New Tools for Coronary Risk Assessment
What Are Their Advantages and Limitations?

Thomas A. Pearson, MD, PhD, MPH

Abstract—The concept of risk assessment and reduction, introduced initially by the Framingham Heart Study and refined in other models, forms the cornerstone of preventive cardiology. Risk factor assessment determines the therapeutic strategy, because the intensity of preventive intervention is tailored to the patient’s risk of coronary heart disease. The conventional risk factors for coronary heart disease include elevated serum total cholesterol and LDL cholesterol, low HDL cholesterol, elevated blood pressure, cigarette smoking, diabetes, vascular disease, menopausal status (women only), and age. Aggressive risk factor reduction, formerly used exclusively in secondary prevention, may be pivotal to optimal patient management in high-risk primary prevention. A number of noninvasive imaging modalities have the potential to measure and to monitor atherosclerosis in asymptomatic individuals and include exercise ECG testing, electron beam computed tomography, magnetic resonance coronary angiography, positron emission tomography, ankle-brachial index, and B-mode ultrasound. Novel serum markers, including C-reactive protein and homocysteine, have the ability to gauge risk in the individual patient. Systemic therapy for risk reduction in primary prevention may be preferable to local therapy (eg, angioplasty and bypass) and may more effectively prevent acute coronary events than these more invasive approaches. (Circulation. 2002;105:886-892.)

Key Words: risk factors ■ heart disease ■ prevention

The Concept of Risk Reduction and Primary Prevention

The concept of risk factors, introduced by the Framingham Heart Study more than 50 years ago, serves as the “gold standard” in risk assessment for coronary heart disease (CHD). Indeed, findings from Framingham have contributed greatly to the recommendations for CHD prevention published by the National Cholesterol Education Program (NCEP).1,2 Risk factor assessment, the first step in primary prevention, guides the therapeutic strategy, because the intensity of preventive efforts is tailored to the patient’s CHD risk status.2 The major risk factors account for >80% of excess risk for premature CHD according to follow-up data from the Multiple Risk Factor Intervention Trial1 (MRFIT) and the Nurses’ Health Study.4

More recently, technological advances in cardiac imaging modalities and novel serum markers have expanded our understanding of the atherosclerotic process and facilitated noninvasive assessment of the coronary and peripheral vasculature. Studies have indicated that the majority of acute coronary events are due to the rupture of early-phase, modest-sized, lipid-rich plaques rather than advanced stenotic lesions.5 Moreover, recent clinical trials with HMG-CoA reductase inhibitors (statins) have shown that lipid lowering reduces the risk of acute coronary events in both primary and secondary prevention, even in patients with average cholesterol levels.6–10 Yet, despite these strides, the Lipid Treatment Assessment Project multicenter survey11 showed that atherosclerosis remains undertreated and that only 38% of patients in clinical practice achieve the target LDL cholesterol levels established by NCEP. Aggressive risk factor reduction, formerly used exclusively in secondary prevention, may be pivotal in optimal patient management in high-risk primary prevention.2

Definition of Risk Refined

The major or “traditional” risk factors identified in Framingham are well known and include elevated serum total and LDL cholesterol, low levels of HDL cholesterol, elevated blood pressure, cigarette smoking, and age.1 Although age per se is not a modifiable CHD risk factor, it relates to the length of time an individual is exposed to risk factors that progressively increase the severity of atherosclerosis and is an important index in the Framingham risk equation.1,12

Additional risk factors for CHD are listed in Table 1.1 Of these, obesity, a family history of premature CHD, and physical inactivity contribute to other risk factors and are now considered major risk factors in their own right.2 Although not included in the Framingham risk equation, their role in the causal pathway leading to CHD provides a strong rationale for their assessment and, as appropriate, their modification.
TABLE 1. Risk Factors for CHD

<table>
<thead>
<tr>
<th>Major Independent Risk Factors</th>
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<tbody>
<tr>
<td>Cigarette smoking</td>
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<tr>
<td>Elevated blood pressure</td>
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<tr>
<td>Elevated serum total and LDL cholesterol</td>
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<tr>
<td>Low serum HDL cholesterol</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Advancing age</td>
</tr>
<tr>
<td>Other (Predisposing) Risk Factors</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Abdominal obesity</td>
</tr>
<tr>
<td>Physical inactivity</td>
</tr>
<tr>
<td>Family history of premature CHD</td>
</tr>
<tr>
<td>Ethnic characteristics</td>
</tr>
<tr>
<td>Psychosocial factors</td>
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<tr>
<td>Conditional risk factors</td>
</tr>
<tr>
<td>Elevated serum triglycerides</td>
</tr>
<tr>
<td>Small LDL particles</td>
</tr>
<tr>
<td>Elevated serum homocysteine</td>
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<tr>
<td>Elevated serum lipoprotein(a)</td>
</tr>
<tr>
<td>Prothrombotic factors (eg, fibrinogen)</td>
</tr>
<tr>
<td>Inflammatory markers (eg, C-reactive protein)</td>
</tr>
</tbody>
</table>

Adapted with permission from Grundy et al.14

Considerations for Global Risk Assessment

Guidelines published by NCEP2 and the Bethesda Conference13 recommend matching the intensity of preventive therapy to absolute risk, defined as the probability of a person developing a hard CHD end point (myocardial infarction [MI] or cardiac death) in the next 10 years. Absolute risk is considered the crucial determinant with regard to whether and when to initiate pharmacological therapy.1 Three categories of absolute risk are identified by NCEP2: (1) very-high-risk candidates for secondary prevention with diagnosed CHD or for primary prevention with vascular disease in noncoronary vascular beds (symptomatic carotid disease, aortic aneurysm, or peripheral arterial disease [PAD]), a high absolute risk (>20% 10-year risk), or diabetes mellitus; (2) moderate-risk candidates for primary prevention with 2 or more risk factors and a 10-year risk of 10% to 20%; and (3) low-risk individuals with 1 or no risk factor.2 However, whereas the accumulation of multiple risk factors may predict the likelihood of a cardiac event in the short term, a single risk factor may increase risk over the long term.14 For example, although a 30-year-old person with a high cholesterol level has a low absolute risk of developing CHD within the next 10 years, he or she has a high relative lifetime risk of developing CHD by age 65 compared with a 30-year-old with low serum cholesterol.15

By contrast, relative risk is defined as the ratio of absolute risk for CHD in a patient with risk factors compared with a person with no risk factors.1,2,15 In other words, relative risk represents the ratio at which absolute risk accrues in a person with 1 or more risk factors.15 Another means of risk assessment, the number needed to treat, uses the difference in absolute risk of patients with versus those without risk factor treatment and calculates the reciprocal to yield the number of patients who must be treated to achieve 1 desirable outcome over a specific time period.16 The number needed to treat therefore links the person’s absolute risk to the cost-effectiveness of various risk modifications.

The Framingham scoring system considers individual risk factors as additive in their predictive power.1 Global risk is cumulative and can be determined by calculating the number of Framingham points assigned to each risk factor (Tables 2 and 3).1,14 The advantage of using a system of graded risk factors (as opposed to the NCEP risk factor system comprising 3 broad risk factor categories) is that it provides a more comprehensive estimate of global risk. Thus, the assessment of global risk should be more accurate in patients in whom multiple, moderately elevated risk factors predominate in the absence of 1 or more greatly elevated risk factors.17 Calculations of short-term (or absolute) versus long-term (lifetime) risk do influence therapeutic decision-making in the context of primary prevention. High-risk status, defined as the probability of developing CHD within the next 10 years, has been used to justify initiation of pharmacological therapy in primary prevention.17 Debate centers around whether the risk of an acute coronary event in an asymptomatic, high-risk person outweighs the potential side effects and treatment costs. As an example, current European guidelines and the NCEP Adult Treatment Panel III guidelines recommend initiation of therapeutic strategies equivalent to those for secondary prevention (ie, drug therapy) when the probability of developing CHD reaches 20% per 10 years or if the person’s risk projected to age 60 reaches that level.2,18 However, in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), the relative risk of an acute coronary event was decreased by 40% with statin therapy in patients with an average absolute risk at baseline far lower than 20% per decade.10 Thus, efficacy alone may not be enough rationale to initiate therapy.

Risk Assessment With Noninvasive Imaging and Novel Serum Markers

Noninvasive imaging techniques and novel serum markers have the potential to directly or indirectly measure and monitor atherosclerosis in asymptomatic individuals and to empirically identify appropriate candidates for aggressive primary prevention.19 These may be best used after global risk assessment with traditional risk factors, to identify persons at moderate risk (eg, 10-year risk of 10% to 20%) for whom additional testing may resolve whether or not they are at high risk and deserving of aggressive intervention.

Noninvasive Imaging: Cardiodiagnostic Modalities

Exercise ECG Testing

In asymptomatic persons, exercise ECG testing generates a high rate of false-positive responses and is thus not considered suitable as a widespread population screening tool (Figure).20 However, an ischemic ECG response at low workloads in asymptomatic patients has been associated with a higher risk of cardiac events.20 Although ST depression ≥1 mm within 6 minutes on the Bruce protocol has been
linked to an increased relative risk of cardiovascular events in men, the absolute risk in the absence of risk factors is low. However, in asymptomatic patients with at least 1 risk factor, exercise ECG testing may be prognostically useful. In men with 1 or more CHD risk factors and 2 abnormalities on exercise testing, a 30-fold increase in 5-year cardiac risk was reported compared with men with no risk factors. Similarly, a 4-fold increase in 7-year CHD mortality was observed among middle-aged men with an abnormal exercise ECG in conjunction with CHD risk factors in the MRFIT database.

Routine use of exercise ECG to screen unselected asymptomatic patients before in-office risk assessment is not recommended. At present, the role of exercise ECG is limited to the cardiovascular workup of asymptomatic men >40 years old with 1 or more risk factors in whom a vigorous exercise program is being considered, in the absence of contraindications to exercise testing. Additional data are required before exercise testing can be recommended in women and the elderly (>75 years old).

Electron Beam Computed Tomography

Electron beam computed tomography (EBCT) is a highly sensitive modality for quantifying calcium, a marker of atherosclerosis within the coronary vasculature, particularly within the context of multivessel disease. EBCT generates scans more rapidly than helical computed tomography through the use of an electron beam and a stationary tungsten target. However, the correlation between arterial calcification and the risk of plaque rupture has not been established, and EBCT is not yet considered suitable for widespread population screening.

Compared with invasive modalities such as intravascular ultrasound, EBCT is less sensitive in detection of single-vessel disease. In other words, vulnerable plaque and severe coronary artery stenosis may be present even in the absence of calcium. In general, however, a high calcium score indicates the probability of vulnerable plaques but fails to identify the site of specific vulnerable lesions. Although EBCT has been associated with sensitivities as high as 95% for the detection of any 50% narrowing, its specificity (ranging from 45% to 50%) is well below that desired in a screening test. Unfortunately, despite these limitations, the use of EBCT to evaluate asymptomatic individuals for risk of developing obstructive CHD has been highly commercialized over the past 10 years.

Opinion is divided over whether EBCT adds to the prognostic information provided by the Framingham risk assessment score, particularly given that EBCT has a low predictive value for acute coronary events. For example, it has been suggested that if the coronary plaque burden could be estimated noninvasively with EBCT, the technique might replace age, a surrogate for coronary plaque burden in the Framingham risk equation, as a risk factor. Several studies support the prognostic value of EBCT compared with traditional risk factors. However, a large study showed that the EBCT calcium score did not contribute additional information to the traditional Framingham risk assessment in predicting future coronary events in high-risk individuals. Although EBCT provides a sensitive measure of coronary artery calcification, its ability to predict coronary events better than traditional risk factor assessment is debatable. However, a major limitation of EBCT, poor reproducibility between scans, appears to have been overcome by the introduction of a new volumetric scoring system useful in detecting small lesions. With this system, EBCT was able to detect the regression of atherosclerotic lesions in response to lipid-lowering therapy. Therefore, serial EBCT may evolve into an important modality if additional studies demonstrate that differences in calcium scores over time, particularly in response to lipid-lowering therapy, correlate with differences in the rate of coronary events.

A recent consensus statement concluded that insufficient data exist to recommend EBCT for general population screening or routine clinical use. Furthermore, EBCT alone does not provide enough information to diagnose obstructive coronary artery disease owing to its low specificity (high percentage of false-positive results). In fact, a high calcium score on EBCT frequently leads to invasive and expensive tests and subsequent revascularization (eg, angioplasty or bypass), thereby creating a coronary event in an asymptomatic individual.

Magnetic Resonance Coronary Angiography

Primarily a research tool, magnetic resonance coronary angiography (MRCA) is still under investigation. MRCA has shown promise in detecting large stenoses and may overcome the obstacle of motion artifact to provide 3D visualization of the coronary arteries. The sensitivity and specificity of MRCA have not been established because results of small-scale studies are conflicting. Sensitivity and specificity are highly variable, with sensitivities of 50% and 100% and specificities of 80% and 90% reported in the detection of left anterior descending stenoses. However, MRCA has the potential to image plaque composition and size, thereby specifically pinpointing areas vulnerable to rupture. Unfortunately, MRCA cannot accurately detect smaller stenoses, an important determinant of risk in primary prevention.

Positron Emission Tomography

Positron emission tomography (PET) can be used to assess coronary flow and flow reserve; however, its use is limited by its inability to detect coronary stenosis <50%. In studies of patients with hypercholesterolemia, PET has documented decreased myocardial blood flow in conjunction with increased serum and LDL cholesterol and improved flow reserve after lipid-lowering therapy. In the future, PET may have a role in the detection of early endothelial dysfunction and in the noninvasive monitoring of aggressive lipid-lowering therapy and risk factor modification in asymptomatic high-risk patients.

Noninvasive Imaging: Extracoronary Vascular Modalities

Ankle-Brachial Blood Pressure Index Testing

A simple and inexpensive diagnostic test, ankle-brachial blood pressure index (ABI) testing requires only a blood pressure cuff and a Doppler ultrasonic sensor to reliably identify lower-extremity PAD in asymptomatic persons ≥50 years. The systolic pressure in both arms is taken with the
blood pressure cuff and Doppler probe, averaged, and divided into the systolic blood pressure in the posterior tibial or dorsalis pedis artery in the leg. The higher reading is used to determine the ABI. ABI should be calculated separately for each leg. An ABI <0.90 in either leg indicates PAD; the lower the ABI value, the more severe the obstruction.19 ABI-detectable PAD has been shown to correlate with a higher prevalence of CHD, which confirms that atherosclerosis is a systemic disease in which PAD signifies disease throughout the vasculature.31 An effective screening modality, ABI testing identifies macrovascular disease between the heart and legs. When performed by well-trained technicians, the accuracy of ABI testing for stenosis ≥50% in leg arteries is high (sensitivity ≈90% and specificity ≈98%).19

An abnormal ABI adds to the information provided by a traditional risk assessment and elevates asymptomatic patients to a higher risk category, justifying therapeutic intervention in primary prevention equivalent to that of secondary prevention. ABI testing is particularly useful in patients with multiple risk factors for CHD, such as smokers or those with diabetes mellitus.

### B-Mode Ultrasound

B-mode ultrasound is a safe, noninvasive, and relatively inexpensive technique for the visualization of intima-media thickness (IMT) in the lumen and selected arteries, including the carotid, aortic, and femoral arteries.19 At least 5 studies have demonstrated that carotid IMT measurement correlates with the presence of coronary atherosclerosis and represents an independent risk factor for CHD events and stroke. Impressive data from 2 large studies32,33 in >15 000 persons without CHD at baseline showed that the higher the IMT, the greater the risk of MI or stroke. At present, it has been established that carotid IMT is an independent predictor of

<table>
<thead>
<tr>
<th>TABLE 2. Global Risk Assessment Scoring (Estimates From Framingham Scores)</th>
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<tbody>
<tr>
<td>Points</td>
</tr>
<tr>
<td>Age, y</td>
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<tr>
<td>Risk Factors</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>20–34</td>
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<td>35–39</td>
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<td>65–69</td>
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<td>70–74</td>
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<tr>
<td>75–79</td>
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<tr>
<td>Total cholesterol, mg/dL</td>
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<tr>
<td>200–239</td>
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<tr>
<td>240–279</td>
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<tr>
<td>≥280</td>
</tr>
<tr>
<td>Nonsmoker</td>
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<tr>
<td>Smoker</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
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<tr>
<td>≥60</td>
</tr>
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<td>50–59</td>
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<tr>
<td>40–49</td>
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<tr>
<td>&lt;40</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>&lt;120</td>
</tr>
<tr>
<td>120–129</td>
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<tr>
<td>130–139</td>
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<tr>
<td>140–159</td>
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<tr>
<td>≥160</td>
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</table>
transient cerebral ischemia, stroke, and coronary events such as MI. Serial B-mode ultrasound measures of the carotid artery also have the potential to monitor changes in IMT in response to therapy. However, standardized protocols for serial IMT measurements from controlled clinical trials require considerable technician training and quality control before B-mode ultrasound can be widely used in the clinical follow-up of patients undergoing lipid-lowering therapy.19

**Serum Markers**

New lipid and lipoprotein fractions such as small dense LDL particles, apolipoproteins A1 and B, HDL subfractions, and lipoprotein(a) have been associated with CHD risk but are not believed to give reliable measures or to substantially improve sensitivity to justify general clinical use. Two novel serum markers, C-reactive protein (CRP) and homocysteine, have been studied to determine their usefulness in risk assessment.

**C-Reactive Protein**

CRP is an established marker of low-grade systemic inflammation, reflecting elevated levels of proinflammatory cytokines such as interleukin-6.34 Other inflammatory markers include fibrinogen, interleukins, and vascular adhesion molecules. Of these markers, CRP can be measured in serum with highly sensitive, cost-effective, standardized assays that meet the standards established by the World Health Organization.34 The assays useful in risk assessment are those highly sensitive for CRP (hs-CRP) that measure gradations of CRP previously considered within the range of normal.

The association of CRP with cardiovascular disease has been documented in 2 large studies: the Physicians’ Health Study35 and the Women’s Health Study.36 In the Physicians’ Health Study, physicians in the highest quartile of hs-CRP at baseline had a 2-fold higher risk of stroke, a 3-fold higher risk

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**TABLE 2. Continued**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Points</th>
<th>Age, y</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td></td>
<td>20–39</td>
<td>40–49</td>
</tr>
</tbody>
</table>

**Women**

**Age**

- 20–34: −7
- 35–39: −3
- 40–44: 0
- 45–49: 3
- 50–54: 6
- 55–59: 8
- 60–64: 10
- 65–69: 12
- 70–74: 14
- 75–79: 16

**Total cholesterol, mg/dL**

- <160: 0, 0, 0, 0, 0
- 160–199: 4, 3, 2, 1, 0
- 200–239: 8, 6, 4, 2, 1
- 240–279: 11, 8, 5, 3, 2
- ≥280: 13, 10, 7, 4, 2

**Nonsmoker**

- 0, 0, 0, 0, 0

**Smoker**

- 9, 7, 4, 2, 1

**HDL cholesterol, mg/dL**

- ≥60: −1
- 50–59: 0
- 40–49: 1
- <40: 2

**Systolic blood pressure, mm Hg**

- <120: 0, 0
- 120–129: 1, 3
- 130–139: 2, 4
- 140–159: 3, 5
- ≥160: 4, 6

Adapted from JAMA.2
of MI, and a 4-fold higher risk of severe PAD. Furthermore, the risk associated with hs-CRP was independent of other CHD risk factors. Similar results were reported in the Women’s Health Study, a cohort of women who were asymptomatic at baseline.

In addition, the secondary prevention Cholesterol And Recurrent Events trial demonstrated that CRP elevation was associated with higher risk for recurrence of cardiovascular events: the risk was 75% at the highest hs-CRP level compared with 13% at the lowest hs-CRP level. Risk reduction was greatest (54%) in statin-treated patients with evidence of inflammation as indicated by elevated CRP, whereas risk reduction was less (25%) in those without elevation in CRP. Whether these results obtained in secondary prevention can be extrapolated to primary prevention was studied in AFCAPS/TexCAPS, in which an elevated hs-CRP added to risk estimation and identified a subgroup with relatively low lipid levels who still benefited from statin therapy. However, routine measurement of CRP is not currently recommended by the American Heart Association pending the results of further studies.

Homocysteine
Elevated serum homocysteine levels have been shown to correlate with CHD risk in cross-sectional studies, although data are conflicting in prospective studies. As a result, routine general population screening for homocysteine levels is not recommended. However, homocysteine testing should be considered in CHD patients who have no CHD risk factors and in asymptomatic patients with a strong family history of premature CHD. Patients with elevated homocysteine levels should be advised to consume the recommended dietary allowance of folic acid.

Conclusions
The concept of risk assessment and reduction, initially introduced by the Framingham Heart Study and refined in other models, forms the cornerstone of patient management directed toward lowering the incidence of acute coronary events. The advent of newer, noninvasive imaging techniques and serum markers extends comprehensive risk assessment and aggressive therapeutic management to asymptomatic high-risk individuals. Improved risk assessment and more sensitive noninvasive imaging techniques have obscured the line between primary and secondary prevention. Systemic lipid-lowering therapy for hyperlipidemia may be preferable to local therapy (eg, angioplasty and bypass) because it appears to more effectively prevent coronary events and death than these more invasive approaches.

References

TABLE 3. Adding up the Points

<table>
<thead>
<tr>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Point Total</td>
<td>10-Year Risk, %</td>
</tr>
<tr>
<td>&lt;0</td>
<td>&lt;1</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
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<tr>
<td>1</td>
<td>1</td>
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<td>2</td>
<td>1</td>
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<td>4</td>
<td>1</td>
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<td>5</td>
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<td>20</td>
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<tr>
<td>16</td>
<td>25</td>
</tr>
<tr>
<td>≥17</td>
<td>≥30</td>
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