Are Biomarkers Necessary to Detect At-Risk Patients?

Agonist

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Cardiovascular risk stratification using traditional risk factors cannot fully explain the development of cardiovascular disease in a community; most patients who develop a heart disease have one or no risk factors such as smoking, high blood pressure, dysplidemia and diabetes, 43% have one risk factor, and 20% have none.

Risk prediction is even more difficult in young populations, since the earlier the event occurs in life, the less conventional factors are present. (1)

Improving the calculation of risk has a high clinical value, both for predicting risk of cardiovascular disease and improving the goal of preventive measures. This is also difficult, since scores based on traditional risk factors fail in detecting individuals at risk for stroke or coronary heart disease. Prospective studies revealed that the Framingham score overestimates the risk for stroke and coronary heart disease in certain populations.

The ROC curve (receiver operating characteristic curve) is a statistical resource that explores the relationship between the sensitivity and specificity of a test, and it is often very useful to assess the efficacy of a diagnostic test based on the sensitivity and specificity of its different critical values. It showed that the predictive value of the Framingham score is poor in the case of women, the elderly, or in people with an early history of heart disease. (2)

That is why new biomarkers have been assessed to stratify the risk in patients, to reclassify them, or to adapt a treatment, both in primary and secondary prevention. Biomarkers are non-specific acute phase reactants used for risk identification including fibrinogen, serum amyloid A protein, and C-reactive protein (CRP), which increase in patients with CVD. (3-8)

Furthermore, established risk factors do not directly reflect myocardial damage, left ventricular dysfunction, renal failure or inflammation. If biomarkers were added to identify those pathophysiologic pathways, we would have more information on risk of death and heart disease.

The interest increased after the publication of the JUPITER study, which revealed that statin therapy reduces cardiovascular risk in patients with low LDL cholesterol and high CRP. (9)

The CRP –the most studied– is an independent prognostic marker of cardiovascular risk, which is associated with coronary heart disease in large populations. (4-10) The MRFIT trial (Multiple Risk Factor Intervention Trial) was the first to detect the significant association of the CRP levels with ischemic heart disease and death independent from smoking. It revealed that apparently healthy subjects with no ischemic events had a plasma concentration of CRP of 2.0 mg/L versus 2.7 mg/L in those who survived an AMI, and 3.34 mg/L in those who died, with a difference of 2.8 between the highest and the lowest quartiles. (10)

In the epidemiological study Physicians' Health Study, the CRP in apparently healthy middle-aged men is significantly associated with risk of heart attack and stroke. (11)

As for its use in secondary prevention, we know that cholesterol is not the only factor to be treated, and this is demonstrated in the PROVE IT study; statin therapy reduced LDL and CRP in patients with acute coronary syndrome, what proves that the lower these two parameters are, the lower the rate of events will be. (12)

These data are used to create the Reynolds risk score, which, as opposed to the Framingham score, includes family history and CRP when calculating the risk; it allows us to relcassify nearly 40% of the patients with great implication in preventive treatment. (13)

Not only has the CRP been studied; the brain natriuretic peptide (BNP) is an accurate marker of heart failure, and its magnitude can reflect the severity of ischemia. Another biomarker of increased interest is the lipoprotein associated phospholipase A2, because it can be inhibited by certain drugs. (14, 15)

The combined use of biomarkers, like CRP, BNP, urinary albumin, homocysteine, and renin, allowed to establish a score to predict disease and death. Individuals with a high score of multiple markers had a high risk for death and cardiovascular events. Anyway, it should be pointed out that the use of this type of multiple markers did not increase very much the possibility to classify at risk on conventional risk factors. (16)

Another significant point is that, with the use of biomarkers, we can reclassify intermediate-risk patients; in the Framingham score –which includes the CRP–, 25% of the patients are reclassified.

All this evidence allows us to analyze that they are useful for intermediate-risk patients in order to reclassify them into high-risk/low-risk patients or in

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elderly patients, to decide how aggressive we should be in primary prevention, to detect risk groups, and to design more specific therapies.

Anyway, we are currently far from being able to use them massively.

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Antagonist

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"All that glitters is not gold,
and all that is gold does not glitter."

ANONYMOUS

For years, traditional risk factors have enabled us to rate the individual global risk in daily practice in a relatively acceptable way; however, a large proportion of individuals with events have one or few risk factors. To improve risk prediction, which is the cornerstone in the cost-effectiveness of prevention, the interest in different biomarkers has increased in order to better categorize the risk and identify individuals who will have events.

It is unquestionnable that inflammation constitutes a tested clinical scenario in the genesis of cardiovascular disease. However, the question is not whether or not inflammation plays a role, but if biomarkers are necessary to identify those individuals in a more accurate way.

As we all know, traditional factors are part of scores –like the Framingham score– that resulted from cohorts in which the impact of different variables on cardiovascular risk was assessed.

These scores, simple and economic, better reflect middle-aged patient populations, and show deficiencies in both young and elderly subjects. In addition, they are less accurate, and often underestimate the risk in women or in individuals with only one –but very high– risk factor.

Despite these weaknesses of traditional factors, it is very difficult to optimize its predictive capacity, even with the use of many additional simultaneous strategies.

Biomarkers need to meet certain features to test their ability: information from prospective studies,

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strength of association with vascular disease, independence of association with respect to other factors, standardized, accessible and reproducible measurement, , biological sense, additional predictability to traditional factors, and possibility of modification. Finally, if its modification changes the risk, causality between factor and disease will be defined.

The biomarker that meets most of these requirements is the ultrasensitive CRP. While the CRP is associated with cardiovascular disease with relative risks of 1.58 with a level > 3 mg/L versus < 1 mg/L, it is not enough to define its routine use. The biomarker should be able to modify risk rating, so that it leads to some change in clinical behaviors that will result in the reduction of events.

MEASURING THE BIOMARKER'S ABILITY TO ADD VALUE

The improvement of the area under the ROC curve with respect to the area linked to traditional factors indicates the ability of the explored biomarker to add information to that of the traditional factors.

While in some studies the ROC curve shows some improvement with the CRP, the majority of the trials show identical values or minor modifications after its addition. The ARIC trial assessed the CRP in 15,792 individuals; the ROC curve improved from 0.767 to 0.770, a difference that was not statistically significant. (1) The modification for the addition of CRP was 0.735 to 0.750 in the Koenig study, 0.64 to 0.65 in the Danesh study, 0.773 to 0.777 in the Rotterdam study, 0.705 to 0.706 in the Quebec study, and the value remained the same, 0.74, in Framingham Offspring. (1In a recent study in which several biomarkers were assessed, including CRP, individually and collectively, the ROC curve for cardiovascular events increased from 0.758 to 0.765, and for coronary events, from 0.760 to 0.769 (ns). (2)

In addition to the ROC curve, new statistical resources are used to assess the contribution of biomarkers to traditional risk prediction models. (3) These are the NRI (net reclassification improvement), which considers the cases that, being in a particular risk category, change to another category, and IDI (integrated discrimination improvement), which considers the change in probability of the subject as a continuous variable.

HOW MUCH INFORMATION DO BIOMARKERS REALLY ADD?

A study explored several biomarkers, including CRP and pro-BNP, in 5,067 patients. (2) The proportion of patients that could be reclassified by the addition of biomarkers was only 8%. NRI improvement was not significant in the general cohort. Only when it was used in the subgroup of intermediate risk individuals there was a predictive improvement of 7% for cardiovascular events, and of 14% for coronary events, with wide confidence intervals. Interestingly, reclassification was confined almost entirely to a decreasing recategorization of individuals who had no events, rather than to an increasing reclassification of those who had been classified as low risk patients and had had events (only 0.8%). The rates for cardiovascular events were 2%, 11% and 24% for low, intermediate and high risk categories respectively when traditional factors were used, and 2%, 11% and 25% when biomarkers were added. Regarding coronary events, rates were 2%, 9% and 27% with traditional risk factors alone, and 2%, 10% and 23% when biomarkers were added. The advantage of adding biomarkers was minimal, and was restricted to that intermediate risk group mainly through the identification of those who had no events. (2)

Similar outcomes were obtained when evaluating 3,209 individuals from the Framingham Heart Study, in which a set of biomarkers added minimum capacity to differentiate risk from traditional factors. (4) In 5,808 individuals from the Cardiovascular Health Study, 6 biomarkers did not add additional value to traditional factors. (5) In the Physicians' Health Study, NRI improvement for cardiovascular events was only 3.2% when biomarkers were added, and in 3,006 patients from the Framingham Heart Study, no ROC curve improvement was objectified, and NRI improvement was only 5.6% for cardiovascular events, and 11% for coronary events. (6)

Conversely, in very homogeneous, high-risk and old cohorts, outcomes with biomarkers were somewhat more favorable; when analyzing only elderly subjects, age restrictiveness reduces or mitigates the impact of this variable on the predictive model of traditional factors, which in turn work worse for elderly subjects than for middle-aged or wide-age range subjects. (7)

CONTROVERSIAL ISSUES OF BIOMARKERS

- In prospective studies of physical exercise, moderate to high doses of exercise were not associated with CRP reduction, even when patients significantly increased their maximumVO_2[8]. (8) While CRP in subjects who exercise regularly is usually lower –on average– than in resting controls from cross-sectional studies, this would be connected to the fact that these individuals are healthier, with lower body weight and fat mass –parameters associated with lower CRP. Moreover, intense exercise is associated with increases in CRP and other markers during the following 12-48 hours of having practised it. For this reason, individuals who exercise intensively 5-6 times a week may have high CRP levels. This represents a 'confusing' factor if the risk according to CRP is categorized in very active individuals, who have high CRP with no real increase of cardiovascular risk. (9, 10)
- There are significant differences in CRP levels among races –despite covariate adjustments– which require standardizations if the association between CRP level and cardiovascular risk is to be properly valued. (11)

– Since it is nonspecific, the CRP may be high due to infections, inflammatory conditions, or other 'non-cardiovascular' sources of increase.
– In a study that analyzed CRP polymorphisms in 50,800 individuals, four variants were identified and associated with high CRP levels (genetically elevated CRP). Although CRP levels were associated with increased vascular risk in the overall cohort, subjects with genetically elevated CRP had no more clinical events. (12)
– Even considering that biomarkers add information, what should we do in the case of a patient with high CRP who was already indicated statins, if, when controlled, CRP remains high? Should we increase the statin, change to a more potent statin, associate a second lipid-lowering drug, use aspirin? What if we assess several biomarkers (CRP, BNP) and some are low and others high?
– While CRP variability is acceptable, it is required to make two separate dosages for a period of at least two weeks in order to establish the reliability of the result.

In short, the absence of correlation between CRP and prospective studies of exercise, the strong association with traditional risk factors, the non-cardiovascular sources of high CRP, and the variability in different ethnic groups and in the individual are some of the most controversial aspects; besides, the distribution of biomarker levels in patients with and without vascular events shows significant overlaps.

OTHER BIOMARKERS

Despite the relative risk of 1.7 for vascular disease and 1.4 for average coronary heart disease, the homocysteine failed in randomized controlled trials like VISP, NORVIT, CHAOS 2, HOPE 2, and SEARCH, since its reduction was not associated with improvement in clinical events.

Fibrinogen, although it is associatied with cardiovascular risk, changes throughout the year on a seasonal basis, with stress, thyroid dysfunction, weight changes, or drugs, making it a factor with high variability. In contrast, the Lp(a) –extremely stable– would only bring additional information in patients with early vascular disease and no traditional risk factors, familial hypercholesterolemia, or family history. Its routine use is discouraged, Class III recommendation (should not be performed) and level of evidence A. (13) Low adiponectin level is associated with type 2 diabetes and vascular risk. Despite the data on this inverse association of the risk (the lower the adiponectin, the higher the risk), when adjusted by lipid variables –especially HDL and Apo A– its predictive ability is attenuated. (14)

Neopterin, metalloproteinase-9, and PAPP-A (pregnancy-associated plasma protein) are some of the most promising new biomarkers, although no information is available for their use in daily practice.

SOME CURRENT RECOMMENDATIONS

Recently, the summaries of the Task Force were published, regarding the following:

1. CRP as risk factor (15): CRP levels are independently associated with vascular risk, but this does not ensure that CRP is useful for reclassification of risk. The strength of evidence of using CRP in patients at intermediate risk is moderate, and there is not enough evidence to causally link CRP levels to clinical events.
2. All biomarkers (including CRP) (16): when assessing the CRP in intermediate risk patients, about 11% of men could be reassigned into high-risk categories; it is estimated that this reassignment would avoid 0.47 events per year, every 100 men between 40-79 years of age.

However, the net benefit is uncertain, since the harms of the assessment and the long term prescription of drugs in patients who would have been wrongly reclassified as high risk patients is unkown. The evidence is insufficient to determine the ultimate effect of this contribution in the occurrence of clinical events.

In a summary for patients, (17) experts concluded that the information that values the benefits and risks of routine assessment of biomarkers is insufficient to rate the risk of vascular events in healthy people.

Recently, the National Academy of Biochemistry produced a recommendation after analyzing the evidence of the use of biomarkers, concluding that CRP in intermediate risk patients (13)

provides modest information because it can only reclassify less than 10% of the individuals.

SO WHAT CAN WE DO WHEN HAVING TO CATEGORIZE THE RISK OF AN INDIVIDUAL PATIENT?

The use of biomarkers to categorize the risk beyond traditional factors is unnecessary in patients with low cardiovascular risk; even high CRP values are unable to recategorize the patient in a different risk segment, therefore criteria are not changed. In this case, we should encourage the patient to keep healthy habits.

At the other extreme, the use of biomarkers –despite their additional predictive ability– is not recommended for very high-risk elderly patients with previous AMI and diabetes, since these are individuals with known high prevalence of events.

The controversy is then focused only on individuals categorized as intermediate risk by traditional factors. The use of ultrasensitive CRP in this subgroup modestly improved reclassification in 7-10%, and above all, allowed reclassification of individuals who had no events in lower risk categories rather than recategorization in those initially classified as lower risk in higher risk categories.

The modest intervention allows doctors to use biomarkers at their discretion and wisdom. Biomarkers assessment may require time, effort and costs, and may

represent a lost opportunity to provide other tried-and-true beneficial health services.

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Declaration of conflict of interests

The author declares she does not have a conflict of interests.

AGONIST'S REPLY

Although all that glitters is not gold, there is no smoke without fire.

I agree with Dr. Melina Huerin in that any intervention performed in the medical practice should be at the discretion and wisdom of the physician, and one of them is the use of biomarkers. We know that a large proportion of individuals with events have one or few risk factors, and that inflammation is proved in the genesis of the cardiovascular disease; therefore, the use of biomarkers is a tool to identify, categorize, reclassify, and optimize, which we should not discard when treating patients.

In addition, scores fail where biomarkers can be useful, as in young people, women, and the elderly, and cardiovascular disease is increasingly prevalent in these groups.

If the CRP measurement is high in individuals who perform physical activity 5-6 times a week, and its use may be a confounding factor, the question is: in a patient with a low pretest, what am I going to use it for?

It is surprising that Dr. Ridker's works are not included in the references, which show that CRP levels are independently associated with cardiovascular risk, and this allows to reclassify patients with new scores and design more specific treatments.

New biomarkers in groups of patients in which there is evidence that they are useful are an extremely valid tool that allows the phisycian to make decisions.

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ANTAGONIST'S REPLY

Two publications with 122,458 and 386,915 individuals from 17 studies have found out that 80-90% of subjects who develop coronary heart disease have at least one of the four traditional factors.

With respect to the Reynolds score –with which "40% women can be reclassified" from a total of 24,558 women–, if figures are carefully analyzed we see that 10% of the women with 5-10% estimated risk (81 women) and 12% with 10-20% (38 women) were changed to higher risk categories with the Reynolds score. This means that 119 of 8,148 women –1.8% of the total or 10.7% of those from the intermediate risk segment– were reclassified as high risk.

The JUPITER study said that individuals with high CRP could benefit from statin therapy. Making a critical analysis of the data, the patients included were a mean age of 66 years, had a systolic blood pressure of 134 mm Hg on average, a BMI of 28.4, more than half of them had a Framingham score > 10%, 15% of them were

smokers, 40% had metabolic syndrome, 25% were obese, 40% were on lipid-lowering therapy, and more than 25% were on antihypertensive therapy. Is it really the high CRP which provides critical information, or was it that statins would have a positive impact on intermediate risk patients who are out of recommendations, beyond their CRP? The JUPITER study did not assess the CRP impact to define risk, since it did not compare patients whose CRP guided the criteria versus patients whose CRP was not measured; all patients had CRP. JUPITER did not assess CRP; it assessed statins.

The event rates according to LDL and CRP reached in the JUPITER study are:

Target reached	Event rate (%)	HR (CI 95% ajusted)
LDL ≥ 70 and CRP < 2	0.54	0.42 (0.18-0.94)
LDL ≥ 70 and CRP < 1	0.64	0.46 (0.11-1.85)

Contrary to what was expected, the event rate with CRP < 2 was lower than that with CRP < 1 mg/L, and the confidence intervals cross the unit.

When analyzing the 3,745 patients enrolled in PROVE IT TIMI 22, the event rate in those who achieved LDL ≤ 70 was identical whether they reached PCR ≥ 2 or PCR ≥ 1, 3.1% in both cases.

In short, measurement of biomarkers should not be a routine, but be limited to selected patients, especially with intermediate risk by traditional risk factors. The ability of biomarkers to improve predictive models is limited, even for this segment of patients. The net benefit of using biomarkers is uncertain, since the harm of their assessment and of the possible drug therapy prescribed as a result of them is unknown. Further evidence that sustains the use of these biomarkers or others currently under research is necessary.

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