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Risk Factors for Atherothrombotic Disease: A Suggested Rank Order

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Abstract

Risk factors for atherothrombotic disease (ATD) do not function in isolation, but rather as part of a milieu. Even so, there appears to be a rank order of importance with respect to their causality of ATD. The author presents data from the Bowling Green Study of the Primary and Secondary Prevention of Atherothrombotic Disease to show that cigarette smoking is more important than dyslipidemia, which in turn is more important than hypertension, with respect to causation of ATD. This data is taken from the ATD risk factor milieu of 870 patients who developed some form of clinical ATD during the study time frame (4 November 1974 - 1 January 2019).

The author has combined the atherogenic low-density lipoprotein (LDL) cholesterol with the anti-atherogenic high-density lipoprotein (HDL) cholesterol into a ratio termed the Cholesterol Retention Fraction (CRF, defined as [LDL-HDL]/LDL) to define dyslipidemia. This permits identification of lipid disorders across the range of lipid values seen in people who develop ATD. The author has further combined systolic blood pressure (SBP) with the CRF to create a graph that accurately characterizes-and hence predicts-the ATD population with high accuracy. This graph can be used to further characterize the ATD population with respect to average age of ATD onset, average age of multisystem ATD, and average age at death.

The prediction of the population at risk of ATD can be further characterized by dividing the graph into CRF-SBP cohorts, stratified by cigarette smoking status. When this is done it is possible to define groups of CRF-SBP cohort patient with early onset, middle-aged onset, and old-aged onset of ATD.

On the basis of these findings, it is possible to assign a rank order (in order of importance) to the various ATD risk factors. Cigarette smoking is the most important of the ATD risk factors since it causes ATD events in the youngest age groups even if the other risk factors are corrected. Similarly, dyslipidemia (as defined by the CRF) is of next importance because it is associated with earlier onset ATD than is hypertension. The author concludes that, though all ATD risk factors must be treated, treatment of a more important risk factor must not be compromised by treatment of a less important ATD risk factor.

Keywords: *Atherothrombotic Disease; Framingham Heart Study (FHS); High Density Lipoprotein (HDL)*

Introduction

The prevention of atherothrombotic disease (ATD, defined as atherosclerotic disease, with an emphasis on the thrombosis [clot] that so often precipitates the acute clinical event such as acute myocardial infarction or cerebral infarction or accelerates the development of other ATD conditions such as abdominal aortic aneurysm) depends upon determining the causes of ATD. The Framingham Heart Study

(FHS) introduced the medical community to the concept of causal factors (originally termed factors of risk and now termed risk factors) that lead to atherothrombotic disease (ATD) [1]. Multiple ATD risk factors were identified and include cigarette smoking, dyslipidemia, and hypertension, with some contribution by the very high blood sugar levels of uncontrolled diabetes mellitus [2-10]. Following the lead of the FHS, the author began collecting ATD risk factor data in November of 1974 and continued until January of 2019 [11-14]. The results of the author's investigation into ATD risk factors and their connection were summarized in a recent article [14] and demonstrate the interaction of the major ATD risk factors (cigarette smoking, dyslipidemia, and hypertension) as it relates to the causality of ATD. As explained in the recent article, the various major risk factors interact to produce various ATD scenarios. The same article demonstrated the prime importance of cigarette smoking in the causation of ATD. However, the relative importance of dyslipidemia versus hypertension was not so clearly defined.

Purpose of the Study

It is the purpose of this article to further solidify the role of cigarette smoking in the pathogenesis of ATD and to attempt to clarify the relative importance of dyslipidemia versus hypertension.

Materials and Methods

The background of the Bowling Green Study (the formal expression of the author's research into the pathogenesis of ATD) has been described elsewhere [11-14]. In brief when the author arrived in Bowling Green, the county seat of Wood County, in northwest Ohio, on 4 November 1974, he began his research to predict the population at risk of ATD. To do this, the author knew that he would need to define the characteristics of the ATD population and to do this he would need an age-sex data base. Following the lead of the FHS, the author collected blood pressure, height, and weight data on every patient who presented to his practice of family medicine. Lipid profiles were collected whenever feasible, initially consisting of total cholesterol (CT) and triglycerides (TG). In 1978, high density lipoprotein (HDL) cholesterol became available and with it the calculation of low density lipoprotein (LDL) cholesterol according to the Friedewald equation [15]. Full data (cigarette smoking, full lipid profile and blood pressure) are known for 870 patients in the author's ATD database. An additional patient has full lipid and hypertension data, but no cigarette smoking data, though a past history of cigarette smoking is likely. If this latter patient is included in the analysis, then the number of patients in this report is 871.

In the earlier paper [14], the author re-introduced the concept of the Cholesterol Retention Fraction (CRF). The CRF incorporates low-density lipoprotein (LDL) cholesterol entering the artery wall and the high-density lipoprotein (HDL) cholesterol being removed from the artery wall by reverse cholesterol transport, in the form of a ratio-specifically, (LDL-HDL)/LDL. This permits the ATD risk of the atherogenic LDL to be modified by the anti-atherogenic HDL. Here it is important to know that prior to 1999, at least in the author's local laboratory, HDL cholesterol was measured by the world-wide accepted methodology of the precipitation method. In 1999, and without telling the medical community in general, the manufactures of the auto-analyzers used in the laboratory to measure lipids switched from the precipitation method to the enzymatic method. The two methods do not give the same results for HDL-cholesterol and hence not for the calculated LDL-cholesterol (by the Friedewald equation). The difference in the methodology is such that the HDL-cholesterol as measured by the enzymatic method is on the order of 10 mg/dl (0.25 mmoles/L) higher than that obtained by the precipitation method. The calculated LDL-cholesterol is therefore on the order of 10 mg/dl (0.25 mmoles/L) lower using the enzymatic method that that obtained by using the precipitation method. This difference is not trivial. The author has reported a case of a patient who sustained an acute myocardial infarction at age 53 years with no other ATD risk factors than undetected dyslipidemia. His lipids were analyzed at another hospital at the time of his myocardial infarction and were slightly abnormal when examined by the enzymatic method, but when those values were converted to the equivalent values had the precipitation method been used, his dyslipidemia was much more severe and his myocardial infarction occurred at an age predicted by the author's methodology [16]. With this in mind, any physician involved in interventional lipidology must know the methodology used in his/her laboratory. In this report, all LDL-cholesterol and HDL-cholesterol values are based on the precipitation method of HDL-cholesterol measurement or the conversion of "enzymatic" methodology to "precipitation" methodology.

In his previous paper [14] the author re-introduced his research tool: the Bowling Green Study (BGS) graph, with the CRF on the ordinant and systolic blood pressure (SBP) on the abscissa. This research tool was derived from examination of the author's ATD data base. The author realized that in order to predict the population at risk of ATD, he would need an age-sex data base as described above. Since the predictive ability of the ATD risk factors was limited in the 1970's, a relatively large number of the author's patients developed clinical ATD. Indeed, by 1981 enough of the author's patients had developed ATD that the author was able to separate out an ATD data base from the rest of the population. Inspection of the ATD data base revealed that ATD risk factors rarely operated alone. Moreover, ATD events could occur in people with low as well as high LDL-cholesterol levels and similarly in people with high as well as low HDL-cholesterol levels. In 1981 a paper was published with the title "Is the LDL:HDL Ratio the Best Lipid Predictor?" (The paper is lost to the author and the author sincerely regrets not being able to give the proper citation.) Re-examination of the ATD data base then revealed that people with low LDL-cholesterol levels who developed ATD generally had very low HDL-cholesterol levels, or were cigarette smokers (younger patients) or hypertensive (older patients), while people with high HDL-cholesterol levels who developed ATD generally had very high LDL-cholesterol levels, or were cigarette smokers (younger patients) or hypertensive (older patients).

With this in mind, the author realized that the best way to describe dyslipidemia was to use a ratio between LDL- and HDL-cholesterol. In 1983 it occurred to the author that what he really needed to know about dyslipidemia was how it predicted cholesterol accumulation within the artery wall. This, he reasoned, was best predicted by the amount of cholesterol entering the artery wall (LDL-cholesterol) minus the cholesterol being removed from the artery wall (HDL-cholesterol), the difference divided by the cholesterol entering the artery wall. In other words, of the cholesterol entering the artery wall, what percentage remains there-or (LDL-HDL)/LDL.

As indicated in his earlier papers [11-13], inspection of the ATD data table revealed that HDL-cholesterol is unable to compensate for unlimited LDL-cholesterol. A CRF of 0.70 is considered abnormal. When LDL-cholesterol levels are 170 mg/dl (4.25 mmoles/L) or higher, ATD eventually develops even if the CRF is not abnormal, though the lower the CRF in such cases, the later in life is the onset of ATD. Because of this scenario, the author has developed the concept of the Cholesterol threshold (C Thr) which occurs when the CRF is 0.69 or lower, but LDL-cholesterol is 170 mg/dl (4.25 mmoles/L) or higher.

Use of the enzymatic methodology results in CRF being abnormal at approximately 0.60 or above, borderline at approximately 0.50-0.59, and ideal at approximately 0.49 or less, and LDL-cholesterol being high enough to warrant a C Thr threshold at approximately 160 mg/dl [4.0 mmoles/L]. For the appropriate graph, see figure 1A for the precipitation method and figure 1B for the enzymatic method. In this presentation, all of the author's data is presented using the precipitation methodology or its equivalent conversion from enzymatic methodology.

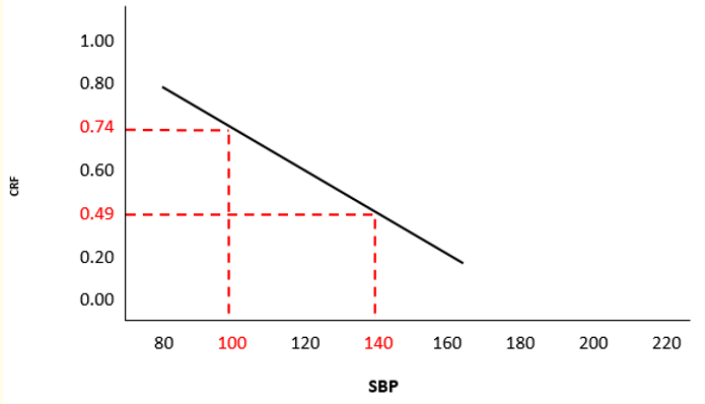

Figure IA: *Precipitation method of HDL cholesterol measurement.*

CRF: Cholesterol Retention Fraction; SBP: Systolic Blood Pressure; HDL: High Density Lipoprotein.

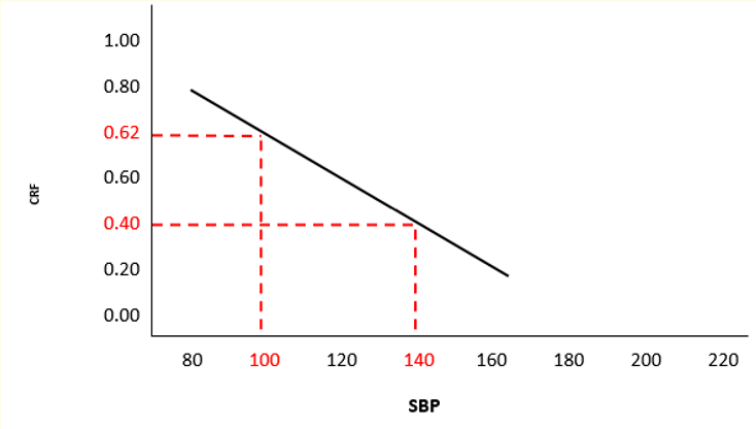

Figure IB: *Enzymatic method of HDL cholesterol measurement.*

CRF: Cholesterol Retention Fraction; SBP: Systolic Blood Pressure; HDL: High Density Lipoprotein.

The purpose of this paper is to compare each of the three major ATD risk factors, a described above, to determine the rank order of importance of those risk factors so that more emphasis can be placed on treatment of the more important risk factors. To this end, cigarette smoking can be divided into three main categories: high risk (current cigarette smoking), medium risk (past cigarette smoking), and low risk (no history of cigarette smoking, though other forms of tobacco may be used). Dyslipidemia can be divided into three main categories: high risk (CRF of 0.70 or higher and/or LDL-cholesterol of 170 mg/dl [4.25 mmoles/L]), medium risk (CRF = 0.60 - 0.69 and no C Thr), and low risk (CRF of 0.59 or lower and no C Thr). Hypertension can likewise be divided into three main categories: high risk (140 mmHg or higher and/or any treated hypertension), medium risk (120 - 138 mmHg with no treated hypertension), and low risk (118 mmHg or lower and no treated hypertension).

Additionally, the author realized that the ATD risk factors for each patient in the ATD data base were rarely present in isolation, so he tested for risk factor combinations that would accurately characterize the ATD population. Many risk factor combinations were tried, but only the CRF-SBP combination showed a characteristic main stream of ATD patients, with a few outliers-and then only when stratified by cigarette smoking status. No other risk factor combination revealed a mainstream of ATD patients with a relatively few outliers. And thus was born the BGS graph, which is featured in this paper.

At the end of the year in 2003, insurance changes were put into effect in Wood County, of which Bowling Green is the county seat. Until the end of 2003, the author had relatively close follow up on his patients. Hence outcomes in the pre-2004 ATD population are reasonably accurate-in the mobile population that comprises the USA, people are always been lost to follow up-and the data to be presented are as accurate as grass roots research will allow. However, when the insurance changes came into effect, the author lost 20-25% of his practice, including a large number of ATD patients. Hence outcomes data beginning in 2004 is not presented, being relatively fragmentary.

Results

The BGS graph is presented in figure 1A and 1B. The graph (in figure 1A) contains a threshold line with foci at CRF-SBP co-ordinates of (0.74, 100) and (0.49, 140) when the precipitation method for HDL-cholesterol measurement is used and the graph in figure 1B has the approximate co-ordinates of (0.62, 100) and (0.40, 140) when the enzymatic method is used. The graph using the precipitation meth-

odology will be utilized in this presentation. This threshold line is not a regression line, but rather is a boundary which separates the majority of ATD patient plots, which form the main stream of CRF-SBP plots on the graph from a few outliers. The line was determined on the basis of the fewest false negatives. In other words, if CRF-SBP plot was below the threshold line and hence the patient was not offered any treatment, the author did not wish to give false assurance concerning future ATD risk. Table 1 shows that 89% (342/384) of male ATD patients have CRF-SBP plots above the threshold line, while 79% (258/325) of female ATD patients have CRF-SBP plots above the threshold line. Of the 42 male patients with CRF-SBP plots below the threshold line, most are cigarette smokers, current (20 patients) or past (14 patients). That leaves only 2% (8/384) of male patients that could not be predicted by CRF-SBP plot position above the threshold line and/or cigarette smoking status. Of the 67 female patients with CRF-SBP plots below the threshold line, about half are cigarette smokers, current (18 patients) or past (15 patients). That leaves only 10% (34/325) of female ATD patients that could not be predicted by CRF-SBP plot position above the threshold line and/or cigarette smoking status. A number of these latter women had husbands who smoked cigarettes and thus were exposed to second hand smoke. Since there is no way to quantify second hand smoke exposure, the authors is unable to consider this qualification. Finally, some of the women were receiving hormone replacement therapy (HRT) at the time their lipids were measured and suffered ATD events despite having their lipids modified by HRT. This was especially true in women taking continuous-combined HRT [17].

			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
		Ave. 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
		Ave 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
		Ave 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
		Ave. 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
		Ave. 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
		Ave. Age of Death	70	79	83	72	76	84

Table I: *ATD w/r to threshold line 1974-2003.*

ATD means Atherothrombotic Disease; "+" means Current Cigarette Smoker; "Past" means Former Cigarette Smoker; "-" means Never Cigarette Smoker; MSD means Multiple System Disorder; ASR Line means Angiographic Stabilization/Regression Line.

Examination of table 1 reveals that cigarette smokers are invariably younger than ex-smokers, who in turn are virtually invariably younger than never smokers (who may have used non-cigarette tobacco products) with respect to average of ATD onset, average age of multi-system ATD (MSD), and average age of death. This is true whether the CRF-SBP plot is above or below the threshold line. Indeed, ex-cigarette smokers with CRF-SBP plots above the threshold line have a later onset of ATD, later onset of MSD, and later age at death, on average, than do current smokers with CRF-SBP plots below the threshold line.

The BGS graph can be divided into CRF-SBP cohorts, as shown in figures 2A-2D. This approach allows one to assess ATD risk at any CRF-SBP cohort in terms of cigarette smoking status and degree of CRF or SBP abnormality. Figure 2A presents the BGS graph for all comers; figure 2B, for current cigarette smokers; figure 2C for ex-smokers and figure 2D for never smokers (who, again, may have used non-cigarette tobacco products). Because the figures are subdivided into the three smoking categories, males are combined with females to bring up the numbers in each figure. The color-coding in figure 2A-2D is presented in terms of average age of ATD onset. A red color code indicates that the average age of ATD onset in that cohort is 64 years or younger; a yellow color code, 65 - 74 years of age; and a green color code, 75 years of age of older. It will be clear that, in figure 2A (all comers), the mainstream of younger ATD patients occurs in cohorts above the CRF equals 0.70 or higher. Figure 2B (current smokers) reveals that virtually all CRF-SBP cohorts are in the red zone. Figure 2C (ex-smokers) reveals that once smoking is eschewed, the green zone begins to re-appear, though mainly for people with CRF values of 0.69 or lower figure 2D (never smokers, though other non-cigarette tobacco products could have been used) reveals that red zone patients are mostly confined to CRF values of 0.75 or higher and that green zone cohorts are much more common, though mainly in CRF values of 0.69 or less.

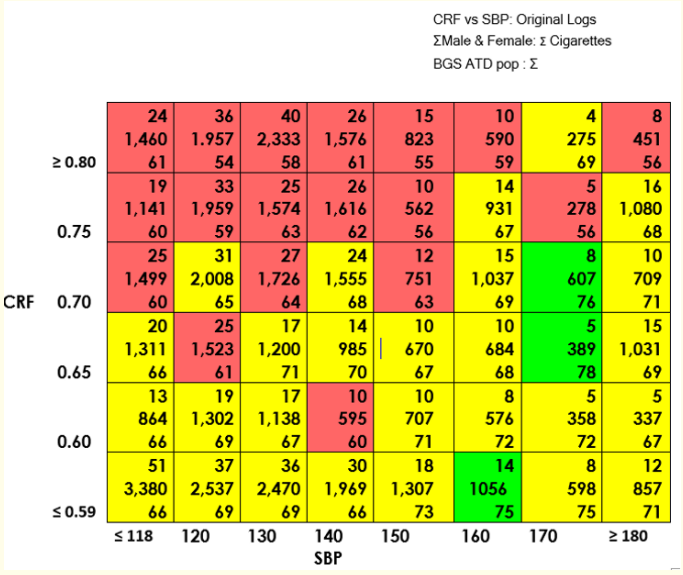

Figure IIA

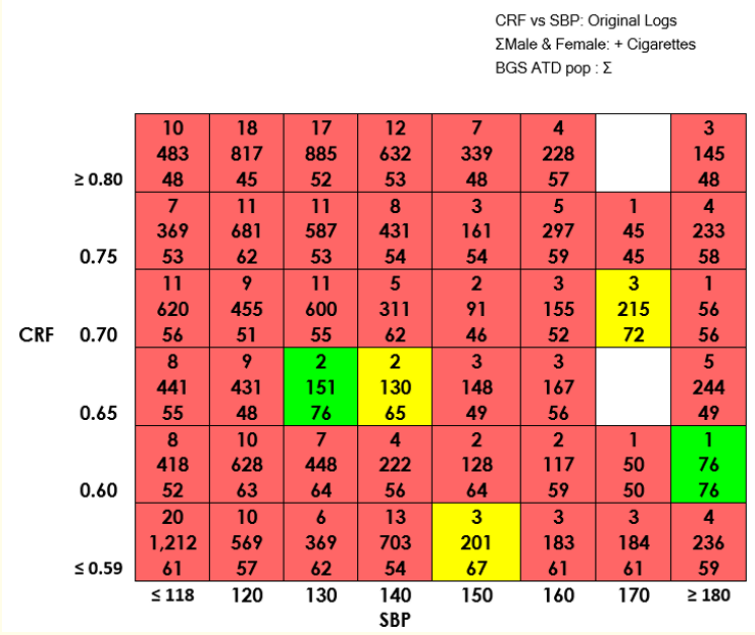

Figure IIB

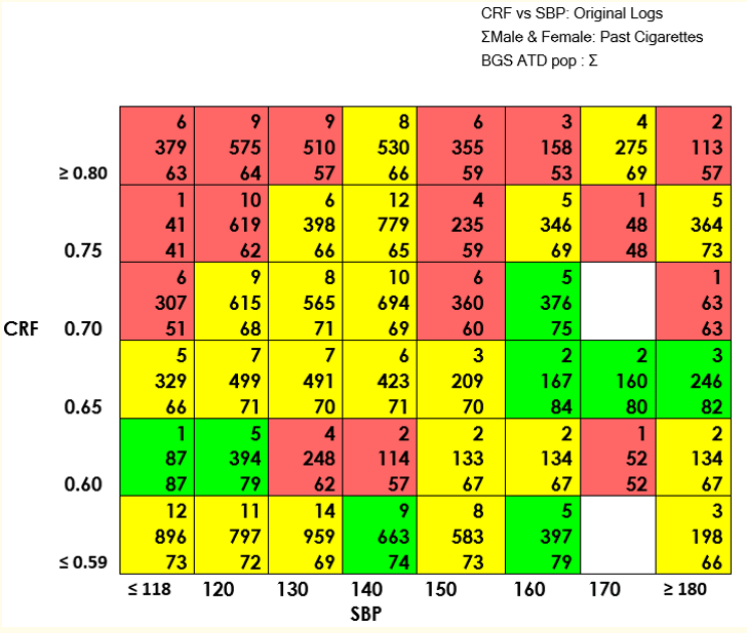

Figure IIC

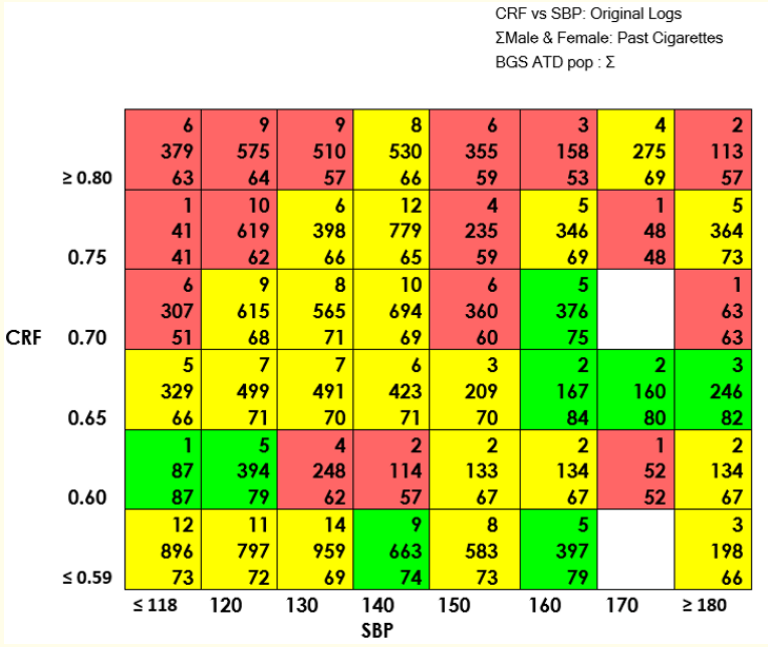

Figure IID

The data presented in table 1 and figure 2A-2D are based on SBP value**s** at presentation levels and hence contain SBP values that have been treated. This may bias the interpretation of the role of hypertension in ATD.

Additionally, if LDL-cholesterol is high enough (see above), then the CRF may be associated with ATD even if the CRF is 0.69 or less, thus adding bias to the interpretation of dyslipidemia and its role in ATD. The table and figure 2A-2D do not differentiate treated from non-treated SBP nor do they account for C Thr. These two factors can be compensated for if one puts all of the hypertensives (SBP of 140 mmHg or higher and all treated SBP levels) into the high risk category, the borderline hypertensives (SBP of 120-138 mmHg, untreated) into the medium risk category, and ideal patients (SBP of 118 mmHg or lower, untreated) into the low risk category.

Similarly, one could place all dyslipidemic patients (CRF of 0.70 or higher and all C Thr patients) into the high risk category, the borderline dyslipidemic patients (CRF of 0.60-0.69 and no C Thr) into the medium risk category, and the ideal lipid values (CRF of 0.59 or lower an no C Thr) into the low risk category. This analysis is presented in table 2A-2D, which encompasses all comers in the ATD population data base.

Review of table 2A revels that high-risk dyslipidemia (CRF of 0.70 or more and/or C Thr [LDL-cholesterol of 170 mg/dl [4.25 mmoles/L]) is present in 58% (505/871) of cases while hypertension (SBP of 140 mmHg and any treated SBP) is present in 55% (482/871) of cases. Medium-risk dyslipidemia (CRF of 0.60 - 0.69, but no C Thr) is present in 19% (168/871) of cases, whereas borderline hypertension (SBP of 120 - 138 mmHg, untreated) is present in 30% (262/871) of cases. Ideal lipids (CRF of 0.59 or lower and no C Thr) are found in 23% 198/871) of cases and ideal SBP levels (SBP of 118 mmHg or lower, untreataed) are found in 15% (127/871) of cases. Only 5% (43/871) of ATD cases have both ideal lipids and blood pressure. Moreover, there is a progressive rise in the average age of ATD onset as the CRF falls, but a fall in average age of ATD onset as SBP falls.

	CRF Zones			
	Red	**Yellow**	**Green**	**∑**
SBP Zones				
Red	280 18201 65	102 7066 69	100 7105 71	482 32372 67
Yellow	163 9609 59	44 2860 65	55 3682 67	262 16151 62
Green	62 3663 59	22 1384 63	43 2772 64	127 7819 62
∑	505 31473 62	505 11310 67	198 13559 68	871 56342 65

	Red	**Yellow**	**Green**
CRF	≥ 0.70 &	0.60 - 0.69	≤ 0.59
	All CThr	No CThr	No CThr
SBP	≥ 140 &	120 - 138	< 118
	All BP-RX	No BP RX	No BP RX

Table IIA: *CRF vs SBP: ∑ RX.*

∑∑ ATD Pop. ∑∑ Cigarettes.

	CRF Zones			
	Red	**Yellow**	**Green**	**∑**
SBP Zones				
Red	82 4634 57	20 1097 55	27 1569 58	129 7300 57
Yellow	71 3688 52	21 1199 57	15 884 59	107 5771 54
Green	28 1473 53	13 679 52	18 1069 59	59 3221 55
∑	181 9795 54	54 2975 55	60 3522 59	295 16292 55

	Red	Yellow	Green
CRF	≥ 0.70 &	0.60 - 0.69	≤ 0.59
	All CThr	No CThr	No CThr
SBP	≥ 140 &	120 - 138	< 118
	All BP-RX	No BP RX	No BP RX

Table IIB: *CRF vs SBP: ∑ RX.*

∑∑ ATD Pop. + Cigarettes.

	CRF Zones			
	Red	**Yellow**	**Green**	**∑**
SBP Zones				
Red	61 4083 67	15 1015 68	22 1602 73	98 6700 68
Yellow	44 2834 64	12 818 68	16 1082 68	72 4734 66
Green	12 658 55	2 139 70	9 660 73	23 1457 63
∑	117 7575 65	29 1972 68	47 3344 71	193 12891 67

	Red	Yellow	Green
CRF	≥ 0.70 &	0.60 - 0.69	≤ 0.59
	All CThr	No CThr	No CThr
SBP	≥ 140 &	120 - 138	< 118
	All BP-RX	No BP RX	No BP RX

Table IIC: *CRF vs SBP: ∑ RX.*

∑∑ ATD Pop. Past Cigarettes.

	CRF Zones			
	Red	**Yellow**	**Green**	**∑**
SBP Zones				
Red	81 5747 71	27 1985 74	24 1828 76	132 9560 72
Yellow	47 3014 64	12 916 76	24 1716 72	83 5646 68
Green	22 1532 70	7 566 81	15 968 65	44 3066 70
∑	150 10293 69	46 3467 75	63 4512 72	259 18272 71

	Red	**Yellow**	**Green**
CRF	≥ 0.70 &	0.60 - 0.69	≤ 0.59
	All CThr	No CThr	No CThr
SBP	≥ 140 &	120 - 138	< 118
	All BP-RX	No BP RX	No BP RX

Table IID: *CRF vs SBP: ∑ RX.*

∑∑ ATD Pop, ∑ - Cigarettes.

This analysis does not take cigarette smoking status into account, primarily because of the reduced numbers of patients as the ATD patients are classified on the basis of cigarette smoking. This is demonstrated in table 2B-2D. Table 2B shows the above analysis in terms of current smoking (295 patients). The changes in age as either the CRF or the SBP decline is much the same as in table 2, but at an earlier age. Table 2C shows the analysis in terms of ex-smokers. But now the changes in average age of ATD onset (rise as CF declines but fall as SBP declines) are more pronounced. Table 2D shows the analysis for never smokers (who may have used non-cigarette tobacco products) and reveals a similar pattern to table 2C.

Table 2A also reveals that hypertensive patients have a high rate of dyslipidemia. Definite dyslipidemia (CRF of 0.70 or higher and C Thr) is present in 55% (280/482) of hypertensive patients (treated or not) and borderline dyslipidemia (CRF of 0.60 - 0.69) is present in an additional 21% (102/482). Only 21% (100/480) hypertensive patients do not have some form of dyslipidemia. Those hypertensive patients with definite dyslipidemia have an average age of ATD onset of 65 years; those with borderline dyslipidemia, 69 years and those with no dyslipidemia, 71 years. A similar pattern is seen for those with borderline hypertension (SBP of 120-138 mmHg, untreated) and for those with ideal blood pressure levels.

The ideal CRF-SBP cohort (CRF of 0.59 or less and no C Thr and SBP of 118 mmHg or lower, untreated) is of interest because it shows that there is a population at low risk of ATD, when only never smokers are considered. The average age of ATD onset in this ideal cohort is 59 years for current smokers, 73 years for ex-smokers, and 65 years for never smokers. In this last scenario, the average age of ATD onset is lower because it contains women with microvascular angina or thrombophilia, with two cases associated with nonsteroidal anti-

inflammatory medication use. Exclusion of these latter women would dramatically increase the average age of ATD onset. Even so, the women were accepted into the data base and the author presents all of his data, so the age in the ideal cohort stands.

Table 2B-2D demonstrate the power of the CRF and cigarette smoking with respect to SBP. In any CRF-SBP cohort, smokers have a younger age of ATD onset than do ex-smokers, who in turn have a somewhat younger age of ATD onset than do never smokers, regardless of CRF or C Thr status, with the proviso noted above about women in the ideal CRF-SBP cohort (CRF of 0.59 or lower and no C Thr cases and untreated SBP of 118 mm Hg or lower).

In table 2A, the average age of ATD onset hypertensive patients (SBP of 140 mmHg or higher and all treated SBP values) recedes as CRF values decrease. The same is true for patients with borderline hypertension (SBP of 120-138 mmHg) or ideal blood pressure values (SBP of 118 mmHg or less). This finding links with the high incidence of dyslipidemia (high risk and medium risk) to high light the more important role of dyslipidemia with respect to blood pressure in ATD.

Discussion

The BGS graph and the concept of the CRF have been vetted in eight published angiographic regression studies [18]. In these eight trials, the number of patients above the threshold line were virtually identical to the numbers of BGS patients, if only BGS patients aged less than 80 years were considered. This paper shows that any therapy that brings the patient's CRF-SBP plot below the threshold line results in plaque stabilization/regression in 75% of cases, if cases from the Program on the Surgical Control of the Hyperlipidemias (POSCH) [19] are excluded due to its not being structured to control hypertension. Had POSCH been structured to control hypertension, the percentage of cases stabilizing/regressing plaque might well have been in the high 90's. Perhaps even more pertinent is the finding that did actually make a difference in fine-tuning the plaque response to therapy. Even when the goal of treatment was achieved (bringing the CRF-SBP plot below the threshold line), some therapies resulted in more plaque progression than did others.

When the goal of therapy was achieved in the eight trials, the percentage of plaque progression cases was 39% in Pravastatin Limitation of Atherosclerosis in the Coronary Arteries compared to 18% in the Familial Atherosclerosis Treatment Study compared to 9% in Saint Thomas Atherosclerosis Regression Study compared to 0% in POSCH [18].

Moreover, in POSCH [19], the CRF predicted plaque response to therapy with 100% accuracy. If the CRF rose, even minutely, at one year post-surgery, then the angiogram at three years always showed plaque progression.

Conversely, if the CRF fell, even minutely at one year post-surgery, the angiogram at three years post-surgery invariably showed plaque stabilization/regression. This finding is compatible with another finding from POSCH, and that is plaque regression/stabilization could occur even if LDL-cholesterol rose, so long as HDL-cholesterol rose more, and that plaque progression could occur even if LDL-cholesterol levels fell, provided that HDL-cholesterol levels fell more [20].

It is important to know which risk factors are more important than others in the prediction/prevention of ATD so that more intense therapy can be focused on the more important risk factors and that a more important risk factor is not worsened by treatment of a lesser risk factor. To this end the author has presented data that indicate that there is a rank order in risk factor importance and that physicians active in the fight against ATD should consider this when initiating therapy.

The author has presented the BGS graph as a predictor of the population at risk of ATD (See table 1). Table 1 gives the outcomes of 709 ATD patients in terms of gender, average age of ATD onset, average age of MSD onset, and average age of death. In virtually every category, cigarette smokers develop their event at a much earlier age than do ex-smokers, who in turn develop their event at a somewhat earlier age than do never smokers.

Indeed patients with CRF-SBP plots above the threshold line who have quit smoking cigarettes have their events at a older age than do patients who have their CRF-SBP plots below the threshold line but continue to smoke cigarettes. And this is also true for average age of MSD onset and death. The finding that there is a smaller difference between ex-smokers and never smokers implies that there is a legacy effect from cigarette smoking, such that ex-smokers do not achieve the results seen in never smokers. Figure 2A-2D show the average age of ATD onset in the various CRF-SBP cohorts. Figure 2B shows that current smoking obliterates the layering effect noted in figures 2C and 2D (ex-smokers and never smokers, respectively). In other words, current cigarette smoking is associated with early onset ATD even in CRF-SBP cohorts, which in ex-smokers or never smokers would be associated with middle age or old age ATD. Finally, in table 2A-2D, the ideal lipid-SBP cohort (CRF of 0.59 or less and no C Thr versus SBP of 118 mmHg or less and no treated SBP) can be analyzed in terms of cigarette smoking, and again the same age regression with respect to cigarette smoking status is noted, with the qualifications concerning the never smoking women being noted.

Table 2A-2D can be used to assess the relative importance of dyslipidemia versus hypertension. It will be noted that dyslipidemia is more common than hypertension. Moreover, the average age of ATD onset rises as dyslipidemia goes from high risk to medium risk to low risk, whereas the average age of ATD onset declines as SBP goes from high risk to medium risk to low risk. Inspection of figure 2A reveals that for high risk dyslipidemia, 68% (254/376) occur in patients with SBP of 138 mmHg or less (treated or untreated) while 32% occur in patients with SBP of 140 mmHg or higher. For medium risk dyslipidemia, the distribution is close (52% [241/460] versus 48% [219/460]) but there are no low risk dyslipidemia patients with SBP of 138 mmHg or lower-all 35 cases occur in patients with SBP of 140 mmHg or higher.

Additionally, the author is aware of a serendipitous finding in the POSCH [19]. POSCH was structured to control lipids, not hypertension. Thus patients with hypertension went untreated, but with intense lipid lowering patients still stabilized/regressed their plaques angiographically. This demonstrates that it is lipid lowering, not hypertension, that is important in plaque stabilization/regression. Moreover, some medications have adverse effects upon lipid levels and hence should be avoided in the treatment of dyslipidemic hypertension [21]. This finding may be pertinent according to the results of the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm [22] in which the amlodipine-perindopril arm was associated with fewer ATD events than the atenolol-bendrofluazide arm.

The demonstration of a rank order of ATD risk factors is important for a number of reasons, but primarily to promote the understanding of how to approach the primary and secondary prevention of ATD. For example, the medical community gives lip service to cessation of cigarette smoking and then moves on to treatment of dyslipidemia or hypertension. This is an error. The patient must be given full knowledge of the consequences of his/her continued cigarette smoking-and this must be repeated frequently during subsequent office visits.

Otherwise, in the author's experience, ATD continues to progress despite optimal therapy of dyslipidemia or hypertension. The patient may/may not quit smoking, but at least the physician will have done everything he/she can to keep ATD events at bay. Since dyslipidemia is more important than hypertension, all hypertensive patients must be screened for dyslipidemia and if present that dyslipidemia must be treated and hypertension must be treated with medications that do not worsen the dyslipidemia.

Conclusion

The author has presented data to indicate that there is indeed a rank order for ATD risk factor importance: first, cigarette smoking; second, dyslipidemia (as defined by the CRF and C Thr); and third, hypertension.

(Diabetics are treated in the same manner as non-diabetics, though in the former case medications to lower the blood sugar level are also necessary.) While all ATD risk factors must be treated in order to prevent ATD events, more emphasis must be given to the more important risk factors and treatment of the less important risk factors must not worsen the more important risk factors.

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