Pharmacologic stress testing: New methods and new agents

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Pharmacologic stress testing in combination with radionuclide myocardial perfusion imaging (MPI) is a widely used noninvasive method for the evaluation of known or suspected coronary artery disease (CAD). This technique has extended stress testing to patients unable to perform maximal exercise and has contributed to the substantial growth of nuclear cardiology. It is estimated that pharmacologic stress testing now accounts for approximately 40% of all MPI studies performed in the United States annually.[1]

Pharmacologic stress MPI may be divided into two categories based on the mechanism of action of the stress agent: coronary vasodilating agents (eg, dipyridamole and adenosine) and catecholamines (eg, dobutamine). Vasodilators work directly on coronary arteries to increase blood flow, creating flow disparities that may then be imaged. Catecholamines, such as dobutamine, are positive inotropic and chronotropic agents that increase cardiac workload and potentially cause myocardial ischemia.

All of the currently used pharmacologic agents in MPI have well-documented diagnostic value and during the past decade have also been shown to have substantial utility for risk assessment and the prediction of cardiac events. In addition, with the increasing use of noninvasive testing in elderly patients and in patients with comorbid conditions that preclude adequate exercise, pharmacologic testing has become an indispensable tool for radionuclide MPI studies.

The purpose of this article is to review the experience with currently available stress agents and newer protocols, as well as to describe active research on new vasodilators that possess the potential to serve as new pharmacologic stress agents.

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DOBUTAMINE: AN ALTERNATIVE STRESSOR FOR MPI

Although adenosine or dipyridamole is usually preferred for pharmacologic stress MPI, dobutamine stress has been used with increasing frequency, especially in patients with contraindications to adenosine and dipyridamole as a result of allergic bronchoconstrictive disease.

Dobutamine is a β_1-adrenergic receptor agonist that increases myocardial oxygen demand by positive inotropic and chronotropic effects.[2,3] Dobutamine also increases blood flow in normal coronaries and reduces the perfusion pressure distal to a coronary artery stenosis.[4,5] Dobutamine is given as a continuous intravenous infusion by a pump, as it has a short half-life (about 2 minutes). It is titrated in 3-minute intervals, up to a maximum dose of 40 or 50 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Atropine (0.5-1 mg) may also be administered to further increase the chronotropic response if the target heart rate is not achieved with maximum dose of dobutamine. The prominent side effects with dobutamine include angina, arrhythmias, and uncontrolled hypertension. In addition, some patients may have a hypotensive response to dobutamine, likely related to β_2-adrenergic agonism. Recent myocardial infarction, uncontrolled hypertension, and significant ventricular ectopy are contraindications for its use.

Overall, dobutamine-atropine MPI has demonstrated an excellent safety profile.[6] On the basis of 20 studies, Geleijnse et al[7] reported that the sensitivity, specificity, and accuracy of dobutamine stress MPI for detection of CAD were 88%, 74%, and 84%, respectively. Some concern has been raised that dobutamine may interfere with technetium 99m sestamibi uptake, lowering its ability to detect CAD,[8,9] possibly related to the induction of calcium influx that blunts the negative mitochondrial membrane driving potential, thereby diminishing uptake of sestamibi.

Dobutamine-atropine stress Tc-99m sestamibi single photon emission computed tomography (SPECT) imaging not only is effective in diagnosing CAD but also provides excellent prognostic information. Patients without perfusion defects had an annual cardiac event rate (cardiac death, nonfatal myocardial infarction) of 0.8% with dobutamine sestamibi testing.[10] Calnon et al[11] demonstrated that patients referred for dobutamine stress

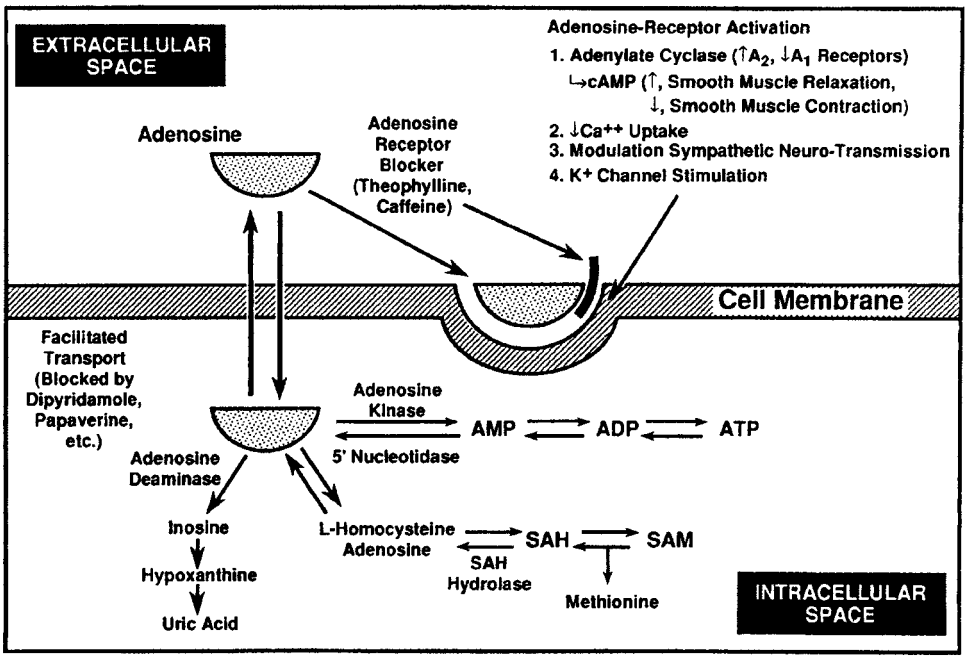

Figure 1. Mechanism of action of adenosine-mediated vasodilation. *cAMP,* Cyclic adenosine monophosphate; *AMP,* adenosine monophosphate; *ADP,* adenosine diphosphate; *ATP,* adenosine triphosphate; *SAH,* S-Adenosyl homocysteine; *SAM,* S-Adenosyl methionine. (Reprinted with permission from Verani MS. Am Heart J 1991;122:269-78.)

imaging are a high-risk population, as even patients with normal dobutamine SPECT study results have a 2.3% annual event rate. However, those with abnormal images have a much higher incidence of myocardial infarction or cardiac death (10.0%), demonstrating the risk stratification abilities of this technique.

Arbutamine, another catecholamine with mixed β_1- and β_2-adrenergic agonist properties, has a similar degree of chronotropic and inotropic activity as dobutamine but less peripheral vasodilating activity.[12] Kiat et al[12] reported that the diagnostic accuracy of arbutamine stress perfusion imaging is similar to that of exercise SPECT. Arbutamine appears to be an effective inotropic agent, although it still has many of the same side effects as dobutamine, including proarrhythmic potential. Presently, arbutamine is not available for clinical use in the United States.

ADENOSINE AND DIPYRIDAMOLE STRESS MPI

The similar mechanism by which adenosine and dipyridamole produce vasodilatation is summarized in Figure 1. Endogenous adenosine is normally produced in myocardial vascular smooth muscle and endothelial cells and is present in the extracellular space, where it may bind to adenosine receptors on the cell membrane. Adenosine also can be derived by the extracellular dephosphorylation of adenosine triphosphate and adenosine diphosphate that are released from nerves, platelets, mast cells, and other cell types. Adenosine can reenter endothelial cells, smooth muscle cells, or red blood cells, where it is phosphorylated by adenosine kinase to adenosine monophosphate or inactivated by deamination or incorporated into other molecules. When adenosine binds to the membrane-bound G protein–coupled adenosine receptors, it produces coronary artery vasodilatation by activating adenylyl cyclase that results in the opening of potassium channels. The opening of these channels in vascular smooth muscle cells hyperpolarizes the cells and inhibits voltage-gated calcium channels and intracellular calcium release, resulting in relaxation. Exogenous dipyridamole inhibits the cellular reuptake of adenosine, thereby increasing the amount of endogenous adenosine available for receptor binding and thus indirectly promoting vascular smooth muscle relaxation.

Both adenosine and dipyridamole can increase coronary blood flow to 3 to 5 times above the baseline flow in regions supplied by normal coronary arteries. Intravenous dipyridamole produces maximum coronary vasodilatation after 5 minutes, and this effect persists for 10 to 30 minutes after infusion.[13] An injection of aminophylline, a nonselective competitive antagonist to endogenous adenosine, will rapidly reverse the vasodilatory

Table 1. Side effects attributable to vasodilator stress testing

	Adenosine* (n = 9,256)	Dipyridamole† (n = 3,911)	Dobutamine‡ (n = 1,076)
Chest pain	35%	20%	39%
Flushing	37%	3%	<1%
Dyspnea	35%	3%	6%
Dizziness	9%	3%	4%
Gastrointestinal discomfort	15%	1%	1%
Headache	14%	12%	7%
Arrhythmia	3%	5%	45%
AV block	8%	0%	0%
STΔ	6%	8%	20%-31%
Any adverse effect	81%	50%	50%-75%

STΔ, ST-segment changes on electrocardiogram.
*From reference 19.
†From Ranhosky A, Kempthorne-Rawson J. The safety of intravenous dipyridamole thallium myocardial perfusion imaging. Intravenous Dipyridamole Thallium Imaging Study Group. Circulation 1990;81:1205-9.
‡Reprinted by permission of the Society of Nuclear Medicine from Elhendy A, et al. Safety of dobutamine-atropine stress myocardial perfusion scintigraphy. J Nucl Med 1998;39:1662-6.

effects of dipyridamole. Adenosine has a very short half-life, approximately 2 to 10 seconds, with the onset of action occurring within a few seconds and maximum coronary dilatation occurring within 2 minutes.[14,15] Thus, unlike dipyridamole, termination of adenosine infusion results in rapid cessation of its vascular effects.

Vasodilator agents, such as adenosine and dipyridamole, cause minimal or no increase in myocardial oxygen demand but produce a disparity of perfusion between normal and diseased arterial territories because of the differential ability of the arteries to dilate.[16,17] Although both adenosine and dipyridamole are very useful clinical tools in the assessment of patients with ischemic heart disease, there is a high incidence of adverse effects associated with pharmacologic stress agents. Lette et al[18] retrospectively examined dipyridamole-related side effects in more than 70,000 patients who underwent intravenous dipyridamole stress imaging and concluded that the risk of serious dipyridamole-induced side effects is low (<0.1%) and is comparable to that reported for exercise testing in a similar population. However, as summarized in Table 1, side effects attributable to vasodilator stress testing are common, with up to 80% of patients describing some symptoms associated with pharmacologic stress testing.[19]

The overall diagnostic sensitivity of pharmacologic MPI with adenosine and dipyridamole ranges from 83% to 97%, with a specificity between 38% and 94% reported. However, pharmacologic stress testing with adenosine and dipyridamole has advanced from simple identification of ischemia to estimation of the burden of ischemia and identification of the specific regions of the underperfused myocardium.[20-25] In addition, this method has been increasingly used for risk stratification of patients with known or suspected CAD, for patients after myocardial infarction, and for patients scheduled for noncardiac surgery who have risk factors for CAD. It appears that in patients who are appropriately referred for testing (ie, patients with intermediate to high likelihood of having CAD), the presence of a normal perfusion scan confers a benign prognosis with an annual cardiac event rate of 1.3%.[26] Pharmacologic MPI with agents such as adenosine may be particularly helpful in patients with acute myocardial infarction, as it can be used safely as soon as 2 days after the acute event.[27]

New Pharmacologic Stress Protocols

Over the last few years, the focus has been on the development of new protocols and/or new pharmacologic stress agents devoid of significant side effects. Recently, a prospective, randomized study was done comparing a 3-minute adenosine infusion with the standard 6-minute infusion; the relative diagnostic accuracy of the abbreviated adenosine infusion in patients who underwent coronary angiography was also assessed.[28] Patients who received the 3-minute adenosine infusion had less frequent flushing, headache, neck pain, and atrioventricular (AV) block while maintaining the same sensitivity (88%) for detection of CAD as patients who received the standard duration of adenosine infusion. However, the perfusion defect size in the abnormal scans was slightly larger in those receiving a 6-minute infusion compared with those receiving a 3-minute infusion. This

large, randomized, prospective study confirmed the earlier observations made in smaller studies that a short duration of adenosine infusion is preferred by patients because of fewer side effects[29,30] and appears to be as accurate as the traditional 6-minute protocol for the diagnosis of CAD.[29-32]

Vasodilator Stress With Adjunctive Exercise

Low-level exercise combined with vasodilator stress imaging has been performed to improve image quality and reduce side effects. When dipyridamole infusion is combined with exercise, improved myocardial perfusion and image quality and reduction of adverse effects have been reported.[33,34] Casale et al[35] studied 100 patients who received dipyridamole infusion combined with treadmill exercise and compared the results with those of another 100 patients who received dipyridamole infusion alone. In this study, combined treadmill exercise and dipyridamole testing was found to be safe, was associated with fewer noncardiac effects, and had a higher target-to-background ratio than dipyridamole alone. Symptom-limited exercise along with standard infusion of dipyridamole also results in a less frequent need to use aminophylline, and the combined approach is without serious adverse effects, even in elderly patients or those with triple-vessel CAD.[33] Stern et al[36] examined the effect of different types of exercise supplementation on dipyridamole thallium image quality and concluded that supplementation with low-level treadmill exercise is superior to isometric handgrip exercise and to dipyridamole infusion alone.

Adjunctive exercise has also been used with adenosine. Low-level bicycle exercise combined with an infusion of adenosine has been shown to be better tolerated and to improve thallium 201 myocardial perfusion image quality in comparison to adenosine testing without exercise. Pennell et al[37] randomly assigned patients to either a standard 6-minute adenosine infusion or an adenosine protocol with submaximal or symptom-limited exercise and revealed that the frequency of adverse effects was reduced by 43% and AV block was decreased by 90% in the group receiving adjunctive exercise. Similarly, Thomas et al[38] demonstrated that low-level treadmill exercise throughout a 6-minute adenosine infusion is safe, is better tolerated, and has improved image quality as a result of lower background activity compared with a 6-minute adenosine infusion alone.

Recently, a trial directly compared the incidence and severity of adverse side effects and image quality using the standard 6-minute adenosine stress test with a unique protocol combining a 4-minute adenosine infusion with 6 minutes of low-level treadmill exercise.[39] All patients underwent both protocols performed on separate days. A marked reduction in the number, duration, and severity of adverse effects was noted during the protocol that combined exercise with adenosine (Figure 2). No episodes of advanced AV block were reported with adjunctive exercise, whereas the adenosine-alone protocol caused complete heart block in 6 patients. This study also demonstrated improved image quality, with heart-liver ratios being significantly higher with adjunctive exercise than with the standard 6-minute adenosine study. Furthermore, a potential cost savings may be realized by using one third less of an adenosine dose in each patient.

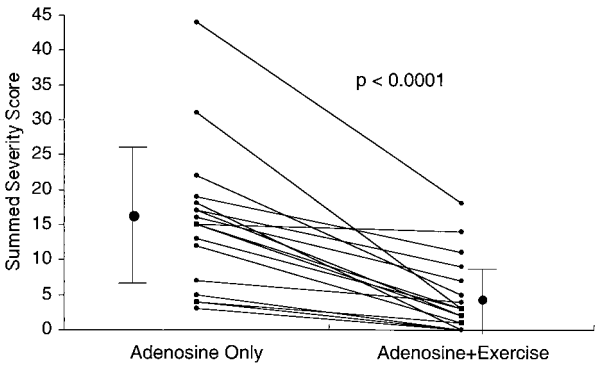

Figure 2. Symptom severity scores for each patient during both adenosine protocols. Compared with a 6-minute adenosine protocol, an abbreviated adenosine infusion with low-level exercise resulted in a significant reduction in symptom severity scores ($P < .0001$). (Reprinted with permission from Elliott et al. J Nucl Cardiol 2000;7;584-9.)

SELECTIVE ADENOSINE A_{2A} RECEPTOR AGONISTS

Ideal vasodilator agents for pharmacologic stress testing should provide selective coronary arterial vasodilatation with minimal systemic side effects.[17,38,40-42] The agent should be short-acting but with an effect lasting long enough to maintain coronary hyperemia during the uptake phase of the radiopharmaceutical. An increase in coronary blood flow of 2- to 3-fold above the baseline is necessary.[43-47] Although the responses to dipyridamole or adenosine are both reproducible and predictable, as previously mentioned, these agents are contraindicated in certain clinical situations and have significant side effects, potentially making stress testing an unpleasant experience for the patient. Finally, adenosine and dipyridamole require a controlled infusion, which makes their administration somewhat cumbersome.

To date, four adenosine receptor subtypes have been characterized and cloned: A_1, A_{2A}, A_{2B}, and A_3 receptors. It has been well established that stimulation of these receptors accounts for the varied effects on electrical

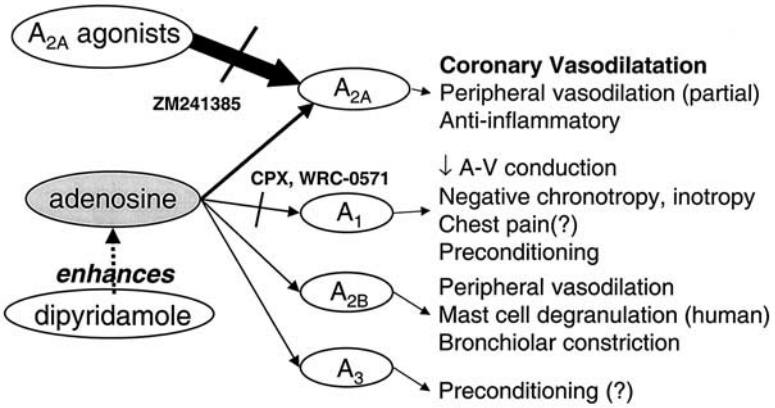

Figure 3. Biologic effects of adenosine receptor stimulation: Adenosine receptor agonists and the physiologic responses that result from stimulation of selective receptor subtypes. (Modified with permission from initial figure created by Dr. Richard Barrett.)

Table 2. Summary of A_{2A} agonists properties

	CGS21680	MRE-0470	ATL-146e	CVT-3146
Selectivity	Low	High	Very high	Moderate
Affinity	High	High	High	Low
Potency	Moderate	High	Very high	Moderate
Stable	Yes	?	Yes	?
Onset	1-2 min	1-2 min	1-2 min	<1 min
Duration	>20 min	<5 min	10-20 min	<5 min
Trials	?	2	1 in 2003	2

conduction, vasodilatation, and bronchoconstriction (Figure 3). Evidence from human studies indicates that adenosine-induced AV conduction abnormalities and possibly the generation of chest pain are due to activation of A_1 receptors.[48-50] Data from animal studies have suggested that A_{2A} adenosine receptors found on the coronary resistance vessels mediate the coronary dilatory response to adenosine, whereas A_{2B} receptor stimulation causes relaxation of conductance vessels.[51] In addition, the A_{2B} adenosine receptors cause peripheral vasodilatation, bronchoconstriction, and mast cell degranulation in human beings.[52,53] The A_3 adenosine receptor is the most recently identified subtype; activation of these receptors may elicit preconditioning against ischemic injury.[54] A_3 receptors also stimulate mast cell degranulation in rodents.[55]

One way of minimizing the A_1 receptor–mediated side effects without compromising coronary vasodilatation is pretreatment with an A_1-selective antagonist such as N-0861 in order to inhibit the A_1 receptor–mediated side effects such as chest pain or AV conduction abnormalities,[48,49,56] thereby improving patient safety and comfort.

Given that the side effect profile observed with dipyridamole or adenosine administration results from the nonselective stimulation of adenosine receptors, an alternative and perhaps superior approach would be to develop a compound that has little or no affinity for adenosine A_1, A_{2B}, or A_3 receptors but selectively stimulates only the A_{2A} receptors, which are responsible for coronary vasodilation. A number of highly potent and selective A_{2A} receptor agonists have now been synthesized and are in various stages of clinical development[57-60] (Table 2). A direct comparison of the pharmacologic properties of the new compounds is hampered by the use of different animal species in various studies and the existence of two agonist affinity states for G protein–coupled receptors.[61] In addition, the pharmacologic properties of the major metabolites of some of the new compounds have not yet been reported. However, all of the new compounds appear to be more selective for A_{2A} over A_1 receptors than adenosine. These compounds differ significantly in their rates of metabolism, with CGS21680 and dipyridamole < ATL-146e and ATL-193 < MRE-0470, CVT-3146, and adenosine. The rapidly metabolized compounds produce sustained

maximal coronary dilation when administered by infusion.

CGS-21680

CGS-21680 is a long-acting A_{2A} receptor agonist that possesses a 170-fold selectivity for the rat A_{2A} versus A_1 receptors and is 125 times more potent than adenosine; the selectivity of CGS-21680 for human A_{2A} receptors is lower. He et al[62] compared its hemodynamic and coronary vasodilatory effects, as well as its potential use as a pharmacologic stress agent, with adenosine in a canine model of critical coronary stenosis. These investigators showed that like adenosine, CGS-21680 caused a 4-fold increase in myocardial blood flow in the region supplied by a normal coronary artery and no increase in flow in the region supplied by the critical stenosis. The drop in systemic arterial pressure with CGS-21680 was less than with adenosine, but heart rate increased to a greater extent with CGS-21680. From an imaging perspective, CGS-21680 produced profound heterogeneity of myocardial blood flow and radiopharmaceutical uptake within the myocardium.[62]

MRE-0470 (Binodisine)

MRE-0470 (formerly WRC-0470) is a highly selective A_{2A} receptor agonist that is 200 times more potent than adenosine in dogs and has a high affinity for adenosine A_{2A} receptors. Glover et al[63] demonstrated the systemic hemodynamic and coronary blood flow responses to an intravenous infusion of MRE-0470 in anesthetized dogs and compared these responses with adenosine in the same animals. In this study they found that MRE-0470 produced greater vasodilation at its peak pharmacologic infused dose than did adenosine, and without significant hypotension.

The hemodynamic properties and experimental studies suggest that MRE-0470 has the potential to provide comparable or enhanced diagnostic accuracy as compared with adenosine, with markedly reduced side effects. Phase II trials with this agent have now been completed, and phase III trials are planned in the near future.

CVT-3146

Trochu et al[64] studied this potent and low-affinity A_{2A} adenosine receptor agonist for clinical use as a stress agent; CVT-3146 was noted to be 100 times more potent than adenosine. The peak coronary blood flow attained with this agent was 2-fold higher than baseline, and the effect lasted longer than adenosine at different dose levels of CVT-3146. For example, after a 10-second injection of CVT-3146 (2.5 μg/kg), the increase in coronary blood flow peaked at 17 seconds and remained 2-fold above baseline for about 97 seconds. With adenosine (267 μg/kg), the peak effect was reached at 16 seconds and remained 2-fold above baseline for approximately 24 seconds. Furthermore, there was no AV block noted during CVT-3146 administration. This study concluded that CVT-3146 was more potent than but equally as effective as adenosine. Clinical trials using CVT-3146 in conjunction with MPI are now under way.

ATL-193 and ATL-146e

ATL-193 and ATL-146e represent a new class of highly potent and selective adenosine A_{2A} receptor agonists.[60] These new ester compounds are 500 times more potent than adenosine at human A_{2A} receptors, and in recombinant human adenosine receptors, ATL-193 and ATL-146e are more highly selective for the A_{2A} agonists than the other selective A_{2A} agonists.[65]

In animal studies, ATL-193 was administered by infusion and ATL-146e was given as a bolus injection, with similar effects on maximal coronary dilation responses.[66] Both selective agents increase coronary blood flow in a dose-dependent manner without producing significant hypotension.[66] After ATL-146e bolus administration, the coronary blood flow increase was sustained for several minutes; coronary blood flow returned completely to baseline in 20 minutes. In this study, Glover et al demonstrated that these two agents appear to be more potent coronary vasodilators than MRE-0470, CGS-21680, and CVT-3146[62-64,66] and the ability to administer ATL-146e by bolus injection may eliminate the need for an infusion pump.

CONCLUSIONS

The combination of vasodilators with exercise stress testing can be used safely and effectively, with improved image quality and with significant reduction of problematic side effects. Dobutamine may be used in patients with bronchospastic lung disease and has an acceptable side effect profile.

Selective A_{2A} receptor agonists are potent coronary vasodilators that should not produce significant hypotension. This selectivity will also likely reduce side effects and AV block produced by stimulation of the other adenosine receptor subtypes, making these agents highly desirable for pharmacologic stress testing. Importantly, if as expected these new A_{2A} agonists do not produce bronchoconstriction, then they can be used safely in virtually all patients. The results from experimental studies appear promising for A_{2A} receptor agonists, and clinical trials of these agents are now under way.

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