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Cardiovascular risk factors and models of risk prediction: Recognizing the leadership of Dr Roy Dawber

As one of the first directors of the Framingham Heart Study, Dr Thomas Royle (Roy) Dawber encouraged investigators to focus on identifying risk factors—an approach that has produced exciting results, including tools for risk assessment.

ABSTRACT: Our understanding of cardiovascular risk factors is based largely on work that began with the Framingham Heart Study. Dr Roy Dawber was the director of the study in the early years and eventually authored or coauthored nearly 100 scientific papers on coronary heart disease and other public health issues. Over the past 60 years the Framingham investigations and other works have led to the development of several risk assessment tools, including the Framingham Risk Score, the Reynolds Risk Score, and ETHRISK. Thanks to Dawber and other pioneers, our understanding of cardiovascular risk has evolved far beyond the identification of risk factors to include a more complex understanding of the pathophysiological mechanisms by which these factors cause coronary heart disease. We have also learned that the earlier we intervene to modify risk factors, the better the outcome for our patients.

With the publication of "Factors of risk in the development of coronary heart disease—six year follow-up experience. The Framingham Study" in the *Annals of Internal Medicine* in 1961, coronary heart disease (CHD) became widely known as the leading cause of death in North America. This groundbreaking paper reported new epidemiological findings that suggested the risk of developing CHD was related to hypertension, elevated serum cholesterol levels, and the electrocardiographic pattern of left ventricular hypertrophy (LVH). Today, we take these and many other findings from the Framingham Heart Study (FHS) for granted, but in the early 1960s, they were truly novel. One of the paper's authors was Roy Dawber, director of the FHS from 1949 to 1966, and an important contributor to the study and to our current understanding of cardiovascular risk factors.

Roy Dawber

Born in Duncan, British Columbia, on 18 January 1913, Thomas Royle (Roy) Dawber graduated from Haverford College in Haverford, Pennsylvania, in 1933 and went on to Harvard Medical School, graduating in 1937. Following medical school, he spent 12 years working with the US Coast Guard, ultimately as chief of medicine at the Brighton Marine Hospital near Boston.

In 1948 the US Public Health Service had recruited over 5000 healthy men and women in the town of Framingham, Massachusetts, into the largest epidemiological study of heart disease undertaken to date. Lacking a clear objective initially, the investigation had difficulty engaging the interest of participants and physicians until 1 year into the study, when Dawber was recruited from his position with the Coast Guard to take over as director of the FHS. He recognized that before focusing on CHD prevention,

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the investigators needed to establish factors that contributed to increased risk. With a new direction and focus, the FHS quickly began producing exciting results.

The Framingham Heart Study

The Framingham Heart Study enrolled 5127 men and women, ranging between 30 and 62 years of age, who were free of CHD at the time of initial examination.[1] Participants were drawn from the predominantly white, middle-income town of Framingham, located 30 km east of Boston. Initial enrollment took place from 1948 to 1950. A detailed history was taken and a physical examination and extensive laboratory investigations were performed on each subject at the time of enrollment, and again every second year. A diagnosis of CHD was made subsequently if a patient developed clear symptoms of classic angina pectoris (substernal discomfort of brief duration, definitely related to exertion or emotional upset, promptly relieved by rest, and seldom if ever occurring during periods of quiet or rest), electrocardiogram (ECG) changes of myocardial infarction, or sudden death.

In the landmark 1961 paper describing the follow-up experience at 6 years, Dawber and colleagues examined the incidence of CHD in the FHS population as well as the association between CHD and elevated serum cholesterol levels, hypertension, and the presence of ECG criteria for LVH.[2] In fact, it was this paper that introduced the term "risk factor," and a number of the findings reported in this article have formed the basis of our understanding of cardiovascular risk ever since. The overall incidence of CHD at 6 years was 36.3 per thousand, but there was a marked difference between men and women in this regard: the incidence of CHD in men (n = 2283) at 6 years was 54.8 per thousand, while in women (n = 2844) it was 21.4 per thousand. This gender gap was far more dramatic in the younger age groups than in the older groups, leading the authors to conclude that the protection of female gender was attenuated by menopause.

In the study population, the authors were able to demonstrate an association between serum cholesterol levels and the development of CHD. In men between 40 and 59 years of age, those in the tertile with the highest cholesterol levels had a greater than threefold higher risk of CHD than those in the tertile with the lowest levels. A similar, though less dramatic, trend was seen in women. Elevated blood pressure was also associated with an increased risk of developing CHD among men and women aged 45 to 59 years at time of study entry, with progressive degrees of blood pressure elevation associated with progressively higher risk. Both systolic and diastolic pressures were predictors of CHD, largely due to the high correlation between the two values. Importantly, elevated blood pressure associated with LVH on ECG was associated with a markedly elevated risk of the development of CHD: at 6-year follow-up, one in three men aged 40 to 59 years of age with hypertension and "definite" LVH on ECG had developed CHD, and one in five men in this age group with hypertension and "possible" LVH on ECG had developed the disease. For each level of blood pressure studied, the presence of LVH was associated with a twofold to threefold increase in the incidence of CHD. Hypertension and LVH on ECG, independent of one another, were both strong predictors of CHD development. Finally, by comparing subjects with CHD to those with no risk factors, the study was able to elegantly demonstrate that for both men and women, having any one of the three risk factors (elevated serum cholesterol, hypertension, or LVH on ECG) increased the risk of CHD by a factor of three, having any two doubled that risk, and having all three risk factors doubled the risk again.

In 1966 Dawber accepted a position at Boston University as the chair of preventive medicine. He brought the FHS with him to Boston, where it continued to thrive. In 1971 a second cohort of subjects, consisting of the original cohort's offspring, was enrolled, and in 2002 a third generation was enrolled. In the nearly 5 decades since the study's inception, over 1200 articles have been published in peer-reviewed journals by the FHS group, covering a wide range of cardiovascular and noncardiovascular topics. Dawber personally coauthored nearly 100 scientific articles on CHD and other public health issues, including the association of cigarette smoking, diet, and obesity with the development of CHD,[3-5] and articles about risk factors for cerebrovascular disease and stroke,[6] the significance of solitary thyroid nodules,[7] and the epidemiology of gall bladder disease[8] and gout.[9]

At age 67, Dr Dawber retired to Naples, Florida. An avid sailor, carpenter, and musician, he was known as a modest man despite his many accomplishments. He died 23 November 2005 of complications of Alzheimer disease at the age of 92. His legacy lives on with the continued work of the FHS, where his work laid the foundations for our current understanding of cardiovascular risk and preventive medicine.

After Dawber: The Framingham Risk Score

The identification of the global risk factors for coronary disease in the early large epidemiological studies led to an interest in the identification

of individual patients at risk of developing CHD, and thereafter in the prevention of disease in these persons.[10,11] In 1998 Wilson and colleagues from the FHS published a study that examined the association of Joint National Committee (JNC-V) blood pressure and National Cholesterol Education Program (NCEP) cholesterol categories with CHD risk.[12] A total of 2489 men and 2856 women from the original or the offspring cohort, ranging in age from 30 to 74 years at the time of initial examination, were used in the derivation sample. In addition to noting the association of risk with blood pressure and cholesterol levels, the authors also estimated the relative risk and attributable risk associated with a number of other cardiovascular risk factors, including cigarette smoking, diabetes mellitus, and age. Using a multivariate regression model, the authors produced cardiovascular risk-prediction algorithms based on findings from this study. The product of this work was the Framingham Risk Score (FRS), a measure of the 10-year risk of developing CHD (angina, coronary artery disease, myocardial infarction, and cardiovascular death) and "hard" CHD in asymptomatic persons (coronary artery disease, myocardial infarction, cardiovascular death). The FRS has been validated by the Framingham group and others,[13] and is currently the most widely used risk assessment tool in North America. Points are assigned for each risk category and the total points are then used to assess disease risk for men (**Table 1** and **Table 2**) and for women (**Table 3** and **Table 4**). The relevance of the FRS is demonstrated by its inclusion in major guidelines such as the ACS/ADA/AHA Scientific Statement on Preventing Cancer, Cardiovascular Disease, and Diabetes.[14]

Framingham limitations and alternative risk models

Although it has been a cornerstone of preventive cardiology, the FRS has

Table 1. Estimating 10-year risk of total cardiovascular disease in men (Framingham Heart Study).

Points	Age	HDL-C	Total cholesterol	SBP not treated	SBP treated	Smoker	Diabetic	
−2		>1.6		<120				
−1		1.3–1.6						
0	30–34	1.2–1.3	<4.1	120–129	<120	No	No	
1		0.9–1.2	4.1–5.2	130–139				
2	35–39	<0.9	5.2–6.2	140–159	120–129			
3			6.2–7.2	160+	130–139		Yes	
4			>7.2		140–159	Yes		
5	40–44				160+			
6								
7	45–49							
8	50–54							
9								
10	55–59							
11	60–64							
12								
13	65–69							
14	70–74							
15	75+							Total points
Points alloted								

HDL-C: high-density lipoprotein cholesterol; SBP: systolic blood pressure. This information was originally published in the *Canadian Journal of Cardiology* 2009;25(10):567-579.

Table 2. Cardiovascular disease risk for men.

Points	Risk
−3 or less	<1
−2	1.1%
−1	1.4%
0	1.6%
1	1.9%
2	2.3%
3	2.8%
4	3.3%
5	3.9%
6	4.7%
7	5.6%
8	6.7%
9	7.9%
10	9.4%
11	11.2%
12	13.3%
13	15.6%
14	18.4%
15	21.6%
16	25.3%
17	29.4%
18+	>30.0%

been found to have limitations. One major criticism of the Framingham model has been its lack of generalizability. The Framingham cohort consists of mostly white, middle-class American family members, and it has been questioned whether the results of this study can be applied to other populations, particularly those of other ethnic origins. For example, D'Agostino and colleagues applied the Framingham prediction functions to six prospectively studied and ethnically diverse cohorts. The functions performed well in white and black individuals, but overestimated the risk in Japanese American and Hispanic men and women, and in Native American women.[15] Aarabi and Jackson evaluated a number of prospective longitudinal studies and found that in nondiabetic South Asians in the UK, the risk of CHD was 79% higher than predicted by the Framingham algorithms.[16] To address this issue, a number of other risk-prediction algorithms have been created. The simplest of these suggests that by simply adding 10 years to a South Asian patient's age, the risk of CHD can be adequately assessed.[17] A more complicated model, the ETHRISK scoring system, is based on the Framingham model, but substitutes mean cardiovascular risk factor levels and survival estimates of British minority ethnic groups for those values derived by the Framingham group. It provides a risk assessment model for British people of Indian, Pakistani, Bangladeshi, black Caribbean, Chinese, and Irish descent, and is available as a web-based calculator at www.epi.bris.ac.uk/CVDethrisk/CHD_CVD_form.html.[18]

In addition to underserving certain ethnic groups, the Framingham risk model may underserve women. Studies have suggested that the classic risk factors may be less predictive of CHD events in women than in men, as up to 20% of coronary events in women occur in individuals with none of the traditional risk factors. In recent years, interest has arisen in using a

Table 3. Estimating of 10-year risk of total cardiovascular disease in women (Framingham Heart Study).

Points	Age	HDL-C	Total cholesterol	SBP not treated	SBP treated	Smoker	Diabetic	
−3				<120				
−2		>1.6						
−1		1.3–1.6			<120			
0	30–34	1.2–1.3	<4.1	120–129		No	No	
1		0.9–1.2	4.1–5.2	130–139				
2	35–39	<0.9		140–149	120–129			
3			5.2–6.2		130–139	Yes		
4	40–44		6.2–7.2	150–159			Yes	
5	45–49		>7.2	160+	140–149			
6					150–159			
7	50–54				160+			
8	55–59							
9	60–64							
10	65–69							
11	70–74							
12	75+							Total points
Points alloted								

HDL-C: high-density lipoprotein cholesterol; SBP: systolic blood pressure. This information was originally published in the *Canadian Journal of Cardiology* 2009;25(10):567-579.

Table 4. Cardiovascular disease risk for women.

Points	Risk
−2	<1
−1	1.0%
0	1.2%
1	1.5%
2	1.7%
3	2.0%
4	2.4%
5	2.8%
6	3.3%
7	3.9%
8	4.5%
9	5.3%
10	6.3%
11	7.3%
12	8.6%
13	10.0%
14	11.7%
15	13.7%
16	15.9%
17	18.51%
18	21.5%
19	24.8%
20	27.5%
21+	>30.0%

number of novel biomarkers to predict cardiovascular risk. C-reactive protein (CRP) has emerged as one of the most promising markers. The Reynolds Risk Score (RRS), initially derived and validated in a group of healthy women, predicts cardiovascular events by incorporating high-sensitivity CRP levels, (hs-CRP) and parental history of myocardial infarction before age 60 into a prediction algorithm with traditional risk factors (age, systolic BP, hemoglobin A1C if subject is diabetic, total cholesterol, high-density lipoprotein cholesterol, and smoking status).[19] With the addition of hs-CRP and family history, 40% to 50% of women in intermediate risk categories according to the FHS model (5% to < 10% and 10% to < 20%) were reclassified into higher or lower risk categories. This reclassification resulted in significantly improved predictive accuracy. Like ETHRISK, the RRS is available as a web-based calculator at www.reynoldsriskscore.org.[19]

The success of the RRS for women was followed by the development of a similar algorithm for men. The RRS for men relied on the same factors used in the women's model, and found 16.7% of the study population were reclassified into higher or lower risk categories, again with greater accuracy than with the FHS model.[20] Thus, in both men and women, the addition of hs-CRP and family history resulted in improved accuracy. This finding has been reproduced by a number of researchers, including Wilson and colleagues from the FHS group. Using a Framingham offspring cohort of 3000 men and women, Wilson found that incorporating CRP into the FHS model led to correctly reclassifying a greater number of subjects upwards or downwards into different risk categories than were incorrectly reclassified.[21] Similarly, the QRISK and QRISK2 algorithms, which include family history along with traditional risk factors and other clinical variables, were found to be more accurate predictors of cardiovascular risk than the FHS algorithm in patients from a variety of different ethnic groups living in England and Wales.[22,23]

Longer-term risk prediction

While the Framingham risk-prediction algorithms and other cardiovascular risk models have great clinical value in identifying individual patients at high risk of developing cardiovascular disease, young patients with few risk factors may be falsely reassured by a low-risk estimate early in life. Cardiovascular disease remains the leading cause of morbidity and mortality in the developed world. The already alarmingly high prevalence of cardiovascular risk factors, including diabetes, obesity, and the metabolic syndrome, continue to increase. Rates of cardiovascular mortality are markedly higher than those for any malignancy, and yet more than half of Americans have identified cancer as their "greatest" health risk.[24] Offering patients a longer-term picture of their future cardiovascular risk may provide incentive for earlier risk factor modification and thus greater prevention. From a resource allocation perspective, 10-year risk prediction does not provide adequate long-term data to estimate the burden of future cardiovascular disease on the population and health care system. To address this issue, Framingham data have been used to derive a 30-year risk-prediction model, using standard risk factors.[25] In a group of participants from the Framingham offspring cohort aged 20 to 59 years, researchers found that male sex, systolic BP, antihypertensive treatment, total and high-density lipoprotein cholesterol, smoking, and diabetes mellitus were significantly associated with the incidence of hard cardiovascular outcomes (coronary death, myocardial infarction, and fatal or nonfatal stroke). The calculated risks accounted for the competing risk of noncardiovascular death.

Perhaps an even more powerful tool than the estimation of 30-year risk is that of lifetime risk. A study by the Framingham group demonstrated that among people free of cardiovascular disease at age 50, the lifetime risk of developing disease was 52% in men and 39% in women.[26] The presence of risk factors at age 50 greatly increased this risk, with the presence of diabetes mellitus conferring the greatest risk of any single factor; the risk of cardiovascular disease by age 75 was 67% in diabetic 50-year-old men and 57% in diabetic 50-year-old women. When the overall risk profile was considered, a dramatic increase in risk was seen with increasing risk factor burden. Optimal risk factor levels were defined as total cholesterol less than 4.65 mmol/L, systolic BP less than 120 mm Hg, diastolic BP less than 80 mm Hg, nonsmoking status, and absence of diabetes, while major risk factors included total cholesterol of 6.20 mmol/L and above, systolic BP of 160 mm Hg or higher, diastolic BP of 100 mm Hg or higher, smoking, and diabetes (see **Table 5**[27] and **Table 6** for Canadian lipid and blood pressure targets). Compared with participants with two or more major risk factors, participants with optimal risk factor levels had significantly lower lifetime risks of cardiovascular disease (5.2% versus 68.9% in men and 8.2% versus 50.2% in women). In addition, median survival rates were prolonged by more than 11 years in men with optimal risk factor levels and more than 8 years in women with optimal risk factor levels, compared with individuals of the same sex with two or more major risk factors. This study high-

lights the importance of early prevention; individuals who can maintain an optimal risk profile to age 50 put themselves at markedly reduced risk of cardiovascular disease later in life.

Summary

It is not an overstatement to say that our current understanding of cardiovascular risk assessment is based largely on the many findings of the Framingham Heart Study over the past 60 years, or to say that Dr Roy Dawber's leadership of the study in its early years provided the momentum necessary to carry it forward. His findings in epidemiological studies led to an interest in identifying individuals at increased risk of developing coronary heart disease and in the prevention of disease in these persons.[10,11] Without Dawber's pioneering work in the area of cardiovascular risk factor identification, the aggressive modification of risk factors that we now achieve in our patients would not be possible. Dawber was a leader in public health who made a contribution to our understanding of cardiovascular disease and preventive medicine that has rarely, if ever, been equaled.

Since Dawber's landmark article in 1961, our understanding of cardiovascular risk has evolved far beyond the identification of risk factors to a more complete understanding of the pathophysiological mechanisms by which these factors cause CHD. We are now able to intervene and modify these factors to prevent CHD, and there is clear evidence that the earlier we intervene, the better. Identifying high-risk patients at a young age allows optimization of risk factor profiles at middle age, thus preventing the development of cardiovascular disease later in life. The foundation laid by Dawber over half a century ago remains relevant and continues to support and advance our understanding

Table 5. Canadian Hypertension Education Program (CHEP) blood pressure targets.

Population	SBP Target	DBP Target	Level of evidence
Nondiabetic, chronic kidney disease	< 130 mm Hg	< 80 mm Hg	C
Diabetes mellitus	< 130 mm Hg	< 80 mm Hg	C (SBP), A (DBP)
All other adults	< 140 mm Hg	< 90 mm Hg	C (SBP), A (DBP)

SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 6. Canadian cholesterol guidelines target lipid levels.

Risk level	When to initiate treatment	Primary targets	
		LDL-C	Alternate
High • CAD, PVD, atherosclerosis • Most patients with diabetes • FRS ≥ 20% • RRS ≥ 20%	Consider treatment in all patients	< 2 mmol/L or ≥ 50% ↓ LDL-C Class I, level A	apoB < 0.80 g/L Class I, level A
Moderate • FRS 10%–19%	• LDL-C > 3.5 mmol/L • TC/HDL-C > 5.0 • hs-CRP > 2 mg/L • Men > 50 years • Women > 60 years • Family history and hs-CRP modulates risk	< 2 mmol/L or ≥ 50% ↓ LDL-C Class IIa, level A	apoB < 0.80 g/L Class IIa, level A
Low • FRS < 10%	• LDL-C ≥ 5.0 mmol/L	≥ 50% ↓ LDL-C Class IIa, level A	

apoB: apolipoprotein B level; CAD: coronary artery disease; FRS: Framingham Risk Score; HDL-C: high-density lipoprotein cholesterol; hs-CRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; PVD: peripheral vascular disease; RRS: Reynolds Risk Score; TC: total cholesterol. This information was originally published in the *Canadian Journal of Cardiology* 2009;25(10):567-579.

How to manage your at-risk patients

- Perform risk assessment (FRS, RRS, ETHRISK, or other).
- Review modifiable risk factors (smoking, BP, lipids, blood sugar) and check lipid targets (LDL-C, TC:HDL-C ratio, ± apoB) and BP targets according to risk category.
- Recommend lifestyle modification.
- Provide pharmacological management where necessary.
- Consider referring patients to a prevention clinic, metabolic syndrome clinic, or cardiac rehabilitation clinic where appropriate.

Note that family physicians and general practitioners in British Columbia may be compensated for cardiovascular risk assessment of their patients (i.e., calculating Framingham Risk Score or other risk assessment). The billing code for this is G14034 (Cardiovascular Risk Assessment). For full details and eligibility, refer to the General Practice payment schedule at www.health.gov.bc.ca/msp/infoprac/physbilling/payschedule/index.html.

of cardiovascular risk and preventive medicine.

Competing interests
None declared.

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