COMMENTS AND RESPONSES

Warfarin or Not Warfarin?

TO THE EDITOR: Warfarin or not warfarin? That is the question. Each day, physicians who treat elderly patients, especially octogenarians, consider this dilemma. Benefits of warfarin are well known in patients 75 years of age or older. However, compared with younger patients, this group is at higher risk for intracranial hemorrhage and other types of warfarin-associated bleeding. Fang and colleagues (1) examined the risk for intracranial hemorrhage according to age and international normalized ratio (INR). However, the patients they examined were not good candidates for warfarin therapy. For many reasons, it is more difficult to control INR in patients 85 years of age or older. A high percentage of these patients have gait disturbances, neurodegenerative diseases, and other prevalent diseases (for example, diabetes, chronic obstructive pulmonary disease, and heart failure). Many take drugs such as amiodarone, antibiotics, corticoids, statins, omeprazole, and nonsteroidal anti-inflammatory drugs, which can increase the effect of warfarin. Other patients have social problems that make accurate INR monitoring difficult. Because we treat patients, not percentages or relative risks, we should avoid generalizing recommendations about oral anticoagulation in very old patients. We should tailor prescription of anticoagulants according to each patient’s associated diseases, concurrent medications, and functional and mental status.

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Reference

IN RESPONSE: High-quality randomized trials demonstrate that warfarin therapy dramatically reduces the risk for ischemic stroke associated with atrial fibrillation (1). These trials and observational studies also indicate that the benefit of anticoagulation is markedly reduced at INRs lower than 2.0 (2). Our study showed that the risk for intracranial hemorrhage increases with age and with INRs above 3.5. However, patients receiving anticoagulation did not have a reduced risk for intracranial hemorrhage at INRs less than 2.0. Thus, it appears that maintaining the INR in the 2.0 to 3.0 range maximizes the benefits of warfarin while minimizing the risks.

Unfortunately, older patients are at higher risk for both ischemic stroke and intracranial hemorrhage; erratic anticoagulation exacts a greater penalty. As Dr. Ruiz-Ruiz notes, numerous factors can lead to difficult warfarin management in the elderly, including polypharmacy, multiple comorbid conditions, and physical and mental frailty. We agree that the anticoagulation decision must be individualized and must engage the patient or patient caregiver. Appropriate decision making should account for whether patients can be safely maintained within a therapeutic INR range of 2.0 to 3.0.

Although intracranial hemorrhage risk increases at older ages, other validated clinical predictors of intracranial hemorrhage are few. As a consequence, individualized risk assessment often represents guesswork. The preponderance of evidence favors the use of warfarin in elderly patients with atrial fibrillation. However, the large proportion of elderly patients with atrial fibrillation, their increased risk for intracranial hemorrhage, and the devastating consequences of intracranial hemorrhage in patients taking warfarin all highlight the need to find better predictors of this condition. Such knowledge would make individualized decisions about anticoagulation in atrial fibrillation much more rational and effective.

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References

Next-of-Kin Responses and Do-Not-Resuscitate Implications for Implantable Cardioverter Defibrillators

TO THE EDITOR: In their article on management of implantable cardioverter defibrillators (ICDs) in end-of-life care, Goldstein and colleagues (1) reported low rates of discussion of ICD deactivation and ICD shocks in the last month of life, according to next-of-kin interviews. Although these data largely support our perception, more attention should be paid to the limitations of the methods used. The challenge of study design is well recognized for those studying quality of care at the end of life and quality of death and dying. Since few small studies have been performed in this area, validity and reliability of bereaved next-of-kin responses in retrospective studies are still a concern and require further research (2). Efforts to complement next-of-kin responses by using chart review, diagnostic codes, or other databases could have better defined the contexts of individual dying patients and added significantly to validity and reliability. Certainly, we can conclude little about whether ICD shocks were appropriate, inappropriate, or accurately perceived by the bereaved next of kin. In the future, society will benefit from ongoing prospective studies following the course of patients with ICDs and the context of their eventual deaths, thus avoiding the issues surrounding recall of the bereaved.

Goldstein and colleagues also raised the issue of what a do-not-resuscitate (DNR) order means for a patient with an ICD. They reported that although patients with DNR orders were statistically more likely to have a discussion about ICD deactivation, discussions were still reported in fewer than 50% of cases. Does a DNR order imply that a patient’s ICD should be deactivated? We both participated in a 2004 American Academy of Hospice and Palliative Medicine conference session (3) where this question generated intense

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IN RESPONSE: We agree with Morrison and Sinclair that bereaved next of kin may well report the experiences of deceased patients inaccurately. Nevertheless, the perspectives of survivors are important as a first estimate of the experience of patients and as evidence of the impact on family, which is important in its own right. Prospective interviews or observation may well provide other insights, but chart review has substantial limitations in completeness of the data, and after-death review of a defibrillator’s memory is uncommon.

As for the issue of what a DNR order means for a patient, our findings of a low rate of discussions about deactivating ICDs in patients with a DNR order is not meant to imply that ICDs “should” be deactivated when a patient or family agrees to a DNR order. Instead, our results call into question why the issue of ICD deactivation was never discussed. We agree with Morrison and Sinclair that conversations about ICDs in patients near the end of life should take place within the much larger context of advance care planning in an effort to help patients weigh the benefits and burdens of various treatments. This will ensure that patients live out their lives in accordance with their wishes.

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References

TO THE EDITOR: We read with interest the article by Bybee and colleagues (1) on transient left ventricular apical ballooning. In March 2004, we reported on a series of 11 patients with the takotsubo syndrome (2). It was originally published in Spanish, but its English version is available online at Revista Española de Cardiología (www.revespcardiol.org). Beyond being one of the largest known series published, our work provides new findings that may serve to better understand this syndrome.

As mentioned by Bybee and colleagues, patients with the takotsubo syndrome meet the criteria for acute myocardial infarction (MI) (3). However, acute MI has been ruled out for 2 reasons: the absence of luminal coronary stenosis and the wide akinetic area not complying with the perfusion territory of a single coronary artery (4). In our initial work in patients with the takotsubo syndrome, we described a well-developed left anterior descending coronary artery with a long distal recurrent segment supplying a significant area of the inferior left ventricular segments. Patients with anterior acute MI due to isolated occlusion of the left anterior descending coronary artery show a left ventricular motion indistinguishable from that of the takotsubo syndrome if the left anterior descending coronary artery has a well-developed recurrent segment (2). Because of these findings, we hypothesized that transient left ventricular apical ballooning could be due to an acute occlusion of the left anterior descending coronary artery followed by early and complete spontaneous reperfusion in patients in whom this artery is well-developed.

To test our theory, we prospectively performed intravascular ultrasonography of the left anterior descending coronary artery in 5 consecutive patients (5). In all 5, and in 2 other patients who were added later, we found a single complicated eccentric atherosclerotic plaque in the middle of the left anterior descending coronary artery that was not visible on angiography. Plaque features included disruption of the intimal layer with cavities inside or intimal dissection. Our findings strongly suggest that the takotsubo syndrome could be, at least in some cases, an acute MI with early resolution of the coronary occlusion, either atherothrombotic or spastic. The rapid reperfusion could explain the minimal enzymatic release and the early left ventricular recovery (stunning rather than necrosis). These novel findings are of practical importance, and we advocate managing this disorder as an acute coronary syndrome.

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References
Left ventricular dysfunction is known to occur in patients with head trauma and intracranial bleeding. In listing exclusion criteria as a part of the diagnostic criteria for ventricular dysfunction after acute insult to the brain is of similar pathogenesis (3), not a totally different clinical entity. Furthermore, we believe such types of reversible ventricular dysfunction, presumably mediated by the nervous system, should also be encompassed within the definition of this syndrome. Therefore, broader inclusion criteria would be suggested for this novel disease concept.

Nonetheless, the authors should be commended for their extensive research and excellent publication. Increased awareness and an interdisciplinary approach involving neurologists, neurosurgeons, psychologists, and cardiologists should further help us understand the nature of this disorder.

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References
transient left ventricular apical ballooning, our intent was to exclude distinct conditions that could potentially present in a similar manner. Tachycardia-mediated left ventricular dysfunction rarely presents as an acute cardiac syndrome and lacks the characteristic distribution of wall-motion abnormalities seen with transient left ventricular apical ballooning. Therefore, we do not feel it is necessary to include this entity as an exclusion criterion, as suggested by Drs. Dehnavi and van der Wall.

Drs. Ako, Honda, and Fitzgerald suggest that head trauma and intracranial bleeding should not be exclusion criteria for the clinical diagnosis of transient left ventricular apical ballooning. Significant head trauma and intracranial bleeding may indeed be associated with reversible apical left ventricular dysfunction; however, the reported distribution of wall-motion abnormalities in consecutive patients with brain injury differs. For example, one study suggests that basal hypokinesis with preservation of apical function is the most common finding in these patients (4). At this point, it is unclear whether left ventricular dysfunction associated with brain injury and transient left ventricular apical ballooning share similar pathophysiologic mechanisms.

The mechanisms responsible for transient left ventricular apical ballooning remain ill-defined, and further research is needed. Collaborative investigative efforts, including the development of a transient left ventricular apical ballooning registry, would probably expedite our understanding of this underrecognized syndrome.

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References

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References

TO THE EDITOR: We read with great interest the article by Rule and colleagues (1) on the use of different creatinine-based equations to estimate GFR. We fully agree with the limitations of the MDRD equation for healthy persons. Nevertheless, we would like to make some comments. First, as Rule and colleagues mentioned, their new equation does not adequately represent elderly persons or persons of nonwhite ethnicity. We think that neither the MDRD equation nor the new proposed Mayo Clinic equation will be satisfactory in certain populations, including obese, anorexic, cirrhotic, or pediatric patients (2). In these populations, the relationship between serum

The New Mayo Clinic Equation for Estimating Glomerular Filtration Rate

TO THE EDITOR: Rule and colleagues (1) analyzed a series of 580 potential kidney donors referred to the Mayo Clinic and found that the abbreviated Modification of Diet in Renal Disease (MDRD) equation significantly underestimated glomerular filtration rate (GFR) in healthy persons (1). This led the authors to develop new equations (reft MDRD equation for healthy persons, refit MDRD equation with healthy indicator, and a quadratic equation) that performed better than the abbreviated MDRD formula in healthy persons. However, as Stevens and Levey pointed out in their accompa-
Table. Accuracy and Precision of the Refit Modification of Diet in Renal Disease Equations and the Quadratic Equation in Healthy Persons and Patients with Chronic Kidney Disease*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with Chronic Kidney Disease†</th>
<th>Healthy Persons‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size, n</td>
<td>882</td>
<td>162</td>
</tr>
<tr>
<td>Mean measured GFR ± SD (range), mL/min per 1.73 m²</td>
<td>87 ± 20 (60 to 166)</td>
<td>98 ± 14 (68 to 153)</td>
</tr>
<tr>
<td>Mean estimated GFR ± SD using the MDRD equation (range), mL/min per 1.73 m²</td>
<td>82 ± 25 (15 to 330)</td>
<td>93 ± 18 (57 to 145)</td>
</tr>
<tr>
<td>Bias ± SE, mL/min per 1.73 m²</td>
<td>–5.7 ± 0.7</td>
<td>–5.5 ± 1.2</td>
</tr>
<tr>
<td>Percentage bias ± SE, %</td>
<td>–6.2 ± 0.8</td>
<td>–5.1 ± 1.2</td>
</tr>
<tr>
<td>Percentage of estimated GFR within 30% of measured GFR, %</td>
<td>51</td>
<td>64</td>
</tr>
<tr>
<td>Mean estimated GFR ± SD using the refit MDRD equation with healthy indicator (range), mL/min per 1.73 m²</td>
<td>90 ± 30 (15 to 393)</td>
<td>130 ± 26 (81 to 207)</td>
</tr>
<tr>
<td>Bias ± SE, mL/min per 1.73 m²</td>
<td>2.6 ± 0.8</td>
<td>32.2 ± 1.7</td>
</tr>
<tr>
<td>Percentage bias ± SE, %</td>
<td>3.0 ± 0.9</td>
<td>33.4 ± 1.8</td>
</tr>
<tr>
<td>Percentage of estimated GFR within 30% of measured GFR, %</td>
<td>54</td>
<td>22</td>
</tr>
<tr>
<td>Mean estimated GFR ± SD using the refit MDRD equation for healthy persons (range), mL/min per 1.73 m²</td>
<td>–</td>
<td>111 ± 10 (90 to 139)</td>
</tr>
<tr>
<td>Bias ± SE, mL/min per 1.73 m²</td>
<td>–</td>
<td>13.1 ± 0.9</td>
</tr>
<tr>
<td>Percentage bias ± SE, %</td>
<td>–</td>
<td>14.7 ± 1.1</td>
</tr>
<tr>
<td>Percentage of estimated GFR within 30% of measured GFR, %</td>
<td>–</td>
<td>50</td>
</tr>
<tr>
<td>Mean estimated GFR ± SD using the quadratic equation (range), mL/min per 1.73 m²</td>
<td>98 ± 24 (13 to 155)</td>
<td>112 ± 15 (82 to 154)</td>
</tr>
<tr>
<td>Bias ± SE, mL/min per 1.73 m²</td>
<td>10.8 ± 0.6</td>
<td>13.3 ± 1.2</td>
</tr>
<tr>
<td>Percentage bias ± SE, %</td>
<td>13.7 ± 0.8</td>
<td>14.9 ± 1.3</td>
</tr>
<tr>
<td>Percentage of estimated GFR within 30% of measured GFR, %</td>
<td>47</td>
<td>52</td>
</tr>
</tbody>
</table>

* GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease.
† Stages 1 and 2; measured GFR ≥ 60 mL/min per 1.73 m².
‡ Potential kidney donors.

Creatinine and GFR is not the same as in normal-weight adults of white ethnicity who are in good health. Specific equations must therefore be developed for these populations, as has been done for African-American persons (3).

Second, using 0.8 mg/dL (71 μmol/L) as the creatinine value in the Mayo Clinic formula seems questionable. Doing so may obscure phenomena such as hyperfiltration, which is frequently seen in obese and diabetic patients. Third, we are not surprised at the inability of the Cockcroft–Gault formula to estimate GFR. In fact, this formula estimates not GFR but creatinine clearance, and we know that the latter is different from GFR because of tubular creatinine secretion. Moreover, the mean creatinine clearance of the 236 patients included in the Cockcroft–Gault study was 72.7 mL/min (1.21 mL/s). Rule and colleagues’ assertion that the Cockcroft–Gault equation was “developed in chronic kidney disease samples” is thus not correct (4). Last, we think that using indexed GFR for body surface area is also theoretically questionable and may cause bias, especially in obese patients (5).

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References

TO THE EDITOR: Rule and colleagues (1) tested the MDRD study equation (2) across a wide range of GFRs and found that it under-estimated GFR by 29% in potential kidney donors. They concluded that the MDRD equation is inaccurate in healthy people and developed a new equation for estimating GFR when the diagnosis of chronic kidney disease is unknown. As suggested by Stevens and Levey in their accompanying editorial (3), we used both of these equations to estimate GFR in a community-dwelling elderly population as part of the Jerusalem Longitudinal Study.

Four hundred fifty-four participants, all 70 years of age at study entry, underwent extensive social, clinical, physical, functional, and laboratory examinations. Baseline serum creatinine concentration was measured in all participants as part of the laboratory profile. Survival was determined for 12 years following the initial cross-section. When the MDRD equation was used, 290 participants were classified as healthy, with a mean GFR of 78.2 mL/min per 1.73 m², and 151 were classified as having renal failure, with a mean GFR of 49.5 mL/min per 1.73 m². The mean GFR for the whole sample was 68.2 mL/min per 1.73 m². When the new quadratic equation was used, 370 participants were classified as healthy, with a mean GFR of...
87.6 mL/min per 1.73 m², and only 71 were classified as having renal failure, with a mean GFR of 48 mL/min per 1.73 m². The mean GFR for the whole sample was 81.2 mL/min per 1.73 m².

We analyzed the relation of GFR derived by each formula to 12-year survival by using a Cox proportional hazards model. We included the following independent variables at age 70 years: sex, independence in activities of daily living, physical activity, self-reported health, diabetes mellitus, hypertension, ischemic heart disease, cerebrovascular and malignant diseases, anemia, smoking, body mass index, and serum cholesterol level. The hazard ratio was 1.19 (95% CI, 0.83 to 1.71; \( P = 0.33 \)) using MDRD and 1.56 (CI, 1.01 to 2.39; \( P = 0.004 \)) using the quadratic equation.

In our sample of community-dwelling elderly persons, a significantly smaller number were classified with renal failure by the new quadratic equation, yet it appears to be a stronger predictor of mortality than the MDRD equation. The differences between these 2 formulas are substantial and may change the frequency with which renal failure is diagnosed. An equation derived by using healthy persons and patients with chronic kidney disease (the quadratic equation) decreased the prevalence of reduced GFR and thus chronic kidney disease. A similar argument exists between cardiac output and cardiac index.

The letter by Maaravi and colleagues nicely illustrates a point. An equation derived by using patients with chronic kidney disease (the MDRD equation) increased the prevalence of reduced GFR and weakened epidemiologic associations between GFR and risk factors. However, an equation derived by using healthy persons and patients with chronic kidney disease (the quadratic equation) decreased the prevalence of a reduced GFR and strengthened epidemiologic associations. To better understand the epidemiology of early chronic kidney disease, we need studies that measure rather than estimate GFR in populations where the diagnosis of chronic kidney disease is unknown.

\[ \text{Potential Financial Conflicts of Interest: None disclosed.} \]

\section*{References}


\section*{IN RESPONSE:}

We are gratified that our article has generated a healthy discussion. It was not our intent to initiate a debate about “whose GFR equation is best.” All of the available equations, including ours, have limitations. Instead, we believe we should concentrate our efforts on whether a generalizable equation based on serum creatinine can be developed (this may not be possible). We also believe that it is important to be cautious when interpreting the prevalence of a reduced estimated GFR in various populations.

The discrepancy between our results and those of Froissart and colleagues may be related to differences in methods. In our study, we compared patients with chronic kidney disease who had an estimated (not measured) GFR greater than 60 mL/min per 1.73 m² with healthy persons. Since the objective was to compare the accuracy of equations in predicting measured GFR, we did not identify or stratify the chronic kidney disease and healthy samples by measured GFR. The quadratic GFR equation (derived by using two-thirds healthy persons and one-third patients with chronic kidney disease) should be tested in populations where the diagnosis of chronic kidney disease is unknown, such as the general population. Even with careful attention to creatinine assay calibration, other investigators showed that at a GFR of 60 mL/min per 1.73 m², the MDRD equation underestimated measured GFR by 30 mL/min per 1.73 m² among healthy persons (1).

We agree with Delanaye and colleagues that the relationship between serum creatinine concentration and GFR differs among many populations and clinical presentations (for example, good health vs. chronic kidney disease). In our equation, the cutoff of 0.8 mg/dL (71 \( \mu \)mol/L) for serum creatinine concentration was determined as the peak of the parabola; otherwise, a further decrease in creatinine concentration would lead to a decrease in estimated GFR. The version of the Cockcroft–Gault equation that we had referenced predicted GFR and was derived from patients with chronic kidney disease (2). Despite its limitations, if GFR was not indexed to body size in some way, smaller persons would be more likely to have a reduced GFR and thus chronic kidney disease. A similar argument exists between cardiac output and cardiac index.

The letter by Maaravi and colleagues nicely illustrates a point. An equation derived by using patients with chronic kidney disease (the MDRD equation) increased the prevalence of reduced GFR and weakened epidemiologic associations between GFR and risk factors. However, an equation derived by using healthy persons and patients with chronic kidney disease (the quadratic equation) decreased the prevalence of a reduced GFR and strengthened epidemiologic associations. To better understand the epidemiology of early chronic kidney disease, we need studies that measure rather than estimate GFR in populations where the diagnosis of chronic kidney disease is unknown.

\section*{Potential Financial Conflicts of Interest: None disclosed.}

\section*{References}


\section*{Correction: Relative Importance of Borderline and Elevated Levels of Coronary Heart Disease Risk Factors}

In an article on borderline and elevated levels of coronary heart disease risk factors (1), the Editors’ Notes contained an error. The last sentence of the Contribution section should have read, “Most events were attributable to elevated risk factors; among men, nearly one sixth occurred before age 55 years.”

\section*{Reference}