RED CELL DISTRIBUTION WIDTH (RDW): AN UNDERAPPRECIATED MARKER FOR INCREASED MORTALITY

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Executive Summary *This article defines red cell distribution width (RDW), its calculation, and factors that influence its level in the complete blood count (CBC). It also explains the role of RDW as a strong marker for all-cause mortality in the general population, including cancer, cardiovascular and lung disease. An elevated RDW portends a worse prognosis in conditions such as heart failure, atrial fibrillation, stroke, peripheral vascular disease, lung cancer and multiple myeloma. It is also a predictive indicator of adverse outcomes with hip fracture, renal disease and liver disease. The increased risk of adverse outcomes is seen in both men and women and at middle and older ages, with the highest risk being those individuals who have a rising RDW value. Practical considerations for using RDW are also discussed.*

The usual red blood cell (RBC) volume is approximately 80-100 fl. However, the size can vary significantly. Heterogeneity of cell volume is known as anisocytosis. The degree of anisocytosis or size variability is quantified by the red cell distribution width or RDW. The RDW equals the coefficient of variation of the mean corpuscular volume (MCV). The actual formula for calculating the RDW is the standard of deviation (SD) of the red blood cell volume divided by the MCV. The RDW is routinely calculated by virtually all automated hematologic analyzers, so the values are reported for almost every complete blood count (CBC). The results are usually expressed as a percentage with the usual upper limit of normal in the 14.5% to 15.0% range.

Several factors may affect RDW values. Erythropoietin, a hormone that regulates the production, maturation and survival of red blood cells, is one of these. Low levels of erythropoietin or resistance to its effects may increase the RDW. There is no significant difference in RDW by gender but values do gradually increase with age. Race is also a factor and individuals of black race have higher readings. There is also a modest increase with strenuous exercise. Pregnancy may affect the RDW but the data supporting this is mixed.

One thing to remember is that, while the RDW is routinely calculated by virtually all automated hematologic analyzers, the actual methodology used by those machines differs somewhat. As a result it is, to some degree, difficult to strictly compare the values generated by different analyzers. This is one reason why the normal range may vary from lab to lab.

The RDW is increased by conditions that modify the shape of the RBCs, i.e., those that lead to ineffective production or increased destruction of red cells. Traditionally, the RDW has been used in combination with the MCV in the assessment of anemia. For example, conditions with a normal RDW and low, normal and high MCV would include (among others) thallasemia minor, acute blood loss and chronic liver disease, respectively. On the other hand, anemias with a high RDW and low, normal and high MCV would include (among others) iron-deficiency anemia, sickle cell anemia and vitamin B12 or folate deficiency, respectively. Of these situations the one most commonly seen in underwriting is using the RDW to separate iron deficiency from thallasemia minor in applicants with anemia and a low MCV.

However, the RDW has a much broader application in risk selection than differentiating various types of anemia. It is a very strong marker for all-cause

mortality in the general population. It is also a predictive marker for adverse outcomes in individuals with known cardiovascular disease of various types. It is an indicator of an increased incidence of and mortality related to venous thromboembolic disease. RDW is also a predictive and prognostic indicator for some cancers. Adverse outcomes with hip fracture, renal and liver disease are more common with an elevated RDW. In addition, it is an indicator of overall cardiorespiratory fitness.

Higher RDW levels are associated with certain personal characteristics. These include older age, lower level of education, current smoking, higher BMI and a greater likelihood of nutritional deficiencies. In addition, elevated values are associated with the following findings: lower glomerular filtration rate (GFR), reduced hemoglobin levels, higher C-reactive protein (CRP) readings, an increased fibrinogen and white blood cell (WBC) count.

The risk of mortality in the general population has been demonstrated in a variety of studies (Figure 1). The elevation of relative risk begins even within the normal range and steadily gets larger as the value of the RDW increases (Figure 2, page 34). This mortality results from a variety of causes, including cancer, cardiovascular and lung disease, but, interestingly, not due to external sources or traumatic events (Figure 3, page 34). The risk is seen in both men and women (Figure 4, page 36) and in both middle and older ages. Interestingly, the increase in mortality is seen in those with and without anemia. In fact, the relative risk is higher in those without anemia (Figure 5, page 36).

Figure 1

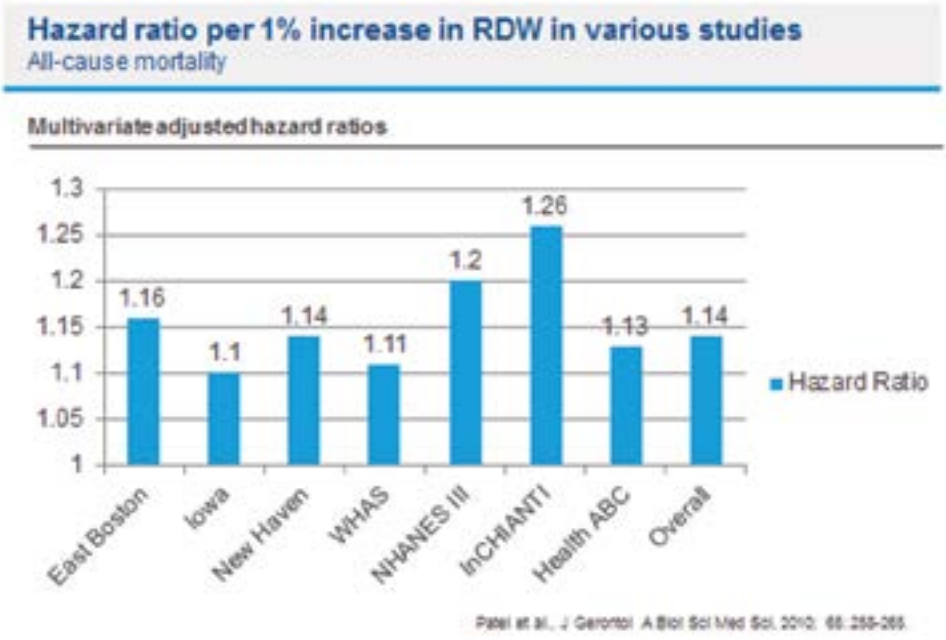


Figure 2

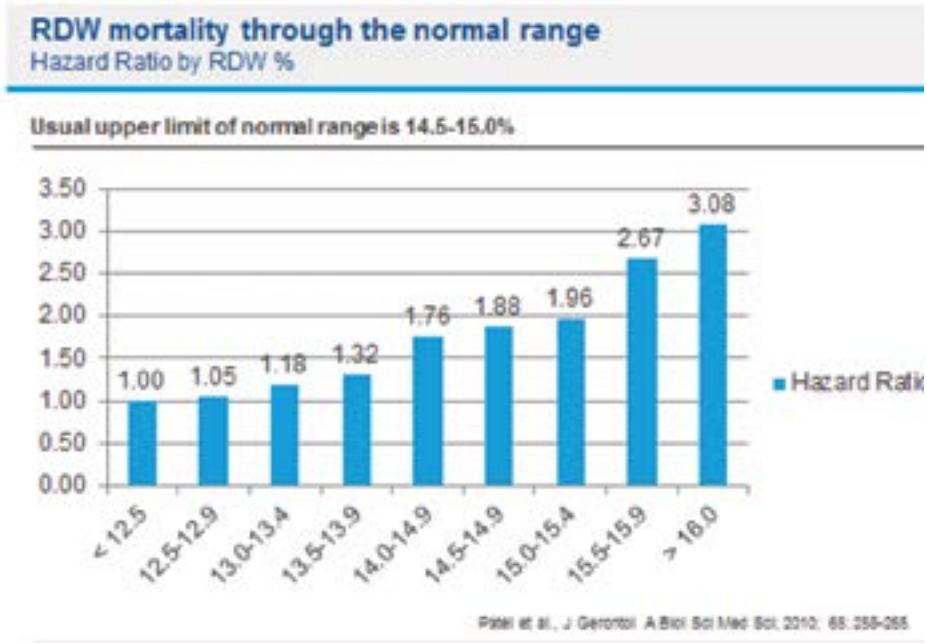


Figure 3

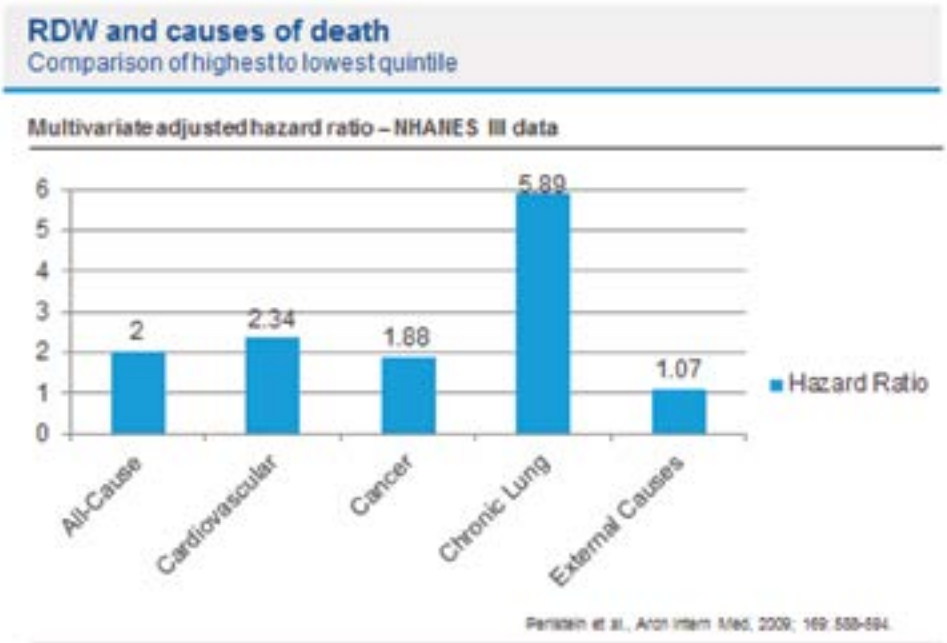


Figure 4

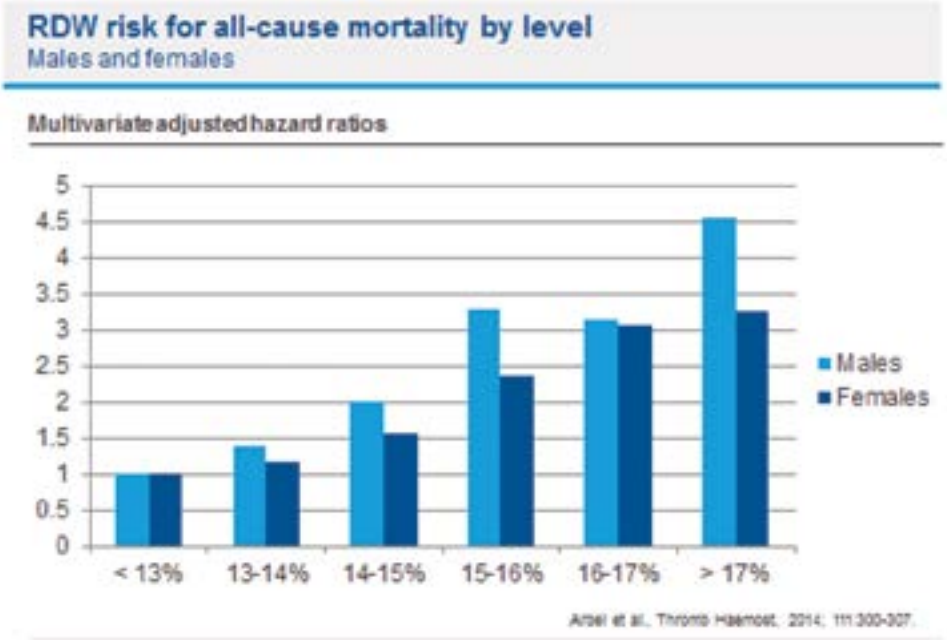
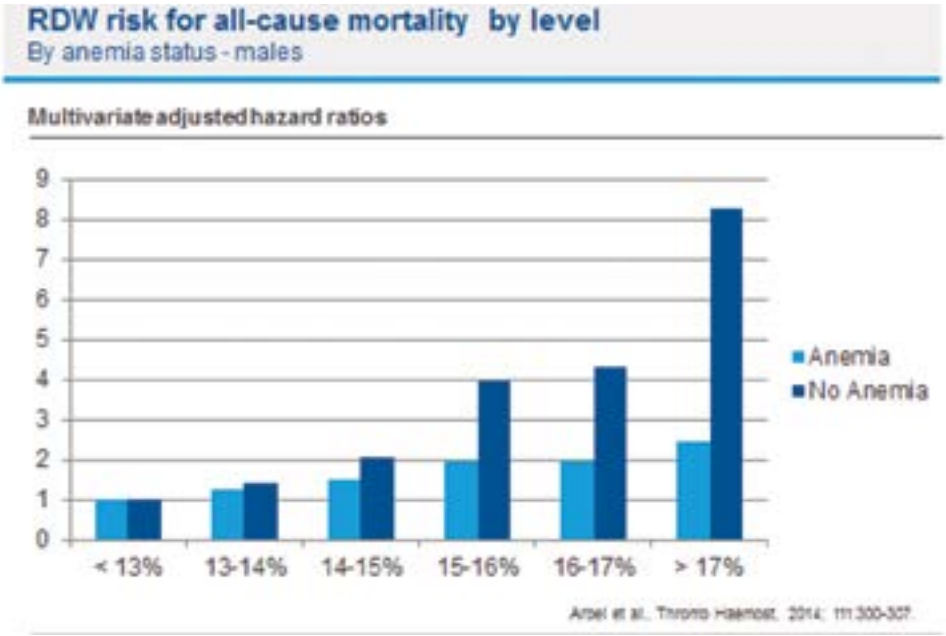


Figure 5



Multiple studies have indicated an increase in all-cause (Figure 6) and cardiovascular mortality (Figure 7) and non-fatal cardiovascular events in individuals with known coronary disease (Figure 8, page 38). Elevated RDW is also an indicator of adverse mortality outcomes in individuals with acute coronary syndrome and those undergoing angioplasty and bypass surgery. Interestingly, this increased risk is evident after a single reading and persists for at least 10 years in some studies. RDW is associated with other known risk factors for adverse cardiac outcomes. It is associated with elevated CRP readings. However, controlling for the latter does not eliminate the risk (Figure 9, page 38). In addition, higher levels of RDW are a marker for lower levels of cardiorespiratory fitness. There is a strong association between RDW and

Figure 6

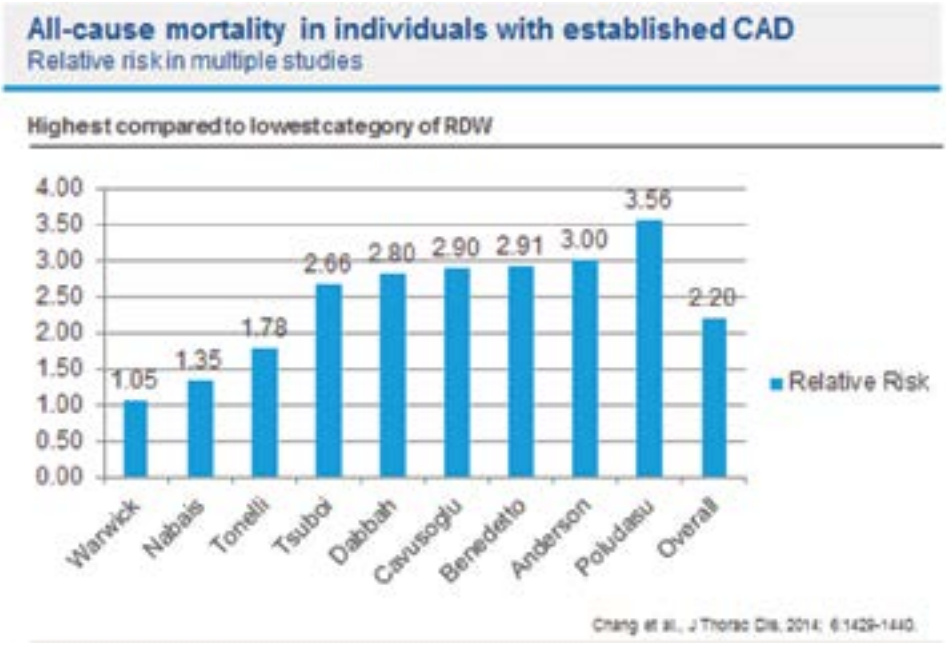


Figure 7

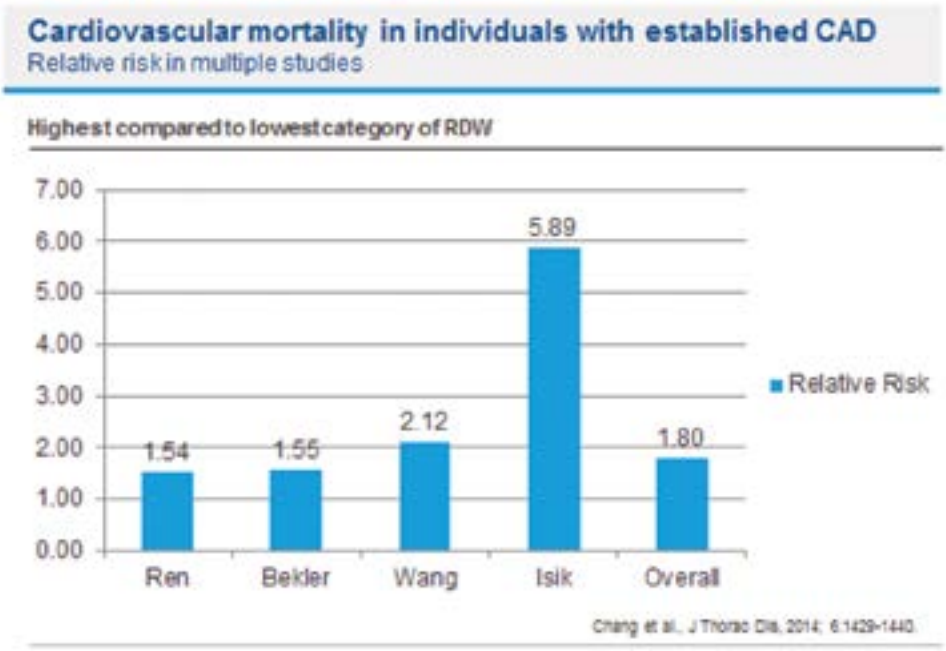


Figure 8

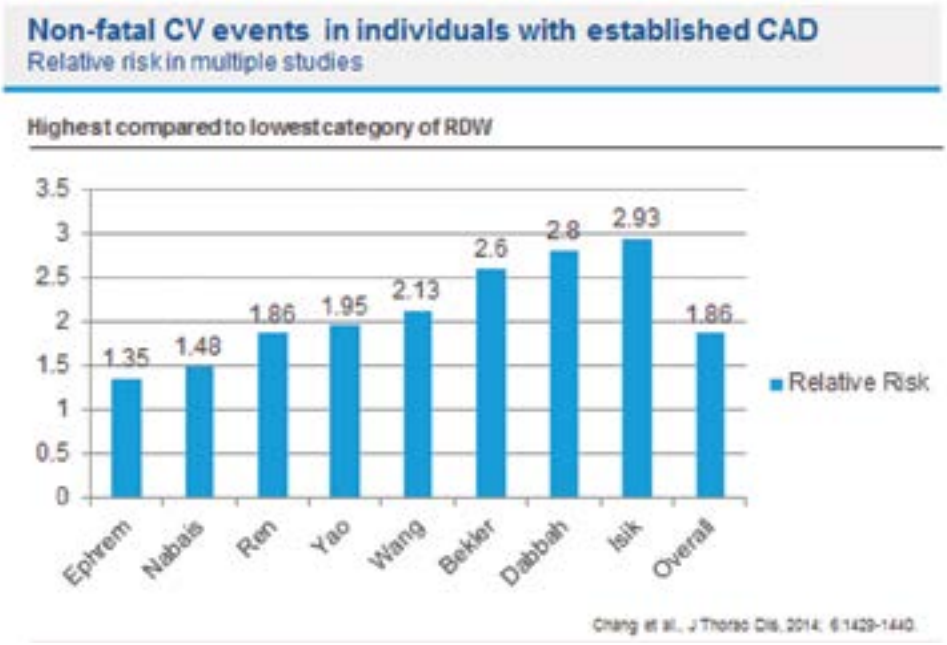
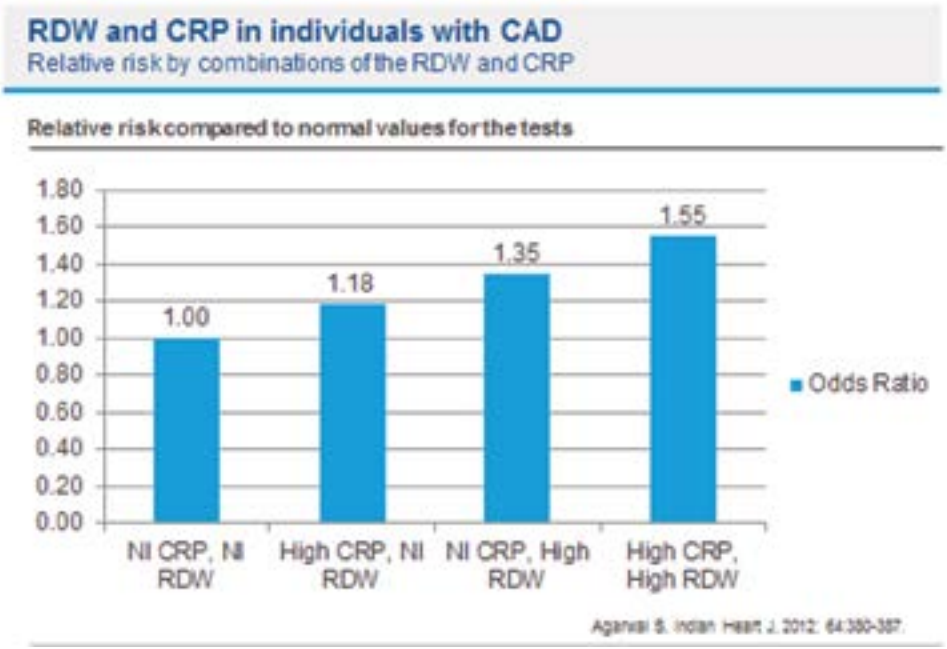


Figure 9



heart failure, including cases with both a reduced and preserved ejection fraction (EF) (Figure 10). This includes individuals with elevations of the NT-pro-B natriuretic peptide (NT-pro BNP) (Figure 11). In one study of individuals with heart failure, both an elevated but stable and a lower but rising level of RDW were associated with increased mortality. The highest risk was in those individuals with an elevated and rising value (Figure 12, page 42).

Figure 10

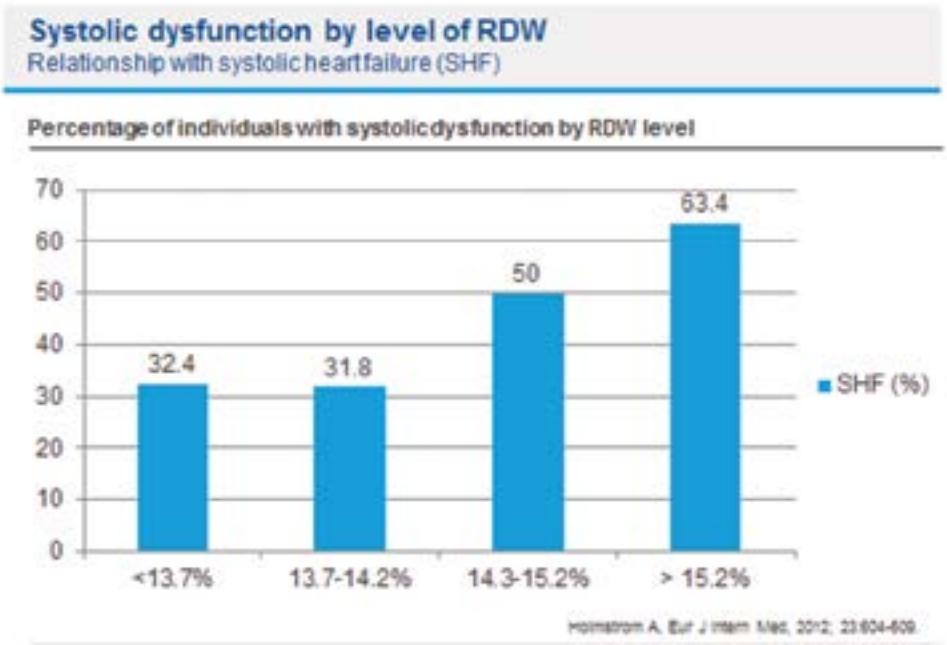


Figure 11

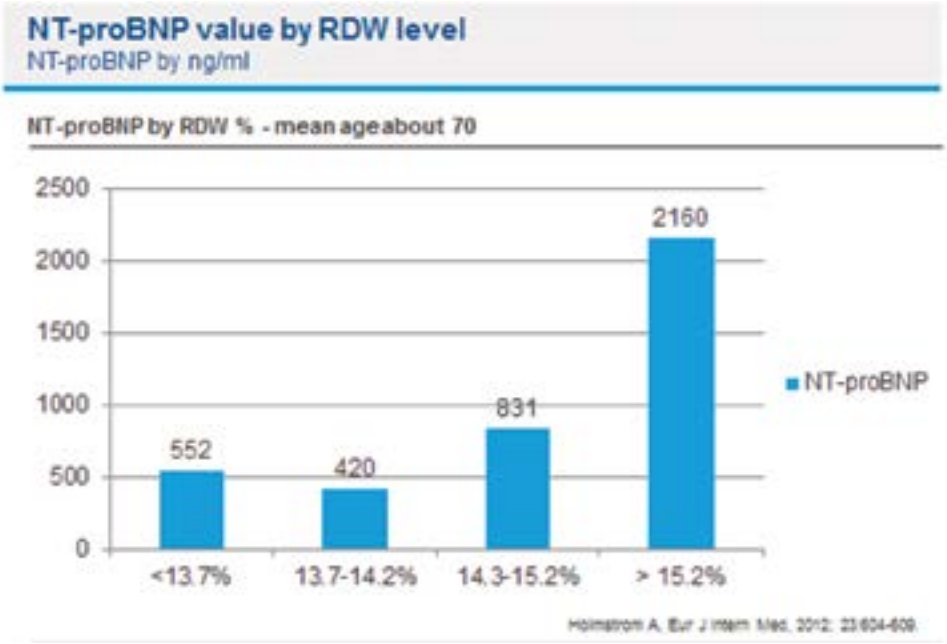
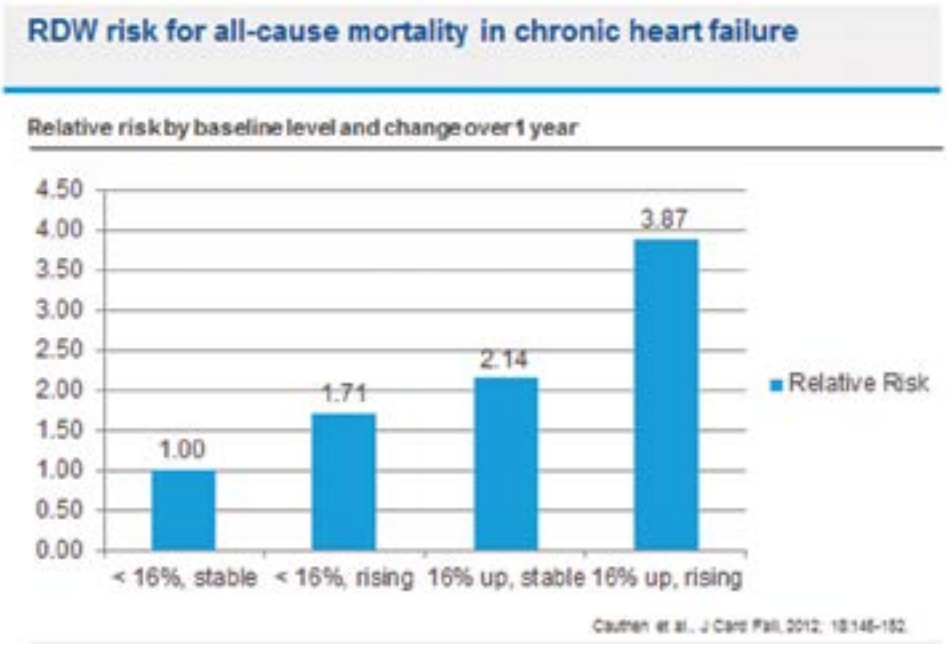


Figure 12



An elevation of RDW is associated with an increased risk of non-valvular atrial fibrillation. In fact, it is more predictive for fibrillation than many other factors, including CRP levels and left atrial volume. The association is seen in the general population and in those where a history of heart failure or previous myocardial infarction has been excluded, even when MCV levels are taken into account.

An increase in the RDW level is correlated with the presence of and mortality risk related to cerebrovascular disease (Figure 13, page 43). The rate of progression of carotid atherosclerosis is greater and the risk of stroke and death from stroke is higher as the level increases (Figure 14, page 43). This increased risk is associated with all types of stroke except subarachnoid hemorrhage.

In those individuals with peripheral vascular disease, an elevated RDW portends a higher mortality rate. A similar pattern is seen with deep venous thrombosis (DVT), where an elevated level of RDW is a marker for both a higher incidence and case fatality rate.

Incidence rates for cancer are higher in those with an elevated RDW. This occurs in both men and women (Figure 15, page 44). It has been shown to be a prognostic marker in some tumors, most notably lung cancer and multiple myeloma.

The RDW is also an indicator of reduced renal function (Figure 16, page 44) and the presence of microalbuminuria (Figure 17, page 45). In addition, it is a marker for adverse outcomes with various types of liver disease including hepatitis B, steatosis/steatohepatitis and cirrhosis.

Interestingly, an elevation of the RDW level has also been shown to be a marker for adverse mortality results in individuals with a hip fracture. Their risk persists for at least over the next 4 years after the event, *even if anemia is not present*.

When the RDW is related to a hematologic condition, the cause for excess death rates may be obvious. However, the reason for the above-noted very strong association with mortality in a variety of other conditions is not clear. One cause may be inflammation. Low-grade inflammation may lead to variability in red blood cell size, and it certainly plays an important part in the adverse events associated with cardiovascular disease and other conditions. However, as noted above, controlling for markers of inflammation such as CRP does not mitigate the risk.

Other factors that have been suggested as driving forces for the association with mortality include oxidative stress (important in many disease processes), shortened telomere length (which is related to both cellular aging and increased RDW levels), reduced erythropoietin levels and increased BNP values. However, none have been definitively proven to be causative at this point.

Figure 13

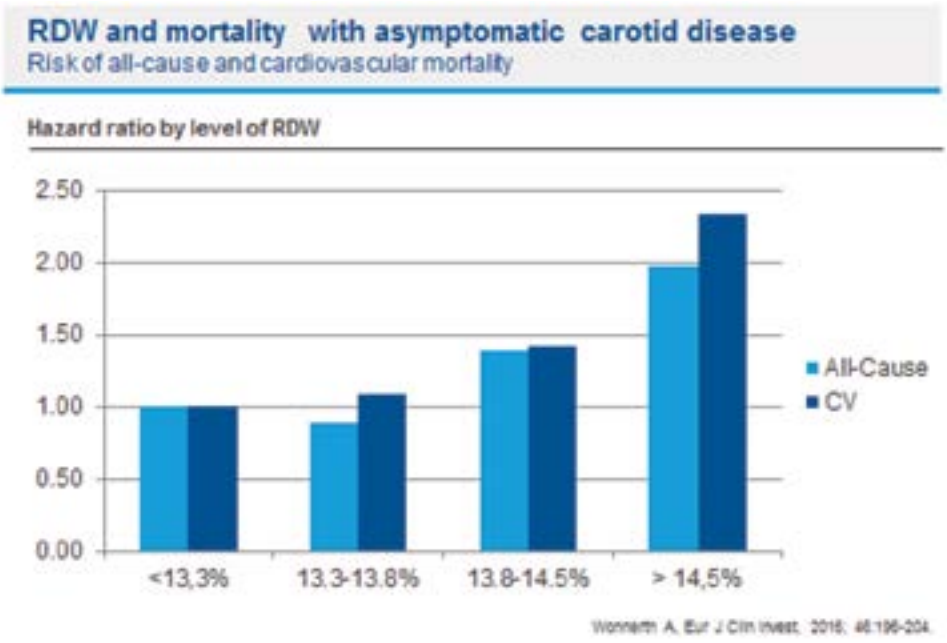


Figure 14

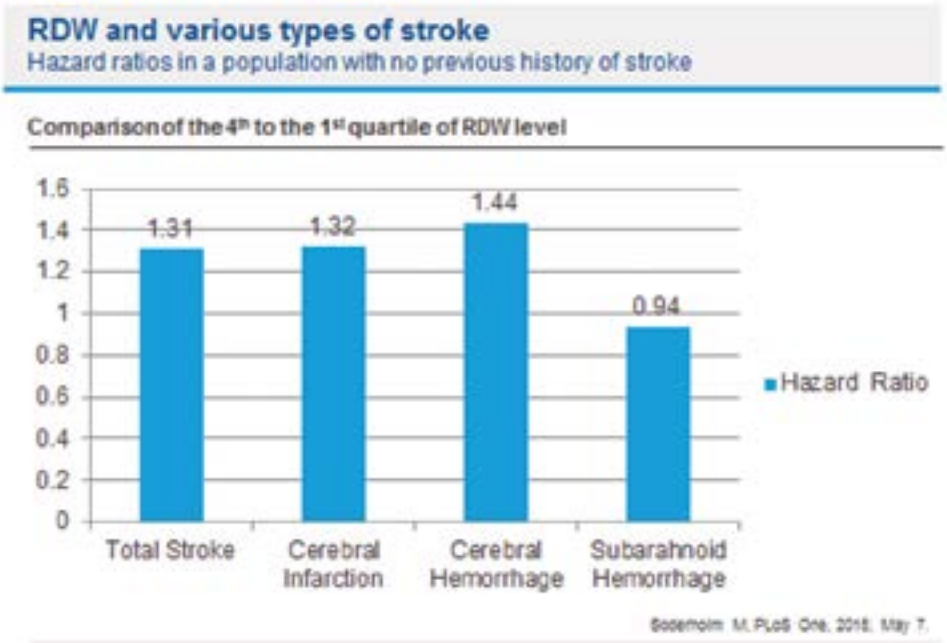


Figure 15

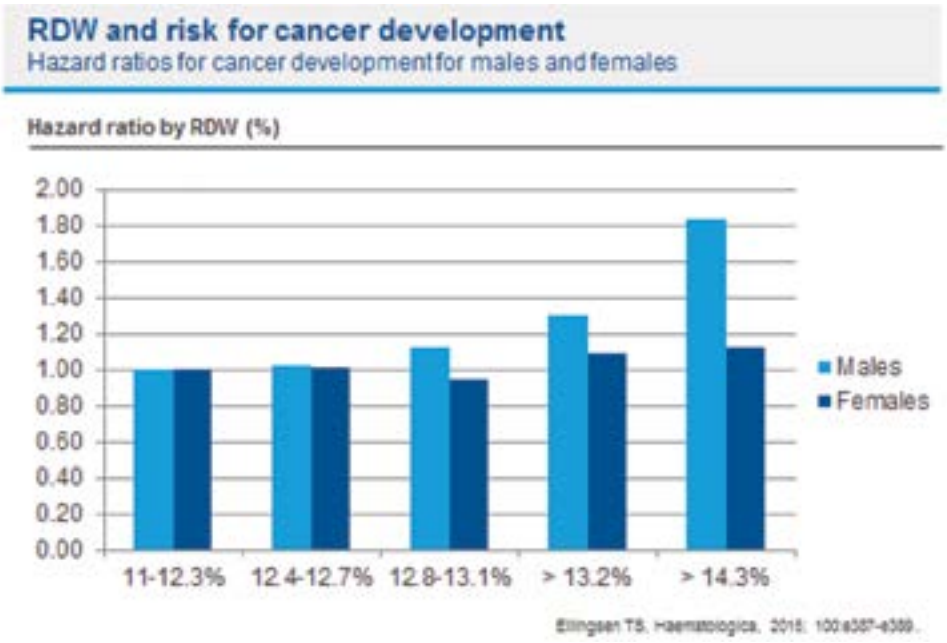


Figure 16

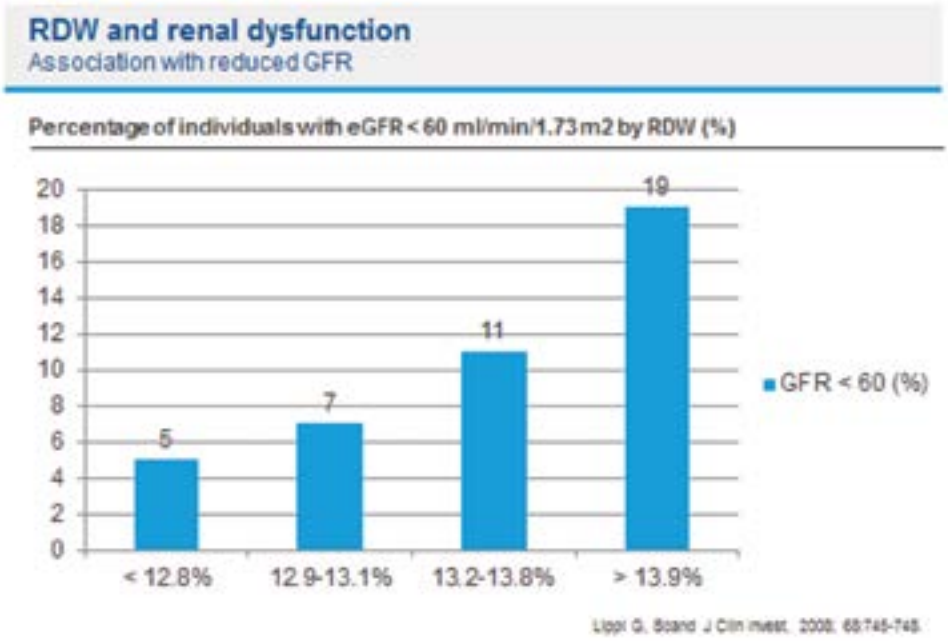
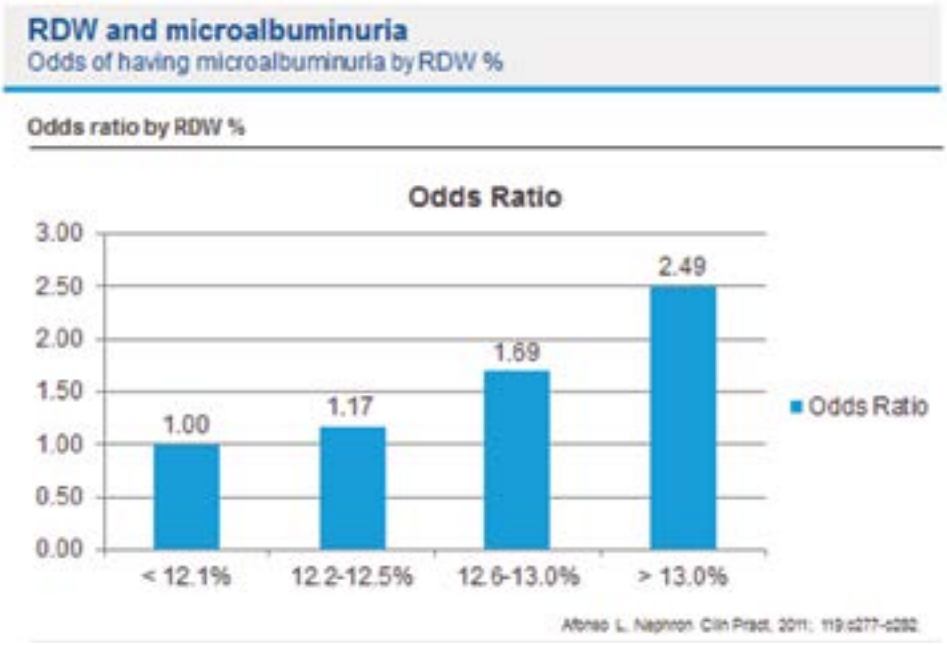


Figure 17



Unfortunately, obtaining accurate RDW results is not practical with the usual insurance blood testing protocols. Prolonged storage of blood before centrifugation, which is common with paramedical collection, frequently leads to breakdown of the RBCs and wide variation in the MCV and RDW, rendering the latter inaccurate. However, the RDW is obtained on virtually every CBC contained in an attending physician statement (APS).

Considering the degree and consistency of the risk associated with an elevated RDW, its use in the underwriting process would seem logical. However, there are important practical issues that should be considered. First, most of the above-cited studies were based on a single reading. However, would an underwriter be comfortable taking an action on a CBC that was performed, say, 5 years ago? Thus, at a minimum, some consideration should be given to a time limit on actionable values.

Second, there is only very limited data available on the risk profile when the RDW level is changing over time. One study, cited previously, showed a higher risk with rising levels over time in patients with heart failure. There is no data on decreasing levels. The fact that readings may differ with different analyzers compounds the issue with serial tests. Nevertheless, if the RDW was to be used in underwriting, the available guidelines should account for the scenario of test variation over time.

Third, although mortality risk scales upward through the normal range and beyond, is it practical to take adverse action on values that do not exceed the laboratory upper limit of normal? One would need to consider at what point in the continuum of readings an action would be taken and debits applied.

Finally, as noted previously, the specific mechanism of action by which the RDW is associated with an increased morbidity and mortality risk is uncertain at this time. In theory, this could pose a problem in explaining adverse actions to agents and attending physicians. However, the weight of the evidence from the clinical literature, as summarized in this article, is so large and compelling regarding excess risk that this is unlikely to be a significant issue in practice.

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