The Friedewald formula requires that TG levels be below 400 mg/dl (4.5 mmoles/L). However, Wilson has published data showing that LDL-c calculations are still accurate at TG levels of 500 mg/ld (5.6 mmoles/L) and the BGS accepts this criterion [23].

ATD prediction by risk factors was fairly primitive in the 1970's. Moreover, the author's research was met with resistance from the local medical community and much of the populace of Wood County was not in lockstep with preventive cardiology and interventional lipidology (Harvey Hecht, MD, with permission). And finally, medications to control dyslipidemia and hypertension were not optimally effective in achieving what are now considered to be target goals for dyslipidemia and hypertension. As a result, a number of the author's patients developed clinical ATD events, such as acute myocardial infarction, acute cerebral infarction, abdominal aortic aneurysm, etc. By 1981, enough of the author's patients had had ATD events for the author to separate out an ATD data base from the general population data base. (The author had always offered therapy to treat dyslipidemia in all identified patients, who in turn could choose to accept or reject that therapy and the consequences to those decisions).

Initially, the author treated the individual ATD risk factors as independent entities. However, in 1981 inspection of the ATD database revealed that patients with ATD events rarely had just a single ATD risk factor and that the usual ATD patient had clusters of risk factors. In 1981, the author began to examine ATD risk factor combinations for their predictability. It was at this time that an article was published, entitled "Is the LDL: HDL Ratio the Best Lipid Predictor." (The author regrets that the article is now lost to him, and he is unable to give proper credit.) After reading this article, the author re-examined his ATD data base and discovered that when ATD events occurred despite a normal or even low LDL-c, the patient's associated HDL-c was usually very low. Likewise, when ATD events occurred despite a high HDL-c, the associated LDL-c was usually very high. (When this was not the case, the younger patients were mainly cigarette smokers and the older patients were hypertensive, with or without attendant diabetes.) As a result, the author abandoned the use of LDL-c and HDL-c as independent risk factors and used the LDL-c: HDL-c ratio.

To determine which ATD risk factor combination best predicted the population at risk of ATD, the author tried various risk factor combinations, but only the LDL-c: HDL-c ratio versus SBP was predictive. And this combination was predictive only when the combination was stratified by cigarette smoking status. In 1983, it occurred to the author that what he really wanted to know about dyslipidemia was how well it predicted cholesterol accumulation within the artery wall. This, he reasoned, could best be estimated by subtracting the amount of cholesterol being removed from the artery wall by reverse cholesterol transport (HDL-c) from the cholesterol entering the artery wall (LDL-c), the difference divided by LDL-c. In other words, of the cholesterol entering the artery wall, what percentage remained there. Thus, was born the concept of the Cholesterol Retention Fraction (CRF, defined as [LDL-HDL]/LDL). The author subsequently compared the CRF with the LDL-c: HDL-c ratio and found that the CRF predicted 5% more ATD patients than the LDL-c: HDL-c ratio. (Feeman, unpublished data) The author then abandoned the LDL-c: HDL-c ratio and relied on the CRF as his best lipid predictor.

It should be noted that if HDL-c is very low, then the CRF will always be elevated. In event of such a scenario, the author relies on LDL-c, keeping it at 99 mg/dl (2.5 mmoles/L) in primary prevention cases and below 80 mg/dl (2.0 mmoles/L) in secondary prevention cases. Conversely, inspection of the ATD data base revealed that if LDL-c was very high (170 mg/dl or 4.4 mmoles/L) then ATD could be manifested even if the CRF were 0.69 or lower, though the lower the CRF in such cases, the later the age of ATD onset. Hence, the author defines dyslipidemia as a CRF of 0.70 or higher and/or a LDL-c of 170 mg/dl (4.4 mmoles/L) and terms it the cholesterol threshold (C Thr).

Here it is important to note that the vast majority of the author's lipid data was determined on the basis of the precipitation method of HDL-c measurement. This was the world-wide gold standard at the time. In 1999, the manufacturers of the auto-analyzers, without telling the medical community in general, switched the HDL-c measurement methodology to the enzymatic method. The different methodologies do not give the same results. Indeed, the enzymatic method gives an HDL-c value on the order of 10 mg/dl (0.25 mmoles/L) higher than the equivalent obtained had the precipitation methodology been used. Since LDL-c is calculated on the basis of HDL-c in the Friedewald formula, the enzymatic method will give an LDL-c value on the order of 10 mg/dl (0.25 mmoles/L) lower than would have been obtained had the precipitation methodology been used. Such differences make large differences in CRF calculations. This is not a trivial matter. In 2008, the author reported the case of a 53-year-old man whom the author had seen on numerous occasions for acute complaints. The patient did not have a family history or dyslipidemia or ATD. He did not have diabetes or hypertension and did not smoke cigarettes. He was not obese. Hence the author did not perform any lipid determinations. In any event, the patient was at work in another city when he sustained an acute myocardial infarction. The physicians at the other hospital obtained a lipid profile and sent the results to the author. HDL-c was measured by the enzymatic method. The CRF was mildly abnormal using the enzymatic method of HDL-c measurement, but markedly abnormal when the HDL-c was converted to its precipitation-method equivalent, and the patient had his ATD event precisely at the age predicted [24]. This case underscores the importance of knowing the laboratory methodology. (In his practice, the author relies solely on the precipitation methodology (or the conversion of enzymatic methodology to its precipitation method equivalent).

RESULTS

Table 1A- Table 1C respectively show the clinical ATD presentations, comparing men versus women, for ATD of the coronary circulation (ATHD) (Table 1A), ATD of the cerebral circulation (ATBD) (Table 1B), and circulation of the peripheral vasculature (ATPVD) (Table 1C). In Table 1A, it is clear that the combination of acute myocardial infarction and acute coronary insufficiency (25% of cases) is more common in men than in women (15% of cases), whereas angina and especially congestive heart failure are more common in women (combined total of 35% of cases) than in men (combined total of 25% of cases). In Table 1B, the only marked difference between men and women is in asymptomatic carotid stenosis, which men have in 16% of cases while women have in only 8% of cases. In Table 1C, men have more abdominal aortic aneurysms (27% of cases) as compared to women ((12% of cases). Conversely, women have more ATPVD of the lower limb arterial tree (48% of cases) versus men (40% of cases).

ATD Event	Male	Female	∑
AMI	121 22%	61 14%	182 19%
ACI	14 3%	6 1%	20 2%
AP	82 16%	83 19%	165 17%
CHF	47 9%	72 16%	119 12%
+ Test	26 5%	11 2%	37 4%
Hx	248 46%	212 48%	460 47%
∑	538 55%	445 45%	983

Table 1A: ATHD events, ∑ATD population. ATHD: Atherothrombotic Heart Disease; ATD: Atherothrombotic Disease; AMI: Acute Myocardial Infarction; ACI: Acute Coronary insufficiency; AP: Angina Pectoris; CHF: Congestive Heart Failure; + Test: Positive Cardiac Test; HX: History of Cardiac Event.

ATD Event	Male	Female	∑
TCVA	44 18%	52 22%	96 20%
TIA	25 10%	27 11%	52 11%
ACS	43 17%	20 8%	63 13%
SVID	12 5%	6 3%	18 4%
HCVA	3 1%	6 3%	9 2%
Hx	124 49%	128 54%	252 51%
∑	251 51%	239 49%	490

Table 1B: ATBD events, ∑ATD population. ATBD: Atherothrombotic Brain Disease; ATD: Atherothrombotic Disease; TCVA: Thrombotic Cerebral Vascular Disease; TIA: Transient Ischemic Attack; ACS: Asymptomatic Carotid Stenosis; SVID: Small Vessel Ischemic Disease; HCVA: Hemorrhagic Stroke; HX: History of Cardiac Event

ATD Event	Male	Female	∑
TAA	8 6%	7 6%	15 6%
AAA	35 27%	13 12%	48 20%
ATPVD	49 37%	53 49%	102 43%
Hx	39 30%	35 32%	74 31%
∑	131 55%	108 45%	239

Table 1C: ATPVD events, ∑ATD population. ATPVD: Atherothrombotic Peripheral Vascular Disease; ATD: Atherothrombotic Disease; TAA: Thoracic Aortic Aneurysm; AAA: Abdominal Aortic Aneurysm; ATPVD: Atherothrombotic Peripheral Vascular Disease; HX: History of Cardiac Event

Table 2A - Table 2C show the respective distributions of ATHD, ATBD, and ATPVD with regards to age. The distribution curve for ATHD appear to show men developing their ATHD events out of phase and somewhat ahead of the curve for women (Table 2A). The distribution curves for ATBD and ATPVD do not show much difference, essentially following the same trajectories, though they do show a preponderance of women in the older age groups.

Age Group	Male	Female	∑
≤39	24 4%	8 2%	32 3%
40-49	104 19%	32 7%	136 14%
50-59	116 22%	68 18%	184 13%
60-69	128 24%	111 25%	239 24%
70-79	107 20%	124 28%	231 24%
≥80	58 11%	97 22%	155 16%
∑	537 55%	440 45%	977

Table 2A: ATHD distribution, by age group: ∑ATD. ATHD: Atherothrombotic Heart Disease; ATD: Atherothrombotic Disease

Age Group	Male	Female	∑
≤39	9 4%	5 2%	14 3%
40–49	18 7%	11 5%	29 6%
50–59	46 18%	25 11%	71 14%
60–69	44 17%	49 21%	93 19%
70–79	84 23%	70 29%	154 31%
≥80	56 22%	78 33%	134 16%
∑	257 52%	238 48%	495

Table 2B: ATBD distribution, by age group: ∑ATD. ATBD: Atherothrombotic Brain Disease; ATD: Atherothrombotic Disease.

Age Group	Male	Female	∑
≤39	1 1%	1 1%	2 1%
40-49	4 3%	4 4%	8 3%
50-59	24 19%	8 7%	32 14%
60-69	36 28%	24 22%	60 25%
70-79	40 31%	35 32%	75 32%
≥80	24 19%	36 33%	60 25%
∑	129 54%	108 46%	237

Table 2C: ATPVD distribution, by age group: ∑ATD. ATPBD: Atherothrombotic Disease; ATD: Atherothrombotic Disease

Cigarette Smoking Status	Male	Female	∑
+	253 39%	144 27%	397 33%
Past	235 36%	112 21%	347 29%
∑ -	167 25%	280 52%	447 38%
∑	655 55%	536 45%	1191

Table 3: Cigarette smoking status, in ∑ATD population. ATD: Atherothrombotic Disease; +: Current Cigarette Smoker; Past: Smoked Cigarettes in the Past; ∑ –: No History of Any Tobacco Products.

Age Group	+	Past	OT	NT	∑
≤39	21 64%	6 18%	1 3%	5 15%	33
40-49	50 70%	9 13%	1 1%	11 15%	71
50-59	75 54%	40 29%	4 3%	21 15%	140
60-69	61 40%	61 40%	5 3%	25 16%	152
70-79	17 12%	71 51%	8 6%	44 31%	140
≥80	8 10%	38 48%	7 9%	26 33%	79
∑	232 38%	225 37%	26 4%	132 21%	615

Table 4A: Cigarette smoking distribution, in ∑male ATD population.
ATD: Atherothrombotic Disease; +: Current Smoker; Past: History of Cigarette Smoking; OT: Use of Other Forms of Tobacco; NT: No History of Smoking

Age Group	+	Past	OT	NT	∑
≤ 39	8 57%	2 14%		4 29%	14
40-49	24 57%	6 14%		12 29%	42
50-59	39 45%	17 20%		30 35%	86
60-69	41 32%	28 22%		59 46%	128
70-79	26 17%	41 28%		82 55%	149
≥ 80	6 5%	19 16%		94 79%	119
∑	144 27%	113 21%		281 52%	538

Table 4B: Cigarette smoking distribution, in ∑female ATD population. ATD: Atherothrombotic Disease; +: Current Smoker; Past: History of Cigarette Smoking; OT: Use of Other Forms of Tobacco; NT: No History of Smoking.

These differences may be related to differences in ATD risk factors in men as compared to women. Table III reveals that tobacco use patterns differ between men and women in the ATD data base. "+" refers to people who were currently smoking cigarettes at time of entry to the ATD data base. "Past" refers to people who have quit smoking cigarettes at least six months, without relapse, prior to entering the ATD data base. "∑- "refers to people who have never smoked cigarettes, though they may have used other tobacco products such as smoking a pipe, smoking cigars, or chewing tobacco. Table 3 shows that cigarette smoking is far more common in men than women in the ATD data base. Table 4A & Table 4B shows that both men and women follow the same course: cigarette smoking predominates in younger ATD age groups and wanes with increasing age. Past smoking increases with increasing age in men, as it does in women. Never cigarette smoking increases with increasing age.

CRF	Male	Female	∑
≥0.80	114 24%	49 13%	163 19%
0.75-0.79	95 20%	53 14%	148 17%
0.70-0.74	86 18%	65 17%	151 17%
0.65-0.69	60 13%	56 14%	116 13%
0.60-0.64	34 7%	53 14%	87 10%
≤0.59	91 19%	115 29%	206 24%
∑	480 55%	391 45%	871

Table 5A: CRF distribution, in ∑ATD population (No lipid RX: ∑∑cigarettes). CRF: Cholesterol Retention Fraction; ATD: Atherothrombotic Disease.

The distribution of CRF values in the ATD population data base is shown in Table 5A. For purposes of this table, the CRF is defined as abnormal when it is 0.70 or higher; defined as borderline abnormal when the CRF is 0.60-0.69; and defined as ideal when the CRF is 0.59 or less. (Recall that these numbers are based on the precipitation method of HDL-c measurement). Table 5A reveals that men are far more likely to have an abnormal CRF than are women (62% versus 44%). Table 4B reveals that if the CThr scenario is considered, then men and women are closer in their rates of dyslipidemia (64% versus 51%). No patients whose lipids have been treated are entered into these tables; however, about 3% (10/391) of the women were taking hormone replacement therapy (HRT) at

the time their lipids were measured. HRT is known to affect lipid levels. Women receiving HRT were included in this analysis because numbers were relatively small and because administration of HRT to peri and postmenopausal women was commonplace in this time frame.

CRF	Male	Female	∑
≥0.70 + all LDL ≥170	305 64%	199 51%	504 58%
0.65-0.69 (No LDL ≥170)	53 11%	38 10%	91 10%
0.60-0.64 (No LDL ≥ 170)	34 7%	44 11%	78 9%
≤0.59 (No LDL ≥ 170)	88 18%	110 28%	198 23%
∑	480	391	871

Table 5B: CThr in ∑ATD. CThr: Cholesterol Threshold; ATD: Atherothrombotic Disease; CRF: Cholesterol Retention Fraction; LDL: Low Density Lipoprotein

Table 6A shows the SBP distribution in the ATD database for men and Table 6B does the same for women. The determination of the role of hypertension in the BGS data base for ATD is made difficult because 20% (129/652) of male ATD patients and 27% (147/540) of female ATD patients presented with treated hypertension when they entered the ATD data base. Table 6C shows the frequency distributions when only those with wild-type SBP determinations are considered. Though women are more likely to have the highest SBP levels, they are also more likely to have the lowest SBP levels. Table 6D shows that if all SBP levels of 140 mmHg are lumped together and then combined with all treated SBP patients, then the frequency of hypertension is much the same between men and women.

SBP	SBP No RX	SBP RX	∑
≥ 180	33 6%	5 4%	38 6%
160-178	67 13%	16 12%	83 13%
140-158	135 26%	37 29%	172 26%
130-138	111 21%	28 22%	139 21%
120-128	104 20%	28 22%	132 20%
≤ 118	73 14%	15 12%	88 13%
∑	523 80%	129 20%	652

Table 6A: SBP distribution, in ∑male ∑ATD. SBP: Systolic Blood Pressure; ATD: Atherothrombotic Disease.

SBP	SBP No RX	SBP RX	∑
≥180	49 12%	11 7%	60 11%
160-178	48 12%	19 13%	67 12%
140-158	81 21%	31 21%	112 21%
130-138	68 17%	31 21%	99 18%
120-128	59 15%	34 23%	93 17%
≤118	88 22%	21 14%	109 20%
∑	393 73%	147 27%	540

Table 6B: SBP distribution, in ∑female ∑ATD. SBP: Systolic Blood Pressure; ATD: Atherothrombotic Disease

SBP	Male	Female	∑
≥ 180	33 6%	49 12%	82 9%
160-178	67 13%	48 12%	115 13%
140-158	135 26%	81 21%	216 24%
130-138	111 21%	68 17%	179 20%
120-128	104 20%	59 15%	163 18%
≤ 118	73 14%	88 22%	161 18%
∑	523	393	916

Table 6C: SBP distribution, in ∑ATD (No BP RX). SBP: Systolic Blood Pressure; ATD: Atherothrombotic Disease; BP: Blood Pressure.

SBP	Male	Female	∑
≥ 140 + all BP RX	364 56%	325 60%	689 58%
120-138 (No RX)	215 33%	127 24%	342 29%
SBP ≤ 118 (No RX)	73 11%	88 16%	161 14%
∑	652 55%	540 45%	1192

Table 6D: SBP distribution, in ∑ATD. SBP: Systolic Blood Pressure; ATD: Atherothrombotic Disease; BP: Blood Pressure.

Since ATD risk factors only rarely act alone to produce clinical ATD events, the author will now focus upon risk factor combinations. In order to determine which risk factor combinations were most effective at predicting the population at risk of ATD, the author examined numerous risk factor combinations, but only one combination was highly predictive: The combination of CRF and SBP-and then only when stratified by cigarette smoking status. The predictive tool is a graph with the CRF on the ordinate and SBP on the abscissa, and this graph is termed the BGS Graph. The BGS Graph is shown in Figure 1A. This graph is based on the precipitation method of HDL-c measurement. A similar graph, but based on the enzymatic method, is shown in Figure 1B. The author has placed the CRF-SBP plots of all of the 871 ATD patients on the BGS Graph. The result is a scattergram. However, once current cigarette smokers are removed, a clear linear stream of CRF-SBP plots is seen, with a lower level of CRF at 0.70. The CRF-SBP plots of a few outliers are present. On the basis of this plot distribution, the author has generated a threshold line, above which lie the CRF-SBP plots of the vast majority of ATD patients in the author's practice, with a few outliers lying below the threshold line. The CRF-SBP loci of this threshold line are (0.74,100) and (0.49,140). This threshold line is not a regression line, but rather a line separating the mainstream of ATD patients' CRF-SBP plots, with a few outliers, on the basis of the principle of the fewest false negatives. If the author had no intention of offering therapy to people with CRF-SBP plots below the line, then he did not want to give false assurance, only to have ATD events occur in that cohort. Examination of the BGS Graph reveals that 89% (342/384) of the male ATD patients' plots lie above the threshold line as do 79% (258/325) of the female ATD patients' plots (Table VI). Of the 11% (42/384) of CRF-SBP plots of male ATD patients that lie below the threshold line, 34 patients are cigarette smokers, current or past, leaving only 2% (8/384) of male ATD patients who could not have been predicted by CRF-SBP plot above the threshold line and/or cigarette smoking status. Likewise of the 67 female patients whose CRF-SBP plots lie below the threshold line, 33 are cigarette smokers, current or past, leaving only 10%

(34/325) who could not have been identified by CRF-SBP plot position above the threshold line and/or cigarette smoking status. Table 7 gives the outcomes of those 709 patients in terms of average age of ATD onset, average of multiple-system disease onset, and average age of death. Both men and women follow the same pattern, though the averages of women are somewhat older than those of men. It will be clear that in the absence of any history of cigarette smoking, a CRF-SBP plot position below the threshold line implies virtual immunity to ATD.

				Above ASR Line			Below ASR Line	
Sex	**Average Age of**		+	**Past**	-	+	**Past**	-
Male								
		Total Patients	126	130	86	20	14	8
	ATD Onset	Total Patient Years	6659	8536	5913	1174	1041	623
		Average Age of ATD Onset	53	66	69	59	74	78
		Total Patients	38	41	32	6	5	1
	MSD Onset	Total Patient Years	2363	2983	2522	382	402	78
		Average Age of MSD Onset	62	73	79	64	80	78
		Total Patients	49	64	47	12	11	4
	Death	Total Patient Years	3153	4780	3805	815	879	374
		Average Age of Death	64	75	81	68	80	94
Female								
		Total Patients	65	56	137	18	15	34
	ATD Onset	Total Patient Years	3852	3908	9955	1145	1003	2543
		Average Age of ATD Onset	59	70	73	64	67	75
		Total Patients	22	24	49	6	7	16
	MSD Onset	Total Patient Years	1534	1800	3931	440	532	1283
		Average Age of MSD Onset	70	75	80	73	76	80
		Total Patients	26	23	79	9	7	23
	Death	Total Patient Years	1830	1824	6542	650	533	1941
		Average Age of Death	70	79	83	72	76	84

Table 7: ATD w/r to ASR Line (1974-2003).
ATD: Atherothrombotic Disease; +: Current Cigarette Smoker; Past: Former Cigarette Smoker; -: Never Cigarette Smoker; MSD: Multiple System Disorder; ASR Line: Angiographic Stabilization/Regression Line.

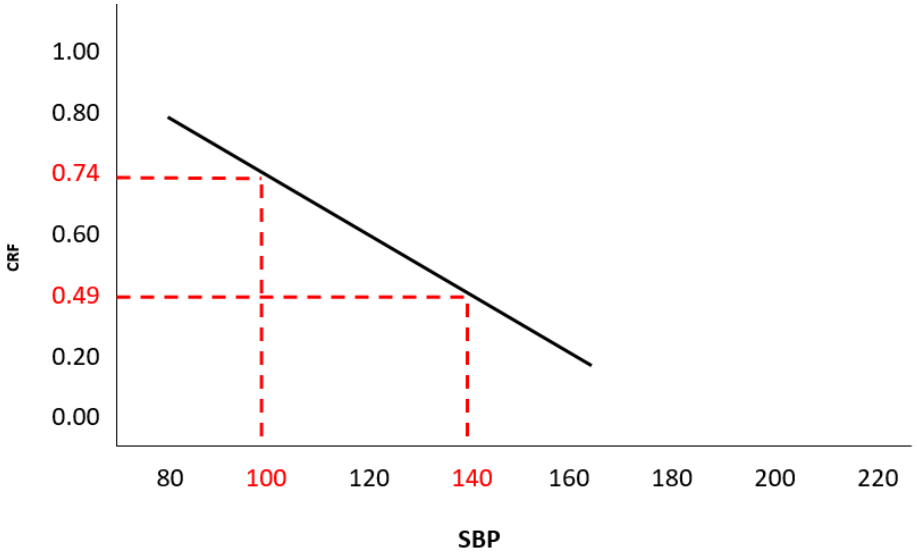


Figure 1A: Precipitation method of HDL cholesterol measurement.
CRF: Cholesterol Retention Fraction; SBP: Systolic Blood Pressure; HDL: High Density Lipoprotein

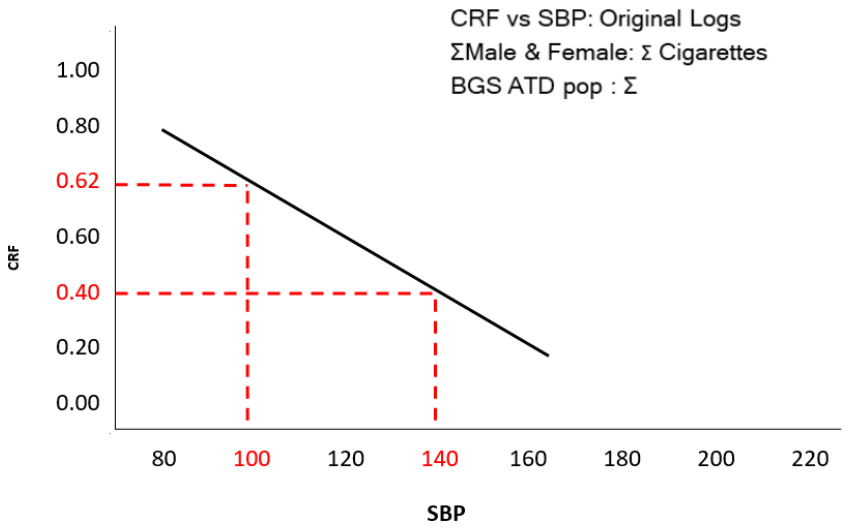


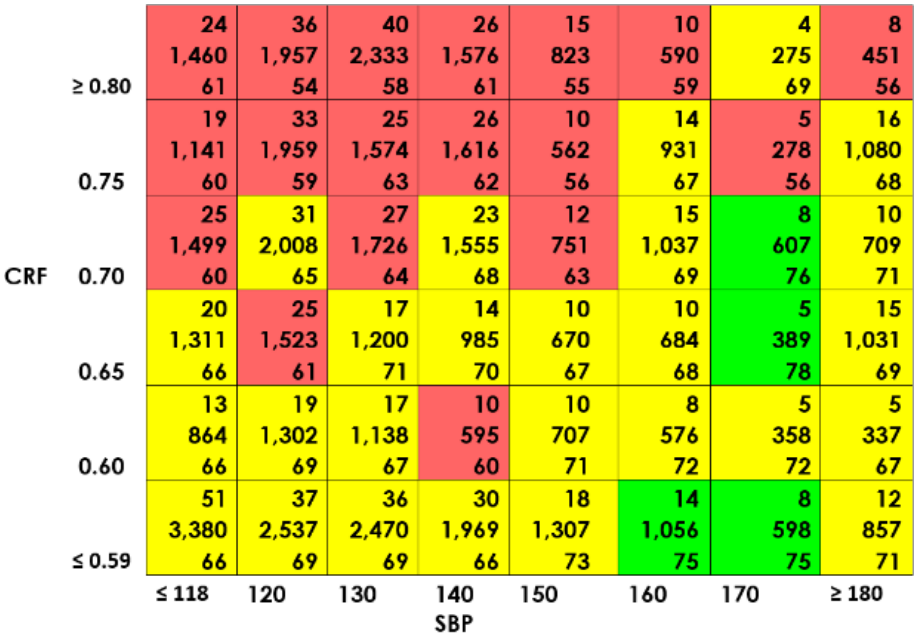
Figure 1B: Enzymatic method of HDL cholesterol measurement.

It will be noted that the outcomes of the 709 patients described in Table VI do not describe the full complement of the 871 patients described earlier. The reason for this is that at the end of the year 2003, there was a major change in insurance coverage in Wood County, the result of which was that the author lost about 25% of his practice, containing a fairly large number of ATD patients. Prior to this change in health insurance, the author had firsthand knowledge of his patients' outcomes, but thereafter, such knowledge was more fragmentary. Hence the patient outcomes after 2003 are not given in Table 7.

The BGS Graph may be examined in another manner. The area on the BGS Graph can be divided into CRF-SBP cohorts (Figure 2A- Figure 2D). The ATD patients can then be put into the appropriate cohort, dependent upon their CRF and SBP data. The average age of ATD onset can then be calculated for each cohort. Each cohort can then be color-coded with respect to average age of ATD onset. A red coloration is given to those cohorts with an average age of ATD onset of 64 years or younger; a yellow coloration to those cohorts with an average age of ATD onset of 65 years - 74 years; and a green coloration to those with an average age of ATD onset of 75 years or older.

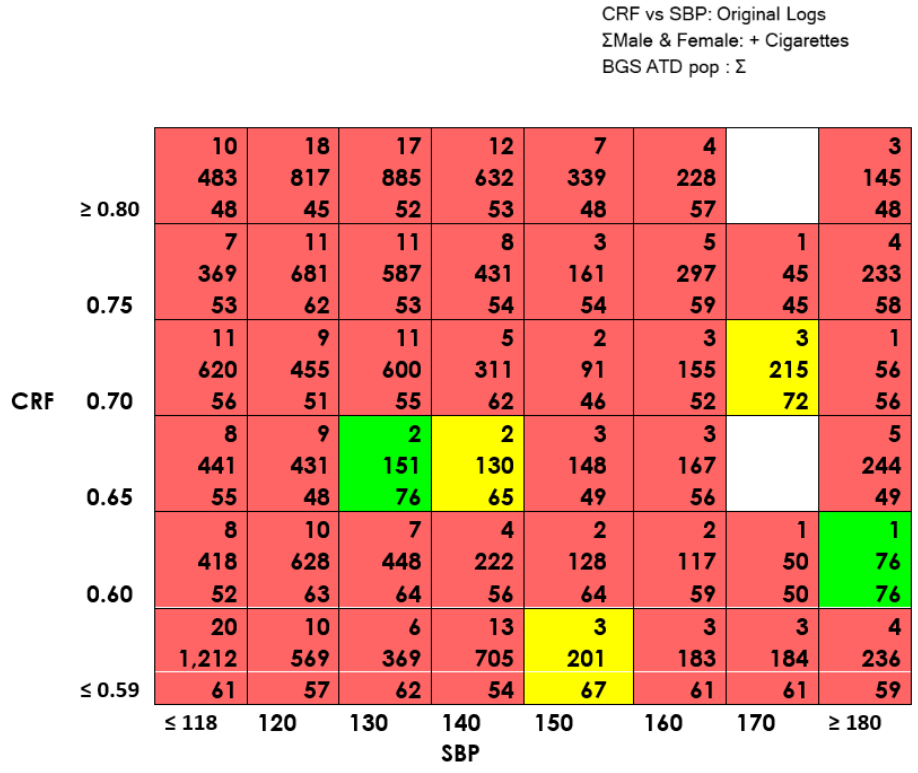
Taking all-comers into consideration, a layering effect is seen with respect to average age of ATD onset. 91% (341/376) of the patients in the red-coded cohorts lie above the CRF 0.70 or higher threshold (Figure 2A). 9% (35/376) of the patients in red-zone cohorts lie in the 0.60-0.69 zone. There are no red-zone patients in the zone of 0.59 or lower. There are relatively few green-coded cohorts, mainly located in the higher SBP zones, though 77% (27/35) lie below the 0.69 and lower threshold. Yellow-coded cohorts fill in the rest, comprising 53% (460/871) of cases. If only current cigarette smokers are considered, then virtually all cohorts are red-coded (Figure 2B). When only past smokers (those who have quit smoking at least six months prior to entering the ATD data base and have not relapsed), the pattern returns to that of all-comers (Figure 2C). If only people who have never smoked cigarettes (but who may have smoked cigars or pipes or chewed tobacco) are considered, then red-coded cohorts are few and 94% (30/32) lie above the CRF of 0,75 or higher threshold. The two people who were in the red-coded cohorts with CRF values of 0.69 or lower both had severe hypertension. There are many more green-coded areas, but 88% (63/72) are located below the 0.69 and lower threshold (Figure 2D).

Figure 2A - Figure 2D show the findings for all-comers and can be used to show general patterns since the numbers in each of the CRF-SBP cohorts are relatively large. If the patients are split up by gender, however, the numbers in each of the CRF-SBP cohorts are much fewer, and the numbers are too few to be stratified by cigarette smoking status (Figures 3A & Figure 3B). The color-coded pattern for all men mimics the pattern for all-comers (Figure 3A). For women, on the other hand, a clear-cut pattern is seen. 93% (85/91) of the people in red-coded cohorts lie above the 0.70 and higher threshold. On the other hand, 71% (27/38) of the people in green-coded cohorts lie below the 0.69 and lower threshold.



CRF	SBP ≤ 118	120	130	140	150	160	170	≥ 180
≥ 0.80	24 / 1,460 / 61	36 / 1,957 / 54	40 / 2,333 / 58	26 / 1,576 / 61	15 / 823 / 55	10 / 590 / 59	4 / 275 / 69	8 / 451 / 56
0.75	19 / 1,141 / 60	33 / 1,959 / 59	25 / 1,574 / 63	26 / 1,616 / 62	10 / 562 / 56	14 / 931 / 67	5 / 278 / 56	16 / 1,080 / 68
0.70	25 / 1,499 / 60	31 / 2,008 / 65	27 / 1,726 / 64	23 / 1,555 / 68	12 / 751 / 63	15 / 1,037 / 69	8 / 607 / 76	10 / 709 / 71
0.65	20 / 1,311 / 66	25 / 1,523 / 61	17 / 1,200 / 71	14 / 985 / 70	10 / 670 / 67	10 / 684 / 68	5 / 389 / 78	15 / 1,031 / 69
0.60	13 / 864 / 66	19 / 1,302 / 69	17 / 1,138 / 67	10 / 595 / 60	10 / 707 / 71	8 / 576 / 72	5 / 358 / 72	5 / 337 / 67
≤ 0.59	51 / 3,380 / 66	37 / 2,537 / 69	36 / 2,470 / 69	30 / 1,969 / 66	18 / 1,307 / 73	14 / 1,056 / 75	8 / 598 / 75	12 / 857 / 71

Figure 2A: The area on the BGS Graph can be divided into CRF-SBP cohorts.



CRF	SBP ≤ 118	120	130	140	150	160	170	≥ 180
≥ 0.80	10 / 483 / 48	18 / 817 / 45	17 / 885 / 52	12 / 632 / 53	7 / 339 / 48	4 / 228 / 57		3 / 145 / 48
0.75	7 / 369 / 53	11 / 681 / 62	11 / 587 / 53	8 / 431 / 54	3 / 161 / 54	5 / 297 / 59	1 / 45 / 45	4 / 233 / 58
0.70	11 / 620 / 56	9 / 455 / 51	11 / 600 / 55	5 / 311 / 62	2 / 91 / 46	3 / 155 / 52	3 / 215 / 72	1 / 56 / 56
0.65	8 / 441 / 55	9 / 431 / 48	2 / 151 / 76	2 / 130 / 65	3 / 148 / 49	3 / 167 / 56		5 / 244 / 49
0.60	8 / 418 / 52	10 / 628 / 63	7 / 448 / 64	4 / 222 / 56	2 / 128 / 64	2 / 117 / 59	1 / 50 / 50	1 / 76 / 76
≤ 0.59	20 / 1,212 / 61	10 / 569 / 57	6 / 369 / 62	13 / 705 / 54	3 / 201 / 67	3 / 183 / 61	3 / 184 / 61	4 / 236 / 59

Figure 2B: Current cigarette smokers are considered, then virtually all cohorts are red-coded.

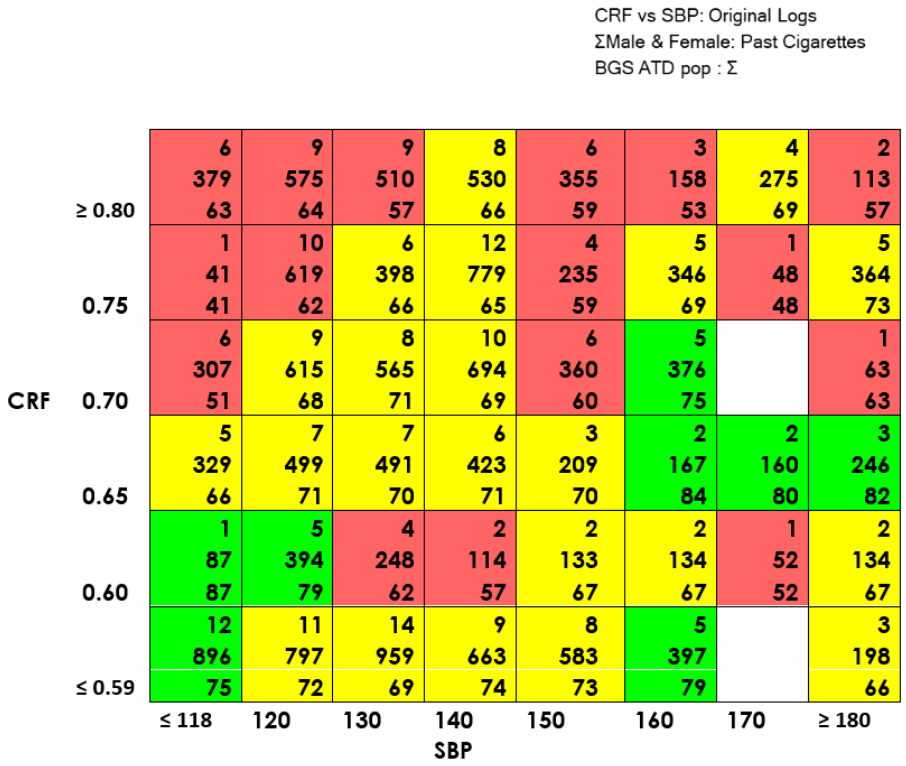


Figure 2C: Only past smokers, the pattern returns to that of all-comers.

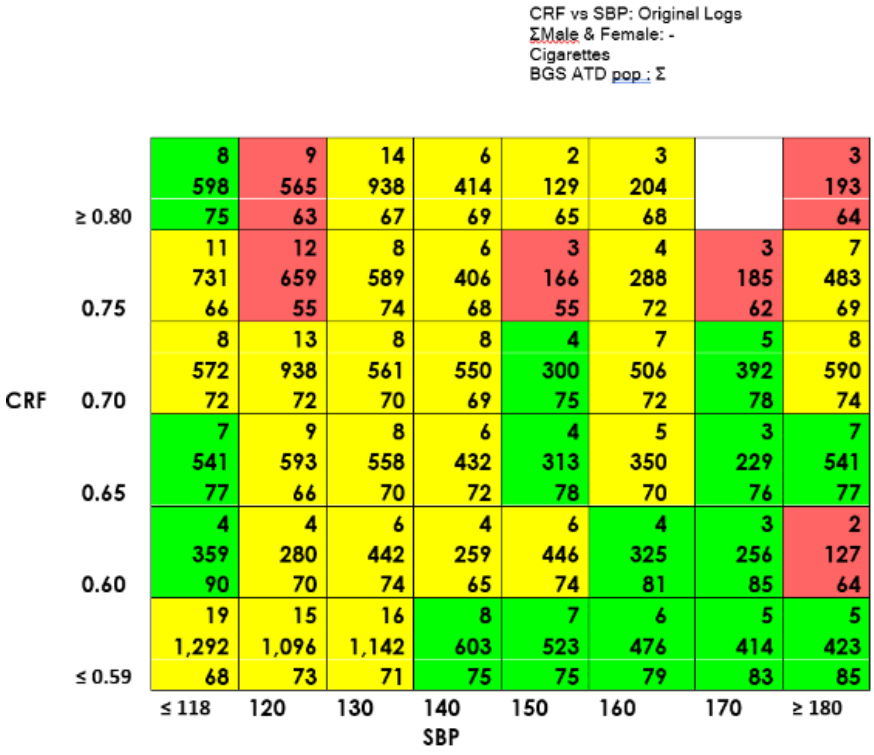


Figure 2D: Many more green-coded areas, but 88% (63/72) are located below the 0.69 and lower threshold.

SBP	≥0.80	0.75-0.79	0.70-0.74	0.65-0.69	0.60-0.64	≤0.59	∑
	3	10	1	8	1	4	27
≥180	154	617	63	523	68	264	1689
	51	62	63	65	68	66	63
	3	3	3	2	1	2	14
170-178	212	139	211	163	81	160	996
	71	46	70	82	81	80	67
	6	11	8	7	5	6	43
160-168	338	727	527	470	336	475	2873
	56	66	66	67	67	79	67
	10	8	9	4	4	9	44
150-158	526	431	537	298	242	615	2649
	53	54	60	75	61	68	60
	20	16	15	5	5	21	82
140-148	1220	948	1020	327	242	1372	5129
	61	59	68	65	48	65	63
	28	16	19	10	4	16	93
130-138	1562	973	1207	683	245	1034	5704
	56	61	64	68	61	65	61
	28	22	21	17	8	13	109
120-128	1518	1293	1330	998	507	829	6475
	54	59	63	59	63	64	59
	16	9	10	7	6	20	68
≤118	1028	608	548	418	397	1320	4319
	64	68	55	60	66	66	64
	114	95	88	60	34	91	480
∑	6558	5736	5443	3880	2118	6069	29803
	58	60	63	65	62	66	62

Figure 3A: The color-coded pattern for all men mimics the pattern for all-comers. CRF vs SBP, ∑male BGS ATD population; SBP: ∑; ∑∑cigarettes.
CRF: Cholesterol Retention Fraction; SBP: Systolic Blood Pressure; BGS: Bowling Green Study.

The BGS Graph can also be used to show the risk profile in the general population. If the data for the general population is put on the BGS Graph and if the appropriate data for each of the CRF-SBP cohorts is entered in terms of ATD patients and total number of patients in each cohort then the prevalence of ATD patients per cohort can be determined.

If the prevalence of ATD in any cohort is 14% or less, then that cohort is color-coded green; if the ATD prevalence is 15%-24%, color-coded yellow; and if 25% or higher, color-coded red. This data is displayed, for all-comers in males and females, in Figures 4A & 4B. It is clear from these figures that the lowest prevalence of ATD per cohort lies in the CRF-SBP cohorts in the southwest corner-virtually identical in men and women.

	CRF						
SBP	≥0.80	0.75-0.79	0.70-0.74	0.65-0.69	0.60-0.64	≤0.59	∑
	5	6	9	7	4	8	39
≥180	297	463	646	508	269	593	2776
	59	77	72	73	67	74	71
	1	2	5	3	4	6	21
170-178	63	139	396	226	277	478	1579
	63	70	79	75	69	80	75
	4	3	7	3	3	8	28
160-168	252	204	510	214	240	581	2001
	63	68	73	71	80	73	71
	5	2	3	6	6	9	31
150-158	297	131	214	372	465	692	2171
	59	66	71	62	78	77	70
	6	10	8	9	5	9	47
140-148	356	668	535	658	353	597	3176
	59	67	67	73	71	66	67
	12	9	8	7	13	20	69
130-138	771	601	519	517	893	1436	4737
	64	67	65	74	69	72	69
	8	11	10	8	11	24	72
120-128	439	666	678	525	795	1708	4811
	55	61	68	66	72	71	69
	8	10	15	13	7	31	84
≤118	432	533	951	893	467	2060	5336
	54	53	63	69	67	66	64
	49	53	65	56	53	115	391
∑	2907	3405	4449	3913	3759	8145	26578
	59	64	68	70	71	71	68

Figure 3B: For women, on the other hand, a clear-cut pattern is seen. CRF vs SBP; ∑female BGS ATD population; SBP: ∑; ∑cigarettes.
CRF: Cholesterol Retention Fraction; SBP: Systolic Blood Pressure; BGS: Bowling Green Study

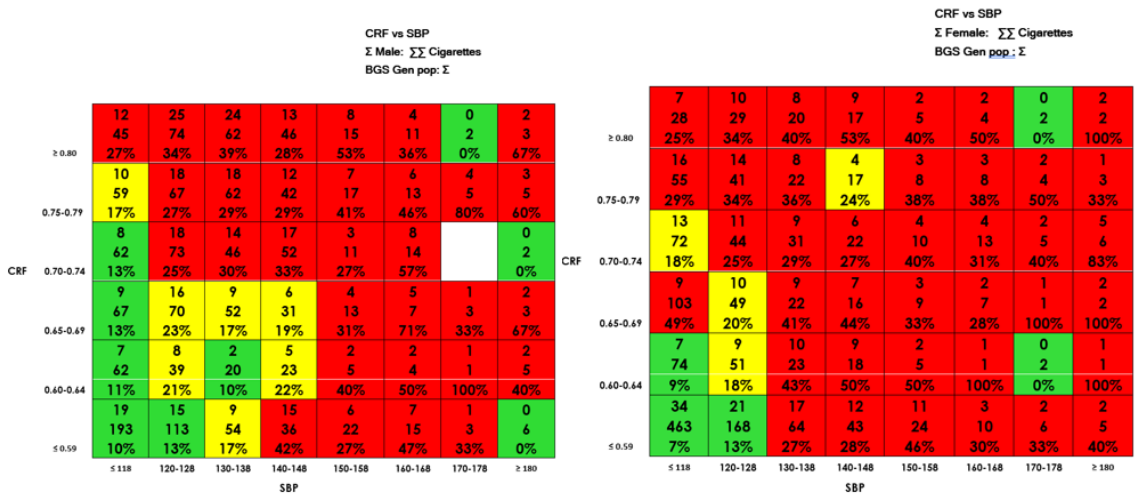


Figure 4A & 4B: Data is displayed, for all-comers in males and females.

Kaplan-Meier curves can be used to determine ATD risk as well. Table 8A & Table 8B show the ATD prevalence in the General Population per CRF sextile and age group for men (Table 8A) and women (Table 8B). Figure 5A - Figure 5F show the Kaplan-Meier curves for men and for women in terms of CRF sextile. Men are coded in brown and women in orange. These curves show time to event

scenarios and reveal that men and women have very similar curves and in some cases are virtually super-imposable.

Age Group	≥0.80	0.75-0.79	0.70-0.74	0.65-0.69	0.60-0.64	≤0.59	∑
	0	2	2	2	3	3	12
≤29	44	50	80	96	77	289	636
	0%	4%	3%	2%	4%	1%	2%
	9	13	11	9	5	8	55
≤39	104	127	135	148	103	350	967
	9%	10%	8%	6%	5%	2%	6%
	44	33	27	17	10	20	151
≤49	185	195	193	185	136	395	1289
	24%	17%	14%	9%	7%	5%	12%
	69	55	42	25	20	42	253
≤59	238	239	234	212	154	443	1520
	29%	23%	18%	12%	13%	9%	17%
	85	72	56	36	24	55	328
≤69	261	270	257	236	167	469	1660
	33%	27%	22%	15%	14%	12%	20%
	95	83	69	49	29	69	394
≤79	273	285	271	253	172	486	1740
	35%	29%	25%	19%	17%	14%	23%
	98	86	75	52	32	76	419
∑	277	289	279	258	175	497	1775
	35%	30%	27%	20%	18%	15%	24%

Table 8A: ATD prevalence in the general population per CRF sextile and age group for men. Cumulative ATD risk; in BGS general population: ∑male; ∑∑cigarettes; CRF ATD: Atherothrombotic Disease; BGS: Bowling Green Study; CRF: Cholesterol Retention Fraction.

Age Group	≥0.80	0.75-0.79	0.70-0.74	0.65-0.69	0.60-0.64	≤0.59	∑
	4	4	4	0	2	6	20
≤29	17	44	57	92	79	420	709
	24%	9%	7%	0%	3%	1%	3%
	7	10	7	4	4	11	43
≤39	39	68	99	127	114	578	1025
	18%	15%	7%	3%	4%	2%	4%
	14	21	13	5	9	24	86
≤49	66	109	134	154	137	685	1285
	21%	19%	10%	3%	7%	4%	7%
	26	26	22	12	18	45	149
≤59	93	128	167	176	159	760	1483
	28%	20%	13%	7%	11%	6%	10%
	38	47	40	33	29	64	251
≤69	110	158	192	210	176	799	1645
	35%	30%	21%	16%	16%	8%	15%
	41	53	50	42	38	84	308
≤79	114	166	207	223	189	831	1730
	36%	32%	24%	19%	20%	10%	18%
	42	55	57	50	44	106	354
∑	115	169	214	232	197	856	1783
	37%	33%	27%	22%	22%	12%	20%

Table 8B: ATD prevalence in the general population per CRF sextile and age group for women. Cumulative ATD risk; in BGS general population: ∑female; ∑∑cigarettes; CRF ATD: Atherothrombotic Disease; BGS: Bowling Green Study; CRF: Cholesterol Retention Fraction.

Figure 5A - Figure 5F: The Kaplan-Meier curves for men and for women in terms of CRF sextile.

DISCUSSION

The author has presented data to support the contention that ATD is predictable in women by the same means as in men. There are differences in the risk factor distribution, but not in the nature of the ATD risk factors. These differences in risk factor distribution may account for differences in the clinical presentation between men and women.

The chief risk factor in men and women is cigarette smoking [3]. This is clear when men and women are combined and stratified by cigarette smoking status. However, when women are segregated from men, numbers become so small that patterns are not clearly seen. As indicated in Table 3 cigarette smoking is more common in men than women in the ATD database. Table IV reveals that cigarette smoking predominates in younger ATD patients.

Indeed, as Figure 2B - Figure 2D show, smoking drives early onset ATD. Therefore, it is reasonable to assume that women follow the pattern for males and hence that the findings evident when combined male and female cohort hold when the cohort is segregated for gender.

Dyslipidemia is causal for ATD. The difficulty lies in defining dyslipidemia. It is well known that women with ATD tend to have elevated LDL-c rather than low HDL-c, which is the opposite of the male lipid distribution pattern. This difference is clearly seen in the author's ATD data base, but this difference disappears when ratios between LDL-c and HDL-c, such as the CRF, are used. Moreover, women may have "normal" lipids when they are young but develop high levels of LDL- c in the peri-menopausal and post-menopausal years. This is clearly seen in the author's general population data base. The use of LDL-c and HDL-c as independent ATD risk factors makes a gender-neutral definition of dyslipidemia problematic, but the use of lipid ratios such as the CRF permits a unified concept of dyslipidemia that is gender neutral. This is clearly evident in Figures 4A - Figure 4F, where the Kaplan-Meier curves for men and women are virtually identical. Moreover, the youngest age groups in the ATD population are associated with the highest CRF values, not the highest SBP values, whereas the oldest age groups in the ATD population are associated with the highest SBP values, not the highest CRF values. Indeed, at any SBP value, a higher CRF value is associated with - and the author might add, leads to - a younger age of ATD onset and conversely a lower CRF is associated with - and the author might add leads to - an older age of ATD onset.

The tendency of women to develop their dyslipidemia in the pre-, peri-, and post-menopausal years complicates the interpretation of their lipid data. This rise in LDL-c later on in life is the probable reason why women tend to have their ATD coronary events later in life than do men, though this is less true for ATD events in the cerebral and peripheral vascular arterial beds. That, and the fact that in the early years of the author's research, older women rarely smoked cigarettes while most men did so. This pattern has changed over the years with more women and fewer men smoking cigarettes (Feeman, unpublished data).

CONCLUSION

The author presents data to show that the prediction of the population of women at risk of ATD is essentially the same as the prediction for men. When the CRF is used as the measure of dyslipidemia, lipid differences between women and men fade, though the later onset of dyslipidemia in women, related to estrogen loss in the pre-, peri-, and post- menopausal years does complicate predictions. Over the years, more women have begun smoking cigarettes and more men have quit smoking. SBP levels are virtually the same. Thus, ATD risk factors in men and women are virtually the same and ATD risk prediction is also virtually the same. The author suggests that studies with large databases, collected over many years, could be analyzed to confirm the author's findings.

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