Correspondence

Letters Regarding Article by Patti et al, "Randomized Trial of High Loading Dose of Clopidogrel for Reduction of Periprocedural Myocardial Infarction in Patients Undergoing Coronary Intervention: Results From the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) Study"

To the Editor:

Patti et al recently investigated the effect of pretreating patients undergoing percutaneous coronary intervention (PCI) with 600 mg of clopidogrel versus the conventional 300-mg dose.[1] Their results showed that the 600-mg dose reduces the composite of death, myocardial infarction, or target vessel revascularization up to 30 days after the procedure. The authors concluded that the study "demonstrated that the higher loading dose was more effective than the conventional dose in preventing ischemic complication." These findings were immediately accepted with enthusiasm.[2] Although this investigation is an important step in understanding the optimal loading dose for clopidogrel, we are concerned about a methodological limitation in the study.

The trial randomized 329 patients scheduled for coronary angiography who actually received a loading dose of either 600 mg or 300 mg clopidogrel. The authors reported only a per-protocol analysis in patients who actually underwent PCI. No safety or efficacy data were reported based on the intention-to-treat principle, which would be the most relevant information, because in clinical practice when the decision is made to pretreat with clopidogrel, the coronary anatomy is frequently unknown. Therefore, the decision to undertake clopidogrel pretreatment would be better understood based on the efficacy/safety data in the overall population, including CABG and medically managed patients. Thus, it would be of utmost interest to know the adjusted odds ratio for the primary end point.

The trial presents other methodological issues as the sample size calculated on the expected rate of any periprocedural CK-MB elevation instead of the major adverse cardiovascular events, which is referred to as the primary end point throughout the article and the fact that the logistic regression model "assessing the risk of the primary end point according to potential confounding" announced in the Methods is not shown anywhere in the article. Finally, the results presented cannot be conclusive because the 95% CI of the unadjusted OR is wide and entails a marginal potential advantage of the 600-mg dose (OR 0.31, 95% CI 0.09 to 0.95)

If the evidence of the efficacy of clopidogrel pretreatment is weak overall, mainly based on a post-hoc analysis, then the evidence that 600 mg is the optimal dose is negligible. The results of the ARMYDA-2 trial support the need of a well-designed and properly powered trial to answer the question whether 600 mg of clopidogrel as the loading dose is indicated in clinical practice.

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1. Patti G, Colonna G, Pasceri V, Pepe LL, Montinaro A, Di Sciascio G. Randomized trial of high loading dose of clopidogrel for reduction of periprocedural myocardial infarction in patients undergoing coronary intervention. Results from the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) study. *Circulation*. 2005;111:2099–2106.
2. ARMYDA-2: 600-mg Clopidogrel Preferable Pre-PCI. Available at: http://www.theheart.org/viewArticle.do?primaryKey=398589&from=/searchLayout.do. Accessed October 10, 2005.

To the Editor:

The Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty (ARMYDA-2) study reported that pretreatment with a 600-mg loading dose of clopidogrel 4 to 8 hours before percutaneous coronary intervention (PCI) resulted in significant reductions in periprocedural myocardial infarction (MI).[1] In the accompanying editorial,[2] Williams stated that these data, together with a recent report from Kastrati et al,[3] suggest that glycoprotein (GP) IIb-IIIa inhibitors are no longer essential in treating patients undergoing PCI.

Multiple clinical factors may have an impact on prognosis, including severity of ST depression, elevated troponin, anatomic lesion characteristics and location, and presence of comorbidities including diabetes, multivessel coronary artery disease, and renal insufficiency. Little information on higher-risk patients can be derived from ARMYDA-2, yet these patients represent a substantial percentage of those undergoing PCI. The 4- to-8-hour pretreatment period further minimizes the applicability of this regimen because some patients who would ideally undergo immediate intervention may be forced to delay treatment to ensure adequate clopidogrel activity. These considerations suggest that the results of ARMYDA-2 are applicable only to low-risk patients.

Because ARMYDA-2 was conducted in Italy, these results must also be interpreted with respect to current practices in the United States. Only 20% of patients in ARMYDA-2 received drug-eluting stents (DES), whereas most patients in the United States currently receive DES. Widespread adoption of the ARMYDA-2 regimen may negatively affect overall outcomes when considered in light of the expanding use of DES in revascularization of lesions of greater complexity in smaller-caliber vessels.

Large randomized studies of GP IIb-IIIa inhibitors consistently show substantial reductions in risk of death, MI, and target vessel revascularization across a broad range of patient populations. In a meta-analysis of randomized trials enrolling >32 000 patients, GP IIb-IIIa inhibitors were associated with both significant reduction in the risk of mortality at 48 to 96 hours and significant benefit at 48 to 96 hours, 30 days, and 6 months for the combined end point of death and MI and the composite end point of death, MI, or revascularization.[4] Current guidelines recommend the use of GP IIb-IIIa inhibitors in most patients undergoing PCI.

Unless the benefits reported in ARMYDA-2 can be reproduced in a clinically representative population, GP IIb-IIIa inhibitors should remain integral to the preferred treatment regimen for the majority of patients undergoing PCI.

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1. Patti G, Colonna G, Pasceri V, Pepe LL, Montinaro A, Di Sciascio G. Randomized trial of high loading dose of clopidogrel for reduction of periprocedural myocardial infarction in patients undergoing coronary intervention. Results from the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) study. *Circulation*. 2005;111:2099–2106.

2. Williams DO. Clopidogrel pretreatment for percutaneous coronary intervention: double, double, dose in trouble? *Circulation*. 2005;111:2019–2021.
3. Kastrati A, von Beckerath N, Joost A, Pogatsa-Murray G, Gorchakova O, Schomig A. Loading with 600 mg clopidogrel in patients with coronary artery disease with and without chronic clopidogrel therapy. *Circulation*. 2004;110:1916–1919.
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Response

We agree with Dr Palabrica that the population of ARMYDA-2,[1] similar to that of the first ARMYDA trial,[2] is at moderate risk (ie, STEMI were excluded). However, 25% of patients had acute coronary syndromes (ACS), 66% had lesions B2-C, and 30% were diabetic, suggesting variable degrees of clinical and/or angiographic complexity. We acknowledge the efficacy of GPIIb-IIIa inhibitors in patients undergoing PCI, but we made no statement suggesting that GPIIb-IIIa inhibitors are no longer essential in treating such patients. To the contrary, we explicitly state that the 600-mg loading dose may be indicated on top of the optimal pharmacological regimen available in specific practice settings, including GPIIb-IIIa, when needed. Of course, whether higher loading doses of clopidogrel may do away with the need for GPIIb-IIIa in ACS including STEMI, will need to be tested in head-to-head comparisons, and we are sure it will be done eventually.

Our response to Dr Tricoci is that ARMYDA-2 was designed to test the effectiveness of higher loading doses of clopidogrel in patients undergoing PCI. However, the safety of this regimen was also evaluated in randomized patients indicated for surgery or medical therapy after coronary angiography. In fact, although it would be impossible to assess the efficacy of a higher clopidogrel loading regimen in reducing procedural ischemic complications in patients not undergoing PCI, we reported no increased risk of perioperative bleeding in the 600-mg patients undergoing elective surgery and no adverse events in patients treated medically.

Logistic regression data and adjusted odds ratios for the primary end point are indeed reported in our article (see Figure 5). Finally, the limitations of the study, including the use of a surrogate end point to calculate sample size, are clearly discussed in the text.

Perhaps the motives for "the surprising enthusiasm" generated by ARMYDA-2 are that this is the first study to provide evidence that 600-mg clopidogrel loading dose pre-PCI (already known to provide faster and more pronounced antiaggregation) confers clinical benefits compared with the conventional 300-mg regimen; accordingly, it is no surprise that the new European Society of Cardiology guidelines have incorporated the indication for 600-mg clopidogrel loading before PCI, recommending the 300-mg regimen only when pretreatment can be performed >6 hours before the procedure.[3]

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1. Patti G, Colonna G, Pasceri V, Pepe LL, Montinaro A, Di Sciascio G. Randomized trial of high loading dose of clopidogrel for reduction of periprocedural myocardial infarction in patients undergoing coronary intervention. Results from the ARMYDA-2 (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) study. *Circulation*. 2005;111:2099–2106.
2. Pasceri V, Patti G, Nusca A, Pristipino C, Richichi G, Di Sciascio G. A randomized trial of atorvastatin for reduction of myocardial damage during coronary intervention. Results from the ARMYDA study. *Circulation*. 2004;110:674–678.
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Letter Regarding Article by Baicu et al, "Left Ventricular Systolic Performance, Function, and Contractility in Patients With Diastolic Heart Failure"

To the Editor:

This timely article by Baicu et al addresses the controversial topic of patients with diastolic heart failure (DHF), a term currently defined as heart failure in the presence of a normal ejection fraction >50%.[1] Forty-seven DHF patients underwent catheterization in association with echocardiography.[2] Ten patients who were catheterized had no evidence of cardiovascular disease and served as controls. From their analyses, the authors concluded that a majority of DHF patients displayed left ventricular normal systolic performance, function, and contractility.

The article's Figures 2 and 4 appear to indicate that both endocardial and midwall fractional shortening are load independent. A reevaluation was therefore conducted and yielded the following regression equations: (1) YU=33.4–.0214 XU (n=28, NS (0.11)), (2) YL =32.7–.0600 XL (n=15, NS (0.6)), (3) Ymid=14.9−0.00314 Xmid (n=26, NS (0.76)), and (4) Ymidout=12.8−0.0092 Xmidout (n=15, NS (0.72)). Here, YU versus XU and YL versus XL refer to the upper and lower endocardial fractional shortening versus stress relationships, respectively (Figure 2), and subscripts mid and midout refer to the midwall fractional shortening versus stress relationships (Figure 4). Note the marked differences in the statistics. Furthermore, the authors need to address the following questions: Why were the control data omitted from Figures 2 and 4 and what was the significance of these control regression equations? What was the rationale for assuming no gender differences? This is an important question that needs further study.

The authors are to be commended for introducing the normalization factors that resulted in dimensionless units for Ees. However, stroke work/end-diastolic volume (SW/EDV; see Figure 1) and the end-systolic pressure/end-systolic volume ratio appeared to indicate differences between the control and DHF groups (employing data in Tables 1 and 2). No comments could be made on Ea and the Ea/Ees ratio for lack of data. Figure 3 is incomplete because SW/EDV could be load dependent and, more important, normalization of preload recruitable stroke work to mean arterial pressure leads to conflicting results.

Finally, it is hoped that these comments are interpreted as constructive in nature and that young investigators, in particular, use this article as a guideline for future studies.

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1. Baicu CF, Zile MR, Aurigemma GP Gaasch WH. Left ventricular systolic performance, function, and contractility in patients with diastolic heart failure. *Circulation*. 2005;111:2306–2312.
2. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med*. 2004;350:1953–1959.

Response

We were pleased to receive Dr Mirsky's commendation for our research.[1] It is worth noting that Dr Mirsky was one of the first scientists to recognize the importance of normalizing indices of systolic and diastolic function. We simply followed his example.

Dr Mirsky correctly emphasizes the fact that all "ejection phase" indices of systolic properties are afterload dependent. Of particular importance, this fact applies to all of the more recently developed Doppler and tissue Doppler techniques used to examine regional systolic properties as well as previously defined global measurements. The mean (solid line in Figures 2 and 4) relationship between fractional shortening and systolic stress in control subjects was linear and inverse such that as stress increased, fractional shortening fell. The prediction intervals for this normal relationship (dashed lines in Figures 2 and 4) were presented to provide the "boundaries" of a normal relationship against which the data from the diastolic heart failure (DHF) patients could be compared.

As pointed out in our article and as noted by Dr Mirskyy, the mean values of the SW/EDV and ESP/ESV ratios and Ees all appear higher in patients with DHF than in controls. However, we do not think that this represents an increase in contractility in the DHF patients compared with controls, but rather reflects the presence of chronic LV remodeling. When these indices are normalized, our data support the conclusion that there are no differences in contractility between controls and DHF patients. Therefore, in patients with chronic heart disease, all indices of LV function must be "normalized" for both preload and afterload and for remodeling (both volume and mass). The resulting data provide robust evidence that LV systolic properties are normal in patients with DHF and that abnormalities in systolic properties do not contribute significantly to the pathophysiology of DHF.

SW and PRSW are useful indices of LV systolic performance and function in part because they "credit" the left ventricle for both pressure development and ejection. Therefore, appropriate components of both preload and afterload are incorporated into their calculation. However, because LV diastolic pressures are elevated in patients with DHF, it is not appropriate to use mean arterial pressure alone in the calculation of SW. Indices of "developed" not "total" pressure should be used to calculate stroke volume; in other words, mean arterial pressure should be replaced by systolic pressure minus diastolic pressure.

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