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Please note: Dr. Woronow has reported that he has no relationships relevant to the contents of this paper to disclose.

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REPLY: Protamine and Bleeding Avoidance Strategies



I greatly appreciate the interest of Dr. Woronow in my recent study published in the *Journal* (1). Protamine binds with heparin or low-molecular-weight heparin to form a stable ion pair with no anticoagulant activity. This compound is routinely used during cardiopulmonary bypass surgery and is also administered to reverse the effect of heparin in patients in stable condition after invasive cardiac catheterization (e.g., post-transplant evaluation, fractional flow reserve estimation not requiring percutaneous coronary interventions [PCIs]). Protamine, as mentioned by the author, is not only important to reverse anticoagulation in case of major bleeding after PCI, but it is also crucial in the uncommon event of cardiac or coronary perforation during procedures that require large doses of heparin (2).

There are several reasons that protamine cannot be routinely used to avoid bleeding after PCI. First, the allergic reactions to protamine are not uncommon and can lead to serious anaphylaxis. Second, even though protamine has been shown to be safe in small series, case-control, and randomized studies, its usefulness has not been proven in large contemporary randomized trials (3). Third, its safety has been tempered with case reports of ischemic complications in patients treated with protamine (4). Fourth, the use of the radial artery for access has diminished the

utility of protamine reversal in favor of radial artery patency requiring anticoagulation with heparin.

The role of protamine should be explored further, and larger, randomized trials need to be planned. In the meantime, patient selection for use of protamine is important. Patients with seafood allergies or previous use of protamine should not be given this drug. However, patients at very high risk of bleeding (e.g., elderly women presenting with acute coronary syndrome and who had femoral access for PCI) would be ideal candidates for protamine administration for heparin reversal, especially if there are bleeding events (i.e., hematoma, retroperitoneal bleed).

Rebound thrombogenicity and allergic reactions to protamine are valid concerns that need to be addressed. Protamine remains a useful tool in the armamentarium of interventional cardiologists, and its judicious use is recommended.

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A Proposal to Incorporate Trial Data Into a Hybrid American College of Cardiology/American Heart Association Algorithm for the Allocation of Statin Therapy in Primary Prevention



Ridker et al. (1) draw attention to the importance of statins as primary prevention agents; they endorse

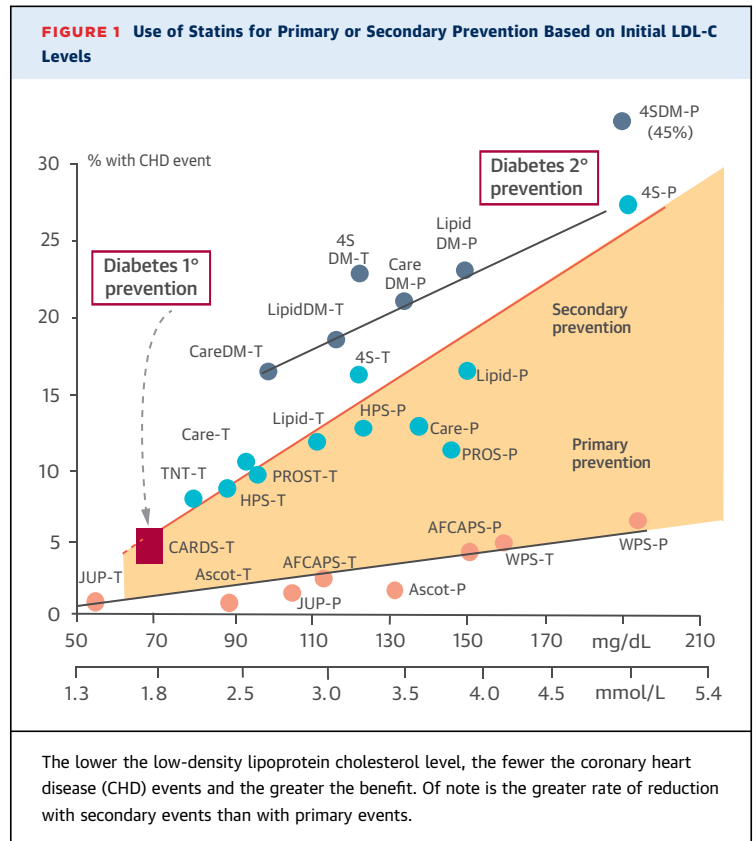
pharmacological treatment for those patients who have estimated 10-year risks $\geq 7.5\%$ and for whom trial-based evidence supports statin efficacy. In addition, the 5-year risk for statin-treated patients had a relative risk of 0.62 (95% confidence interval: 0.47 to 0.81). Another important point they highlight is the effect of age (Figure 4 in Ridker et al. [1]). They warn against overestimation of the 10-year risk, implying that primary prevention is overused at present.

There is, however, an alternate way of looking at indications for the use of statins for primary prevention, on the basis of the initial level of low-density lipoprotein cholesterol (LDL-C) as shown in the lower part of Figure 1 (2). This approach shows that the higher the initial pre-treatment LDL-C level, the greater the effect of statin therapy and the greater the reduction in 10-year mortality (Figure 1). For primary prevention by a statin, a pre-treatment LDL-C level of 200 mg% (approximately 5 mmol/l) would substantially reduce the 10-year risk of a coronary heart disease event, whereas starting statin therapy at an initial level of 120 mg% would provide only slight improvement in the reduction of absolute risk. Thus, the absolute pre-therapy LDL-C level could be crucial in deciding whether to prescribe a statin.

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