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Enhanced Prediction of the Population at Risk of Atherothrombotic Disease: Back to Framingham

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Abstract

Background: There are many tools that attempt to predict the population at risk of atherothrombotic disease (ATD). These tools are not well accepted and are often not accurate; most are not used at all. The Framingham Heart Study pioneered the prediction of the population at risk of ATD and still remains the basis upon which the current predictive tools are based. The predictive tool to be discussed in this paper is founded upon the original fundamental tenets devised by the Framingham Study and is based upon the risk factor complex of 872 people who developed some clinical form of ATD in the Bowling Green Study (BGS) during the 1 January 1978-1 January 2019 timeframe.

Objectives: The author will demonstrate that it is possible to predict the various risk profiles of the population at risk of ATD. This is important because the primary prevention of ATD requires knowledge of whom is at risk and an estimation of what that risk is.

Methods: The author has performed a chart review to collect a database of the ATD risk factors of the 872 people who developed some form of clinical ATD during the study timeframe. The ATD risk factors include dyslipidemia, cigarette smoking, and hypertension, with some contribution by the very high blood sugar levels of uncontrolled diabetes. He has analyzed this risk factor data to create a tool that defines the population at risk of ATD with high accuracy.

Results: Using the Cholesterol Retention Fraction (CRF, defined as low-density lipoprotein [LDL] cholesterol minus high-density lipoprotein [HDL] cholesterol, the difference divided by low-density lipoprotein cholesterol) as a measure of dyslipidemia and systolic blood pressure (SBP) as measure of hypertension, the author created a graph with the CRF on the ordinate and SBP on the abscissa. When the CRF-SBP plots of all of the author's ATD patients are plotted on the BGS graph, a scattergram appearance is noted. Once current cigarette smoking patients have been excluded, the CRF-SBP plots of the remaining ATD patients fall into a mainstream collection that lies above the CRF demarcation line at 0.70. A relatively few outliers exist. Initially, a threshold line, based on the principle of the fewest false positives, is generated. The average age at ATD onset, multi-system ATD onset, and age at death with respect to the threshold line is described. Subsequently, the area on the BGS graph can be divided into 48 CRF-SBP cohorts based on CRF sextiles and SBP octiles. The average age of ATD onset is determined for each of the 48 CRF-SBP cohorts and risk is assigned according to average age of ATD onset in each cohort. Highest risk is assigned to those people whose cohorts are characterized by an average age of ATD onset of 64 years or less; intermediate risk, by an average age of ATD onset of 65-74 years, and lowest risk, by an average age of ATD onset of 75 years and older. The incidence of ATD per these same CRF-SBP cohorts, in the general population, reveals that the incidence of ATD is lowest where the CRF and SBP cohorts are lowest, in the southwest corner of the graph and conversely, highest where the CRF and SBP cohorts are highest, in the northeast corner of the graph. Finally, the cumulative ATD incidence per CRF sextile can give an estimation as to when dyslipidemic therapy should be initiated.

Conclusion: Based of the characteristics of patients with known clinical ATD, the author has generated a graph that defines the ATD population with high accuracy. People whose CRF-SBP plots lie above the threshold line can be expected to develop clinical ATD at some point in their lives, depending upon the severity of their risk factors and the length of time those risk factors have been operative. People whose CRF-SBP plots lie below the threshold line, in the absence of cigarette smoking, are at little risk of ATD events until very late in life. For people at risk of ATD, that risk can be further defined by dividing the BGS graph area into CRF-SBP cohorts as described

Keywords: *Atherothrombotic Disease; Prediction of the Population at Risk; Cholesterol Retention Fraction; Cigarette Smoking; Hypertension*

Introduction

The holy grail of interventional lipidology and preventive cardiology is the prediction of the population at risk of atherothrombotic disease (ATD, or atherosclerotic disease, with emphasis on thrombosis, which so often precipitates the acute event). As initially shown by the Framingham Heart Study, the ATD population differs from the non-ATD population by a number of factors of risk, now called risk factors [1]. These differences in ATD risk factors are quantitative, not qualitative-that is, in the ATD population, those risk factors are more severe and occur more frequently in combination than in the non-ATD population. Put another way, the ATD risk of any individual ATD risk factor is not spread evenly throughout the continuum of that risk factor, but rather tends to be concentrated at or towards the higher risk end of the spectrum. There are no known ATD risk factors that are unique to the ATD population, that are not also found in the non-ATD population. The three major ATD risk factors are cigarette smoking, dyslipidemia and hypertension, with a possible contribution from severe elevations of blood sugar in uncontrolled diabetes mellitus [2-17].

There have been numerous attempts to utilize these risk factors in an attempt to predict the population at risk of ATD. The author has listed a few of the various predictive scenarios [1,18-33]. None of the predictive tools, however, has gained unqualified acceptance. The author has compiled a database, founded on his own practice of family medicine in northwest Ohio [34-36]. The database was begun on 4 November 1974 and terminated on/or about 1 January 2019 and thus is a database that covers a 43 year period. The author has also created a predictive tool, based on the data from 4 November 1974-4 November 2003, that predicts the population at risk of ATD with high accuracy, possibly because the various ATD risk factors are treated as dependent variables and not independent variables. Additionally, the author has shown that in eight published angiographic regression trials, that the studied population in each of those trials has characteristics identical to the author's tool in the vast majority of cases, and that any therapy that corrects those abnormalities is associated with plaque stabilization/regression [37].

Purpose of the Study

The purpose of this paper is to present the author's predictive tool and then to fine-tune it in light of data from the 5 November 2003 - 1 January 2019 time frame.

Materials and Methods

The author set up his practice of family medicine in Bowling Green, the county seat of Wood County, in northwest Ohio on 4 November 1974. Wood County had a population of about 128,000 people at the time of the last census in 2010. The county populace is mainly Caucasian, of European descent. The county is mainly rural, with the biggest city being Bowling Green, with about 28,000 people. Bowling Green State University is the area's biggest employer, though there are many small businesses and many people are involved in agriculture. At the time he set up his practice, the author decided to make a contribution to the fields of interventional lipidology (Harvey Hecht, MD, term used with permission) and preventive cardiology. To achieve this goal, he created an age-sex database, comprised of all of the patients of both sexes and all ages in his practice. He measured blood pressures on each and every patient, as well as height and weight, and these measurements were repeated virtually each and every time the patient visited the author's practice. Additionally, whenever feasible, the author obtained a fasting lipid panel and two hour post-prandial blood sugar. The lipid panels obtained from 4 November 1974 until 1 January 1978 consisted only of total cholesterol and triglycerides, high-density lipoprotein (HDL) cholesterol not being available until after 1 January 1978. Low-density lipoprotein (LDL) cholesterol was calculated based on the Freidewald equation [38]. Once the author had established the prime importance of cigarette smoking in the pathophysiology of ATD, he began determining the use of tobacco products on all of his patients aged 15 years or older, and in the 1990's extended the age on information gathering down to all patients aged 10 years or older. Details have been published in references 34-36.

During the time frame discussed in this paper, the author has obtained 1774 full lipid profiles in his male populace and 1783 full lipid profiles in his female populace, all as outpatients. This means that there are LDL-cholesterol and CRF values for 1774 male and 1783 fe-

male patients. However, some of those patients do not have associated SBP determinations or cigarette smoking status. That leaves 1538 male patients and 1467 female patients with simultaneous CRF values, LDL-cholesterol levels, SBP determinations, and knowledge of cigarette smoking status-a total of 3005 patients with the full data set for the analyses required by this paper.

In the 1970's the list of ATD risk factors was long and extensive, and the ability to predict the population at risk of ATD was relatively poor. As a result, a number of the author's patients developed acute ATD syndromes. The database of these patients was then segregated from the general population base and compared with the database of those patients who were not known to have developed some form of clinical ATD. When this was done, it immediately became obvious that the three major ATD risk factors were cigarette smoking, dyslipidemia, and hypertension. Rarely, however, did these risk factors occur in isolation. Moreover, some patients with high LDL-cholesterol had ATD events, but many ATD patients had low LDL-cholesterol. Likewise, some patients with low HDL-cholesterol levels had ATD events, but so did some patients with high levels of HDL-cholesterol. In 1981, an article was published asking the question "Is the LDL: HDL ratio the best lipid predictor?" (The author regrets that the article is lost to him and that he is unable to give the authors proper credit). The author then re-examined his ATD database and noted that those ATD patients with low LDL-cholesterol had very low associated HDL-cholesterol levels. Moreover those ATD patients with high HDL-cholesterol levels had very high associated LDL-cholesterol levels. As a result it became clear that it was indeed the ratio between LDL- and HDL-cholesterol that was critical to defining the lipid portion of ATD risk. When these relationships did not hold, the younger patients were virtually always cigarette smokers and the older patients were virtually always hypertensive, with or without attendant diabetes.

In 1983, it occurred to the author that the most significant aspect of dyslipidemia was the accumulation of cholesterol within the artery wall. This he reasoned was best estimated by the difference between the cholesterol entering the artery wall (LDL-cholesterol) and the cholesterol being removed from the artery wall by reverse cholesterol transport (HDL-cholesterol), that difference divided by the cholesterol entering the artery wall. In other words, of the cholesterol entering the artery wall, what percentage remains within the artery wall. Thus, was born the concept of the Cholesterol Retention Fraction or CRF, defined as (LDL-HDL)/LDL. However, inspection of the BGS ATD database revealed that if LDL-cholesterol was very high (170 mg/dl or 4.25 mmoles/L), then ATD events occurred even if the CRF was not elevated (See below). Thus, was born the concept of the cholesterol threshold (CThr): CRF of 0.70 or greater and/or LDL-cholesterol of 170 mg/dl (4.25 mmoles/L) or greater. Moreover, if LDL-cholesterol was very low, then the CRF would always be high and yet , in the absence of cigarette smoking in younger patients or SBP of 140 mmHg or higher in older patients, not impact ATD risk.

As noted earlier, the author's examination of the ATD database revealed that only rarely did the various ATD risk factors act alone in causing ATD events. It was apparent that the various risk factors inter-acted in a milieu, that the atherogenicity of LDL-cholesterol was intimately related to its associated HDL-cholesterol, that cigarette smoking status was paramount in the clinical expression of ATD, leading to ATD events in patients with no dyslipidemia and accelerating the rate at which ATD develops in those with dyslipidemia. The author therefore decided to examine risk factor combinations but found that the only predictive ATD risk factor combination was systolic blood pressure (SBP) and the CRF-and then only when stratified by cigarette smoking status. The author then generated a predictive graph, with the CRF on the ordinate and SBP on the abscissa. When he plotted the CRF-SBP plots of all of his ATD patients, a scatter gram resulted. However, once current cigarette smokers were excluded, a mainstream sequence of ATD patients' CRF-SBP plots was noted, lying in a horizontal band above the CRF equals 0.70 level. Only a relative few ATD patients' CRF-SBP plots lay below this mainstream sequence. On the basis of the principle of the fewest false negatives, the author generated an ATD threshold line with CRF-SBP loci of (0.74, 100) and (0.49, 140) when the precipitation method of HDL-cholesterol measurement was used, but (0.62, 100) and (0.40, 140) if the enzymatic method is used. (The original threshold line described in references 32-34 was modified in the year 2000 to the present configuration in a subsequent publication [37]). See Figure I.

As just noted, there are two ways to measure HDL-cholesterol in common practice: the precipitation method and the enzymatic meth-

od. The HDL-cholesterol measurements described in this presentation were based on the precipitation method, which was in world-wide use at the time. In or about the year 1999, the manufacturers of the auto-analyzers that measure lipids decided, without informing the medical community as a whole, to change the methodology by which HDL-cholesterol was measured over to an enzymatic method. The resultant values of HDL-cholesterol, unfortunately, are not the same as those that would have been obtained with the precipitation method. The enzymatic methodology gives an HDL-cholesterol value on the order of 10 mg/dl (0.25 mmoles/L) higher than those achieved by the precipitation method. Since LDL-cholesterol is usually calculated by the Friedewald formula [38], the resultant LDL-cholesterol will be on the order of 10 mg/dl (0.25 mmoles/L) lower than those levels that would have been calculated using the precipitation method. This difference is not trivial. In 2008, the author reported a case of a patient (never smoker, normotensive, non-diabetic, slim patient with no family history of ATD or dyslipidemia) who had an acute myocardial infarction at age 55 years. He had had no reason to have his lipids measured prior to the acute event, but lipids measured at the time of the event were only slightly abnormal when the enzymatic method of HDL-cholesterol was used, but much more abnormal when the obtained values were converted to their precipitation method equivalents [39]. The lipid values discussed in this paper are either done using the precipitation method of HDL-cholesterol measurement or using the enzymatic results, converted to their precipitation method equivalents. For the auto-analyzer in the author's local hospital, the conversion formula is HDL-cholesterol (precipitation) = [HDL-cholesterol (enzymatic) minus 12]/0.93.

Results

The Bowling Green Study (BGS) graph is depicted in figure 1. When the CRF-SBP plots of all the ATD patients in the author's practice with full lipid data available (872 patients) are plotted upon the BGS graph, then 721 (83%) of those plots lie above the threshold line. Of the 150 ATD patients whose CRF-SBP plots lie below the threshold line, 92 (11% of the total ATD population) are cigarette smokers, current or past. That leaves only 57 (7% of the total ATD population) ATD patients who could not be identified by CRF-S BP plot position above the threshold line and/or cigarette smoking (current or past) status. Table 1 gives the outcomes of all 869 ATD patients with full lipid data and known cigarette smoking status. (One 75 year old man whose EKG showed an old AMI, but whose cigarette smoking status is not known to the author is excluded. His CRF-SBP plot lies below the threshold line. His elevated HDL-cholesterol may have been due to his use of phenytoin) (See table 1). It will be obvious that a CRF-SBP plot position below the threshold line in the absence of any history of cigarette smoking implies an average age of ATD onset so late in life as to suggest virtual immunity to ATD. Quitting smoking cigarettes results in outcomes almost as good as those in people who have never smoked cigarettes. Due to changes in insurance coverage, etc. in late 2003, the author lost a great many patients (including ATD patients) from his practice. Therefore, he was unable to do full follow-up on those patients. Table 2 shows the ATD outcomes for 709 patients, 1 January 1978-1 January 2004 time frame, for which more complete follow-up is available, giving the average age of ATD onset, average age of multi-system ATD onset, and average age of death. It is clear that a CRF-SBP plot below the threshold line, in the absence of any history of cigarette smoking, gives average ages of ATD onset and death so late in life that this risk factor scenario implies virtual immunity to ATD and no treatment necessary unless CThr is exceeded or SBP is elevated.

Sex			+	Past	-
Male					
	Above ASR Line	Total Patients	158	151	108
		Total Patient Years	8307	9969	7258
		Ave. Age of ATD Onset	53	66	67
	Below ASR Line	Total Patients	27	23	13
		Total Patient Years	1537	1668	974
		Ave. Age of ATD Onset	57	73	75
Female					
	Above ASR Line	Total Patients	85	63	156
		Total Patient Years	4915	4353	11429
		Ave. Age of ATD Onset	58	69	73
	Below ASR Line	Total Patients	24	19	44
		Total Patient Years	1459	1283	3157
		Ave. Age of ATD Onset	61	68	72

Table 1: *Average age of ATD onset.*

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

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

Table 2: *ATD w/r to ASR 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.

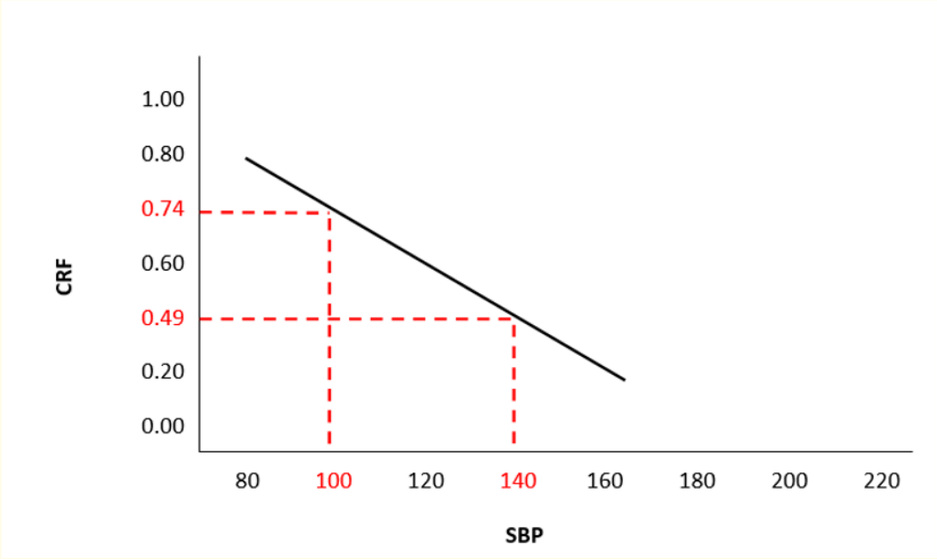

Figure 1: *Precipitation method of HDL cholesterol measurement.*

CRF: Cholesterol Retention Fraction ([LDL-HDL]/LDL); SBP: Systolic Blood Pressure; Line Loci are (0.62, 100) and (0.40, 140) if enzymatic method is used.

Since the CRF-SBP plots of the ATD Population database are mostly drawn from the BGS General Population database, the author then plotted the percentage of people in the General Population database whose CRF-SBP plots had transgressed the threshold line and the percentage of people who had developed some form of clinical ATD, both in terms of age groups. The trajectories of these plots run essentially parallel, with a 40 year gap between the trajectories in men and a 20 year gap in women (See figure 2A and 2B).

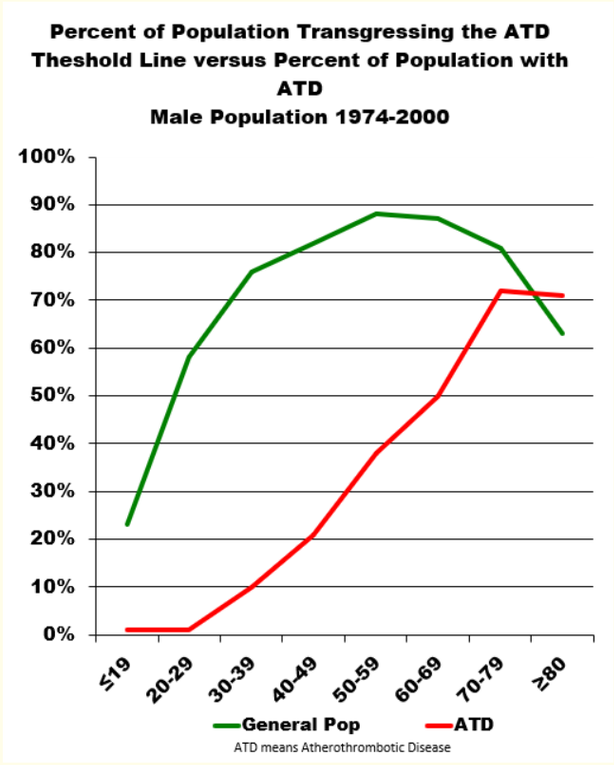

Figure 2A

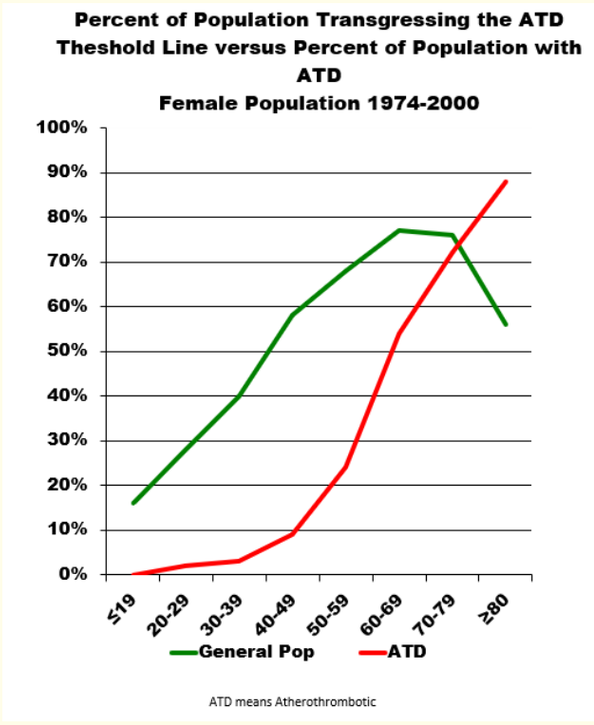

Figure 2B

The area of the BGS graph can be divided into 48 CRF-SBP cohorts based on the CRF sextiles and SBP octiles. In the general population, the number of ATD events per CRF-SBP cohort and the total of people with CRF-SBP plots within that cohort can be determined, giving an ATD prevalence per CRF-SBP cohort. (See figures 3A to 3D). Using criteria that an ATD lifetime prevalence of 14% or less constitutes a low prevalence, that an ATD lifetime prevalence of 15 - 24% constitutes an intermediate prevalence, and an ATD lifetime prevalence of 25% or greater constitutes a high prevalence, it is clear that the low lifetime prevalence is seen in that area of the BGS graph where CRF and SBP levels are lowest (green cohorts) and that CRF-SBP cohorts with intermediate prevalence (yellow cohorts) and high risk (red cohorts) radiate out from the southwest corner.

CRF vs SBP in BGS Gen Pop

Σ Cigarettes SBP: Σ

Σ Male & Female:

CRF	≤ 118	120	130	140	150	160	170	≥ 180
≥ 0.80	19 73 26%	35 103 34%	32 81 40%	22 63 35%	10 20 50%	6 15 40%	4 0%	4 5 80%
0.75	25 113 22%	32 107 30%	26 82 32%	16 60 27%	10 25 40%	9 22 41%	6 9 67%	4 8 50%
0.70	22 137 16%	28 116 24%	24 78 31%	23 74 31%	7 20 35%	12 28 43%	2 5 40%	5 8 63%
0.65	18 170 11%	25 118 21%	20 75 27%	13 47 28%	7 22 32%	7 14 50%	2 4 50%	4 5 80%
0.60	14 138 10%	17 90 19%	12 43 28%	15 41 37%	4 10 40%	3 5 60%	1 3 33%	4 7 57%
≤ 0.59	52 655 8%	36 284 13%	25 118 21%	27 81 33%	17 44 39%	10 25 40%	3 9 33%	2 11 18%

SBP

Figure 3A: *CRF means Cholesterol Retention Fraction; SBP means Systolic Blood Pressure; BGS means Bowling Green Study; ATD means Atherothrombotic Disease.*

CRF vs SBP in BGS Gen Pop

+ Cigarettes SBP: Σ

Σ Male & Female:

CRF	≤ 118	120	130	140	150	160	170	≥ 180
≥ 0.80	9 31 29%	22 46 48%	19 42 45%	7 25 28%	6 7 86%	3 9 33%	0%	3 3 100%
0.75	11 41 27%	11 36 31%	13 33 39%	7 19 37%	2 4 50%	3 8 38%	3 3 100%	1 3 33%
0.70	9 48 19%	8 35 23%	10 31 32%	9 24 38%	2 0%	5 11 45%	1 2 50%	0%
0.65	10 42 24%	10 37 27%	2 23 9%	3 16 19%	2 3 67%	1 3 33%	0%	1 2 50%
0.60	6 36 17%	8 27 30%	5 10 50%	4 13 31%	1 1 100%	2 0%	1 1 100%	2 3 67%
≤ 0.59	18 137 13%	13 71 18%	5 34 15%	13 30 43%	7 14 50%	2 0%	1 0%	1 6 17%

SBP

Figure 3B: *CRF means Cholesterol Retention Fraction; SBP means Systolic Blood Pressure; BGS means Bowling Green Study; ATD means Atherothrombotic Disease.*

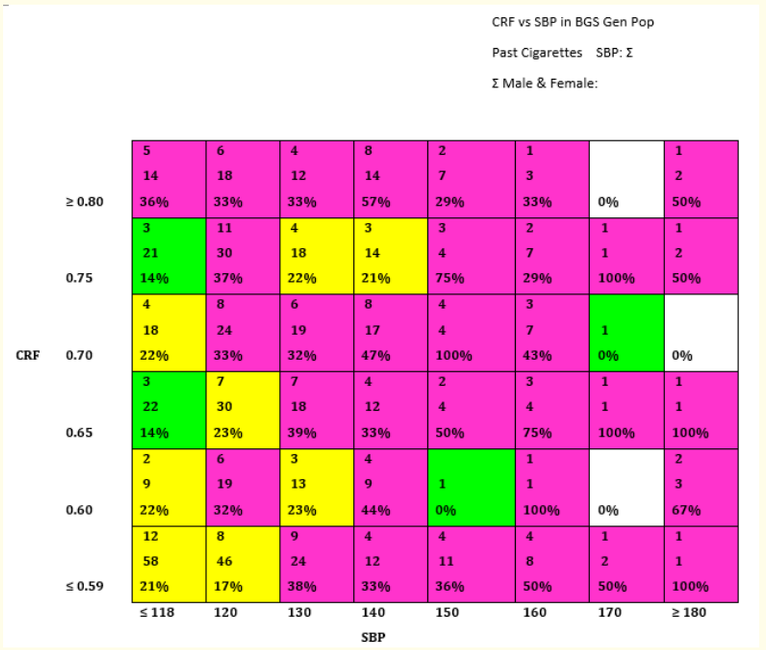

Figure 3C: *CRF means Cholesterol Retention Fraction; SBP means Systolic Blood Pressure; BGS means Bowling Green Study; ATD means Atherothrombotic Disease.*

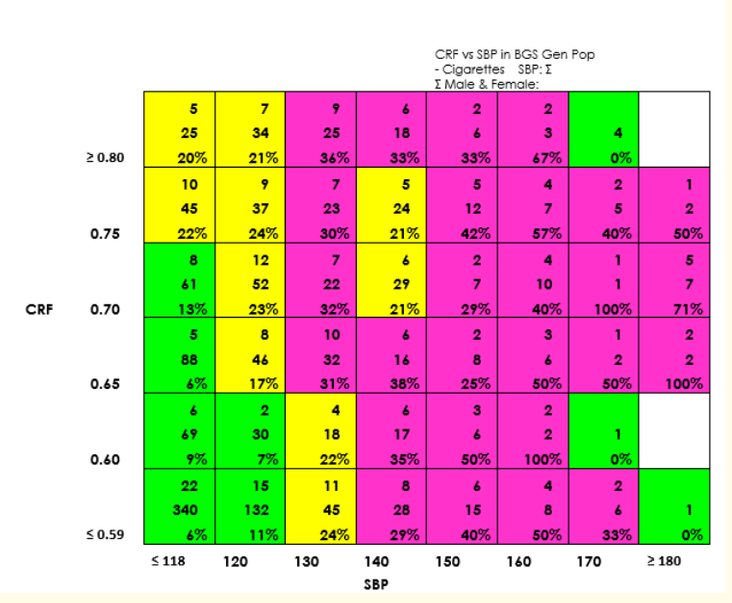

Figure 3D: *CRF means Cholesterol Retention Fraction; SBP means Systolic Blood Pressure; BGS means Bowling Green Study; ATD means Atherothrombotic Disease.*

For patients in the general population, ATD risk can be further defined by consideration of the cumulative ATD incidence in any give CRF sextile per age group. Such data generates ATD prevalence curves that resemble Kaplan-Meier curves in reverse-that is time to event curves rather than survival curves. To generate the ATD cumulative incidence curves, the incidence of ATD events is given in terms of increasing age groups (See table 3 and figure 4A and 4B). To know when to begin dyslipidemic therapy, simply determine the lifetime

ATD risk that is acceptable, on the vertical axis, and move horizontally until the cumulative risk curve is reached and then drop down to the horizontal axis to find the age group at which the pre-determined ATD risk level is reached. For example, if a 15% lifetime ATD risk is selected, and if the CRF is 0.80 or higher, then the age group at which that risk is achieved is the 39 years and younger group. However, if the CRF is 0.59 or less, then the 15% lifetime risk is never reached. Since all people with CRF of 0.70 or higher were offered dyslipidemic therapy, the cumulative ATD risk curves (Figure 4A) for the higher CRF sextiles are likely shifted to the right with respect to the age group.

Age Group	≥ 0.80	0.75-0.79	0.70-0.74	0.65-0.69	0.60-0.64	≤ 0.59
≤ 29	4	6	6	2	5	9
	61	94	137	188	156	709
	7%	6%	4%	1%	3%	1%
≤ 39	16	23	18	13	9	19
	143	195	234	275	217	928
	11%	12%	8%	5%	4%	2%
≤ 49	58	54	40	23	19	44
	250	304	328	339	273	1080
	23%	18%	12%	7%	7%	4%
≤ 59	95	81	64	38	38	87
	330	367	402	388	313	1203
	29%	22%	16%	10%	12%	7%
≤ 69	123	119	96	70	53	119
	370	428	450	446	343	1268
	33%	28%	21%	16%	15%	9%
≤ 79	136	136	118	92	67	153
	386	451	478	476	361	1317
	35%	30%	25%	19%	19%	12%
∑	140	141	131	103	76	182
	391	458	493	490	372	1353
	36%	31%	27%	21%	20%	13%

Table 3: *Cumulative ATD risk with respect to CRF sextiles, ∑∑ BGS general population.*
ATD Means Atherothrombotic Disease; CRF Means Cholesterol Retention Fraction; BGS means Bowling Green Study

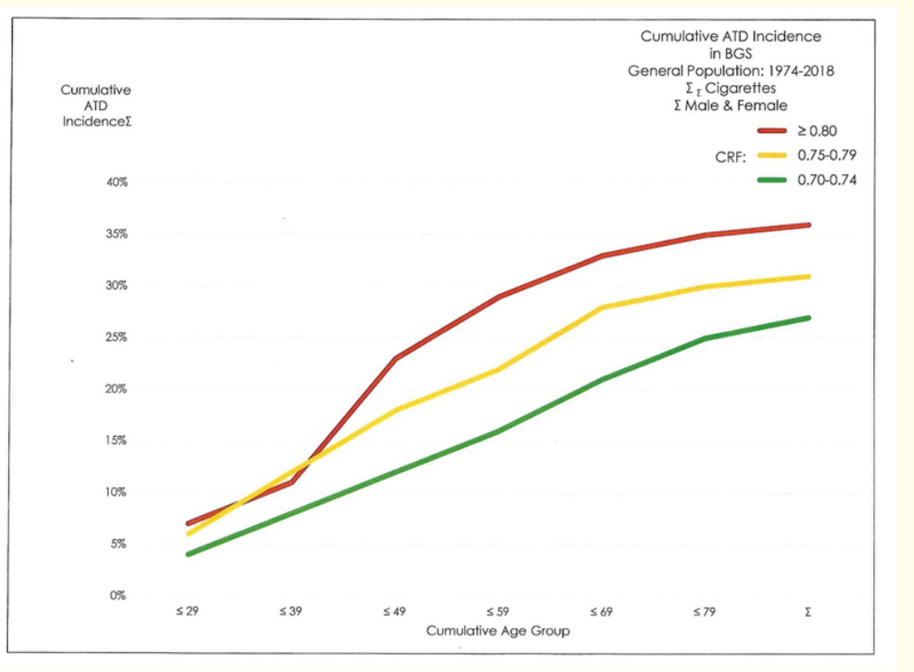

Figure 4A: *ATD means Atherothrombotic Disease; BGS means Bowling Green Study.*

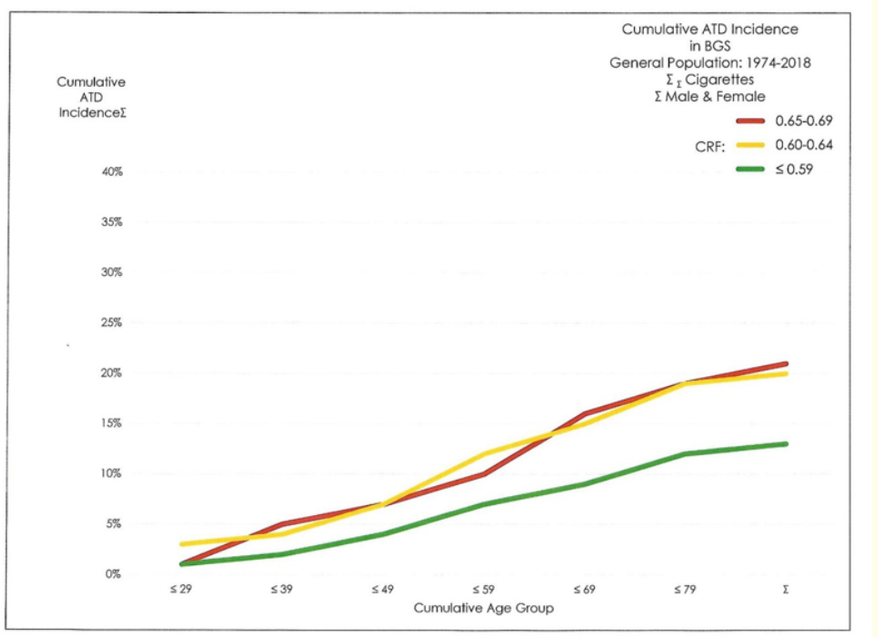

Figure 4B: *ATD means Atherothrombotic Disease; BGS means Bowling Green Study.*

The area of the BGS graph (in the BGS ATD population) can be divided into CRF-SBP cohorts as shown in figure 5A-5D. Within each cohort square is the number of people in that cohort, total patient years of age, and the average age of ATD onset. The figures shown are for all comers (Figure 5A), for current smokers (Figure 5B), for past smokers (Figure 5C) and for never smokers (Figure 5D). The color coding shows pink for those people with an average age of ATD onset of 64 years or less, shows yellow for those with an average age of ATD onset of 65-74 years of age, and shows green for those with an average age of ATD onset of 75 years or more. Hence to fine tune the risk of ATD, it is necessary to determine to which cohort the patient belongs and his/her cigarette smoking status. For example, a patient with a CRF-SBP cohort of 0.75-138 who has never smoked cigarettes would be placed in the appropriate square, which would show an average age of ATD of 74 years. Had that patient been a current cigarette smoker, the average of ATD onset would have been 53 years. When all comers are considered, 376/401 (94%) of patients in the pink cohorts (early onset ATD) lie above the CRF 0.70 or higher threshold.

CRF vs SBP: Original Logs
ΣMale & Female: Σ Cigarettes
BGS ATD pop : Σ

CRF	≤ 118	120	130	140	150	160	170	≥ 180
≥ 0.80	24 1,457 61	36 2,010 56	40 2,333 58	26 1,576 61	15 823 55	10 590 59	4 275 69	8 451 56
0.75	19 1,145 60	33 1,958 59	27 1,694 63	26 1,615 62	10 562 56	14 931 67	5 278 56	16 1,080 68
0.70	24 1,436 60	31 2,009 65	25 1,609 64	24 1,634 68	12 751 63	15 1,037 69	8 607 76	10 709 71
0.65	20 1,311 66	25 1,525 61	17 1,200 71	13 908 70	10 698 70	13 912 70	5 389 78	15 1,031 69
0.60	13 864 66	19 1,305 69	17 1,139 67	10 595 60	10 707 71	5 337 67	5 358 72	5 337 67
≤ 0.59	51 3,386 66	37 2,537 69	36 2,465 68	30 2,004 67	18 1,307 73	13 974 75	8 595 74	12 857 71

SBP

Figure 5A: *CRF means Cholesterol Retention Fraction; SBP means Systolic Blood Pressure; BGS means Bowling Green Study; ATD means Atherothrombotic Disease; - means no history of cigarette smoking.*

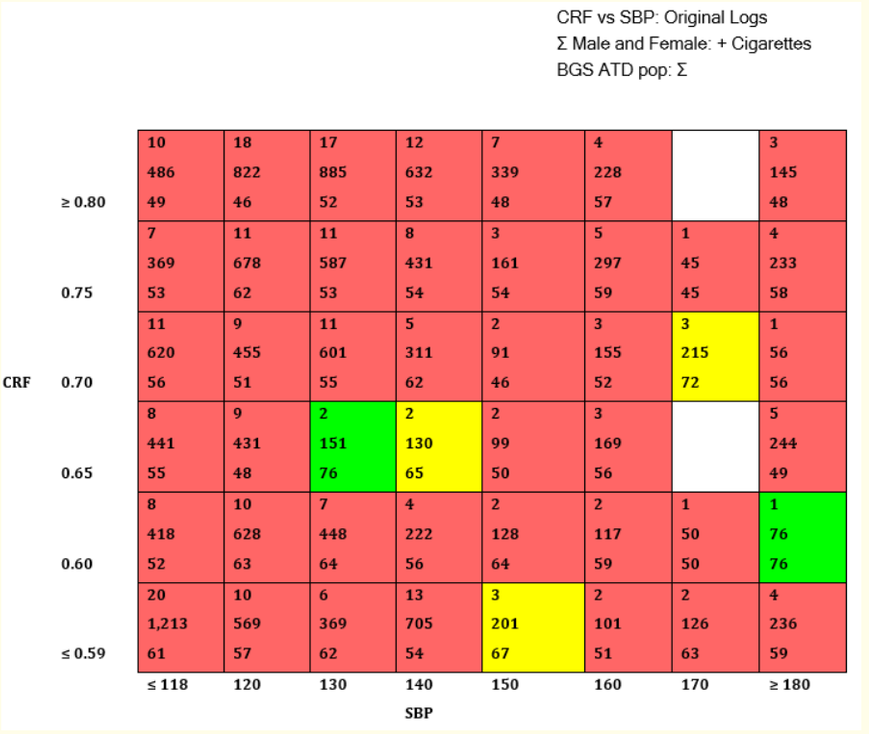

Figure 5B: *CRF means Cholesterol Retention Fraction; SBP means Systolic Blood Pressure; BGS means Bowling Green Study; ATD means Atherothrombotic Disease; - means no history of cigarette smoking.*

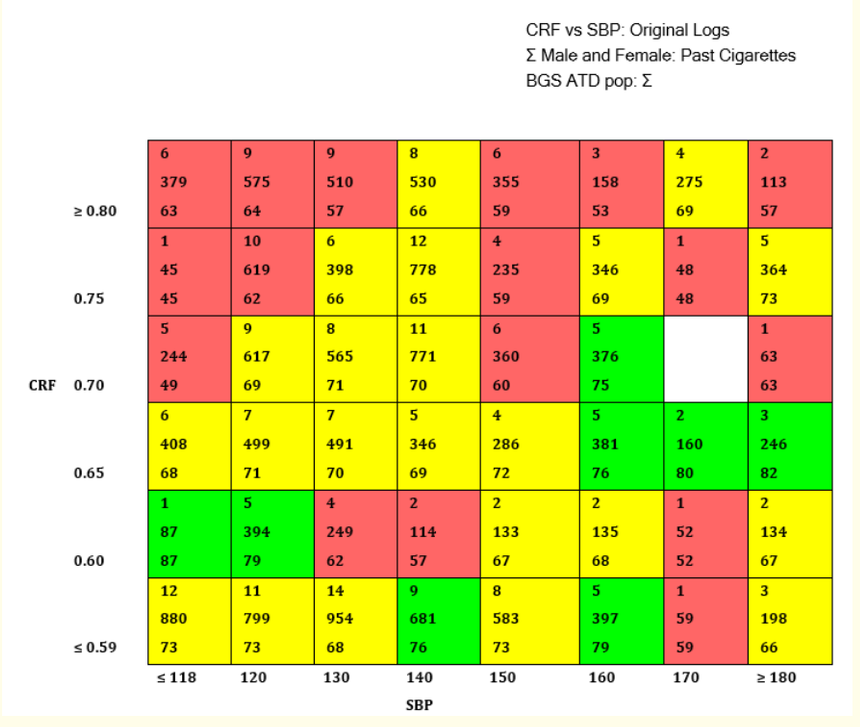

Figure 5C: *CRF means Cholesterol Retention Fraction; SBP means Systolic Blood Pressure; BGS means Bowling Green Study; ATD means Atherothrombotic Disease; - means no history of cigarette smoking.*

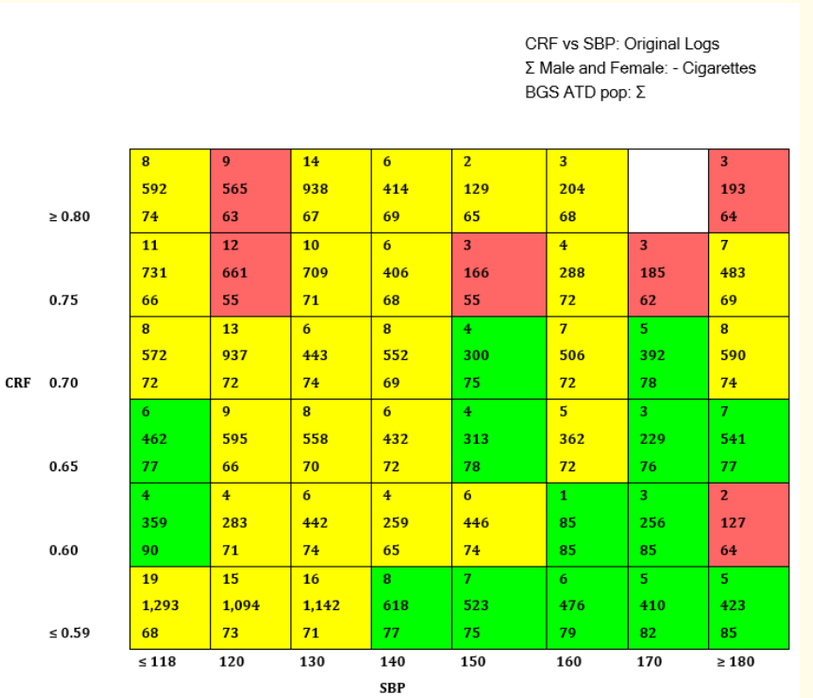

Figure 5D: *CRF means Cholesterol Retention Fraction; SBP means Systolic Blood Pressure; BGS means Bowling Green Study; ATD means Atherothrombotic Disease; - means no history of cigarette smoking.*

Since all presented studies require external validation, the author examined the position of the CRF-SBP plots in seven published angiographic regression trials and one ATD outcomes trial [37]. The trials are named and the results listed in table 4. All of the angiographic regression trials were done in people known to have clinical ATD. An overall average of 95% of patients had CRF-SBP plots above the threshold line on enrollment into the various trials. The BGS, however, took in patients of all ages, and only 83% had CRF-SBP plots above the threshold line. Additionally, almost half of the BGS patients were female-unlike the other trials, which had nowhere near the same numbers of female patients. Validation attempts could also examine the CRF distribution in these angiographic regression trials. This analysis is revealed in table 5, which shows that in the trials the CRF is shifted toward higher values than in the BGS. If, however, only BGS patients aged 65 years or younger are considered, then the BGS numbers align much more closely with the various trials. (Data not shown) Compromising this attempt at validation is that all of the angiographic regression trials were done using selection criteria, thus introducing selection bias into any comparisons.

	CRF-SBP Plot Above the Threshold Line	CRF-SBP Plot Below the Threshold Line	Percent CRF-SBP Plots Above the Threshold Line
Trial			
NHLBI	116	0	100%
POSCH	725	3	99.5%
Heidelberg	84	3	96.6%
LOCAT	363	9	97.6%
STARS	72	2	97.3%
PLAC-1	388	19	95.3%
LCAS	275	65	80.9%
Total	2023	101	95.2%

Table 4: *CRF-SBP plots with respect to threshold line in eight angiographic regression trials.*
CRF means Cholesterol Retention Fraction; SBP means Systolic Blood Pressure; NHLBI means National Heart Lung and Blood Institute Type II Secondary Prevention Trial; POSCH means Program on the Surgical Control of Hyperlipidemia; LOCAT means Lopid Coronary Angiography Trial; STARS means St. Thomas Atherosclerosis Regression Studyl PLAC-1 means Pravastatin Limitation of Atherosclerosis in the Coronary Arteries; LCAS means Lipoprotein and Coronary Atherosclerosis Study.

	≥ 0.80	0.75-0.79	0.70-0.74	0.65-0.69	0.60-0.64	≤ 0.59
Trial						
NHLBI	66	17	3	4	0	0
POSCH	332	218	114	47	9	11
Heidelberg	44	26	11	6	1	1
LOCAT	130	129	77	26	3	7
STARS	26	27	8	8	0	5
PLAC-1	95	142	94	51	14	10
LCAS	22	69	111	50	45	43
Total	715	628	418	192	72	77
	34%	30%	20%	9%	3%	4%
BGS ATD Population	126	121	130	101	73	159
	18%	17%	18%	14%	10%	22%

Table 5: *CRF-SBP plot distribution in eight angiographic regression trials CRF. CRF means Cholesterol Retention Fraction; SBP means Systolic Blood Pressure; NHLBI means National Heart Lung and Blood Institute Type II Secondary Prevention Trial; POSCH means Program on the Surgical Control of Hyperlipidemia; LOCAT means Lopid Coronary Angiography Trial; STARS means St. Thomas Atherosclerosis Regression Study; PLAC-1 means Pravastatin Limitation of Atherosclerosis in the Coronary Arteries; LCAS means Lipoprotein and Coronary Atherosclerosis Study.*

Discussion

The Framingham Heart Study (FHS) has led the way in the fields of preventive cardiology and interventional lipidology. The FHS, in its initial publications, laid out the basic tenets of the prediction of the population at risk of ATD. These are as follows:

1) ATD events do not occur as a bolt out of the blue. Rather, ATD events are due to certain characteristics of the person who develops those events.

2) The main ATD risk factors are cigarette smoking, dyslipidemia, and hypertension, with some contribution by the very high blood sugar levels of uncontrolled diabetes. (Rank order by the author) The best measure of dyslipidemia according to the FHS is the ratio between total and HDL-cholesterol [40].

3) In the absence of these risk factors, clinical ATD events are uncommon at least until very late in life.

4) There are no risk factors unique to the ATD population. The risk factors leading to ATD are shared amongst those who develop ATD and those who don't.

5) ATD risk factors are not a present-or-absent phenomenon. Each risk factor exhibits a spectrum of risk. Each spectrum is characterized by a higher ATD risk zone and a lower risk zone. Such spectra are not "black and white" but rather shades of gray." The higher the risk, the earlier the ATD event is likely to occur, and the lower the risk the later the ATD event is likely to occur.

6) ATD risk factors rarely act by themselves, but rather act in a milieu of all of the ATD risk factors. It is the result of this interplay of this milieu of risk factors that determines whether a person develops or does not develop clinical ATD. Thus, the various ATD risk factors are dependent variables, not independent variables. The more risk factors that are in play, the earlier is the likelihood that ATD events will occur.

7) There is an incubation period between when the various ATD risk factors begin to interact and the clinical ATD event occurs. This incubation period, as indicated above, is shorter when the person has higher ATD risk from any given risk factor or when multiple risk factors are in play and longer when risk factors are less potent or only a few are in play [41-50].

The author has utilized these FHS precepts to define the constellation of ATD risk factors that define the ATD population-and separate the ATD population from the non-ATD population. In doing so, it is important to realize that virtually no one escapes some aspect of ATD if they live long enough. This is borne out in the BGS General Population database, which includes people in their 80's and 90's. Even people with none of the classic ATD risk factors develop some form of clinical ATD very late in life, often heart failure in the tenth and eleventh decades of life. This rationale underlies the ATD risk prediction presented here. Since virtually every one who lives long enough and does not die of other causes will eventually develop an ATD event, the goal of any predictive tool should be the prediction of the high risk (under age 65 years) and intermediate risk (ages 65-74 years) cohorts, and to do this, one must know the patient's actual ATD risk factors.

The method of predicting the population at risk of ATD, at least prior to the mid-eighth decade of life is a three step process. The initial step in the process is to determine the CRF-SBP plot position with respect to the threshold line on the BGS. A CRF-SBP plot position above the threshold line implies that the person is at risk of ATD, whereas a CRF-SBP plot position below the threshold line, in the absence of any history of cigarette smoking, implies little risk of ATD, and hence no therapy is offered. There are two caveats to this statement. First, cigarette smoking can cause ATD events even when lipid and blood pressure levels are ideal; hence, to delay ATD events in the future, a cigarette smoker with a CRF-SBP plot below the threshold line MUST quit smoking. While a person who has quit smoking cigarettes gains a significant survival advantage over a person who continues to smoke cigarettes, that advantage is not as great as if the person had never smoked cigarettes. See table 1 and 2 and compare figure 5C with 5D. These findings support the earlier observation of Stamler that there is a population at low risk of ATD [51] and the suggestion that there is an ATD threshold line, at least for ATD death, by Goldbourt [52]. It is understood that "Low risk is not no risk" (Lale Tokgozoglu, MD, 28 May 2019).

The individual patient's ATD risk depends upon how long he/she has had a CRF-SBP plot above the threshold line, as well as the degree of CRF/SBP severity (degree and duration). The critical role of cigarette smoking has already been noted. Figure 4 and 5 show that the higher the CRF, the earlier is the average age of ATD onset. However, the duration of time that the patient's CRF-SBP plot has been above the threshold line is also important, as indicated in figure 2A and 2B and figure 4A and 4B. Therefore, a spectrum of ATD risk exists with respect to the degree and duration of the risk factor. A person within any given cohort of CRF-SBP values may be at immediate ATD risk (if the patient has been above the threshold line long enough) or at delayed risk (if the patient has not been above the threshold line long enough). This finding supports the importance of early and repeated testing for ATD risk factors. Obviously, a CRF-SBP plot position in the "pink" areas on the figures 5A-5D, is worrisome and demands immediate treatment, whereas a CRF-SBP plot position in the "yellow" areas is less worrisome, but requires immediate treatment in people aged 60 years and older, and a CRF-SBP plot position in the "green" areas is of little concern, though the author would still treat any CRF of 0.70 or greater, any LDL-cholesterol of 170 mg/dl (4.25 mmoles/L) or greater, (based upon the precipitation method of HDL-cholesterol measurement, but a CRF of 0.60 or higher and/or an LDL-cholesterol of 160 mg/dl [4.0 mmoles/L] or higher if the enzymatic method is used) or a SBP of 140 mmHg or higher. In people aged 60 years or older, the author would treat a CRF of 0.60 or higher (precipitation method, but 0.50 or higher when the enzymatic method of HDL-cholesterol measurement is used), any LDL-cholesterol of 170 mg/dl [4.25 mmoles/L] (precipitation method of HDL-cholesterol measurement, but 160 mg/dl [4.0 mmoles/L] if the enzymatic method is used), and perhaps any CRF-SBP plot above the threshold line.

The results for women are not as good as those for men. There are a number of reasons for this. First, women have smaller coronary arteries than do men, and hence are easier to obstruct. Second, many women in the BGS database did not smoke cigarettes themselves, but had husbands who smoked heavily; such women were exposed to passive cigarette smoking. Passive cigarette smoking is a known risk factor for ATD [53]. Unfortunately, it is not possible to quantitate this effect. Third, several ATD women were taking hormone replacement therapy (HRT), which favorably modifies lipids when the cyclic-sequential formulation is used, but which can create a hypercoagulable state when the continuous-combined formulation is used [54]. If the woman ceases her HRT, her lipids return to pre-treatment levels, and these levels are usually not available to the author. Hence, some women whose lipids on HRT were ideal or almost ideal will have gone on to have ATD events when they stopped taking HRT and their lipids returned to pre-treatment levels. A number of women on continuous-combined HRT had thrombotic ATD events, as was seen in the Heart and Estrogen/Progestin Replacement Study (HERS) [55]. Moreover, arterial thromboses can occur in women due to thrombophilia, as due to the anti-phospholipid syndrome [56] or in conjunction with nonsteroidal anti-inflammatory medications [57]. In the BGS database, ATD events from these two conditions were separate from those induced by continuous-combined HRT. And fourth, dyslipidemia in women classically occurs in the pre-, peri-, and post-menopausal time-frames, and the degree of dyslipidemia in such cases is variable from woman to woman as is the timing of the onset of the dyslipidemia. This has been seen in the BGS, both on a population and individual basis. Hence the length of time the dyslipidemia has been present may be difficult to determine unless prior lipid panels are available for examination. As previously noted, some women have high HDL-cholesterol levels, in the face of high LDL-cholesterol levels, putting them at risk even when the CRF is lower. Finally, vasospasm is a not uncommon event in the coronary arteries and can lead to ATD events, especially in women [58-60].

Using this approach, the author's treated patients have been largely free of ATD events under age 75 years. The last treated non-smoking male patient to sustain an acute myocardial infarction was a 46 year old male with known systemic sclerosis and insulin-dependent diabetes mellitus who contracted pneumonia and sustained a myocardial infarction despite being on a super-statin for six months; this occurred in 2011. The last treated never-smoking female patient to sustain an ATD event was an 85 year old female with carotid stenosis who was deemed to be too frail to be submitted to carotid endarterectomy and who sustained a massive stroke; this occurred in 2015. In 2013, a 66 year old male ex-smoker sustained a fatal intra-cerebral hemorrhage. . In 2017, a 90 year old female with known ATD on statin therapy was forced to walk on an unrecognized hip fracture and sustained an acute myocardial infarction in response to the intense pain that resulted from the forced walking program. The last paralytic stroke to occur in a treated patient did so in 2004—and he had only been in treatment for one month, and was still smoking cigarettes.

The strengths of this study are that it involves a dedicated family physician in one office site over a 43 year time span, with the relative constancy of the population, at least until late 2003. The weakness of this study, however, is not a randomized controlled clinical trial (RCCT)-which would be impossible to perform in any event for ethical/financial reasons. All patients deemed at risk of ATD were offered dyslipidemia therapy; some accepted and some declined. Instead, it is a real world trial, with patients that sometimes leave the author's practice for such reasons as job changes, insurance changes, refusal to accept offered treatment, etc. In light, this study is not as rigorous as a RCCT and cannot be expected to have the same import as a RCCT. The author therefore presents this research as a hypothesis-generating proposal for a better way to predict the population at risk of ATD and invites other researchers to test his hypothesis. Since the various laboratories around the world are not standardized, the various physicians active in the fight to prevent/ameliorate ATD may need to put in their own patients' data into the templates that the author has presented. There are many RCCT's in existence to which the precepts describe here could be applied, and indeed the FHS population could be studied in this fashion.

Conclusion

This paper presents a means of defining the population at risk of ATD. This predictive tool is highly accurate and simple enough in concept to be used in physicians' offices. It requires the measurement of a lipid panel and determination of blood pressure and cigarette smoking status. These parameters are of relatively low cost and make this approach a financially feasible means of predicting and prevent-

ing ATD. Additionally, the graph is a predictive tool that is easily understood by the patient who can track his/her progress by following the course of the CRF-SBP plot in response to therapy. At least in the author's practice, patients understand the concept of plot position above/below the threshold line and if above the threshold line, how far above. Such understanding essential in maintaining the patient's interest in his/her therapy for dyslipidemia and/or hypertension and helps keep him/her taking their medications. Clearly, patients at higher risk would be treated sooner and those at lower risk could be treated later.

In practice, one plots the patient's CRF-SBP plot upon the BGS graph. Any CRF-SBP plot above the threshold line indicates ATD risk. A plot location in the "pink" zone implies immediate danger and hence immediate treatment with a super-statin, whereas a plot location in the "yellow" zone implies intermediate risk and treatment may be urgent depending upon the age of the patient in question . A plot in the 'green" zone implies little ATD risk and the patient may be offered basic lifestyle changes or even no treatment at all, again depending upon the patient's age. (The author would always treat any CRF of 0.70 or higher (precipitation method of HDL-cholesterol testing, or 0.60 if the enzymatic method is used or any LDL-cholesterol of 170 mg/dl or higher (precipitation method of HDL-cholesterol testing, but 160 mg/dl if the enzymatic method is used) or any SBP of 140 mmHg or higher.) This is also evident when using the ATD cumulative risk curves for the various CRF sextiles. Clearly, any cigarette smoking must be halted immediately, and diabetes treated.

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