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Troponin Reference Range Changes

With the imminent implementation of a major chemistry analyzer change on the horizon (see *A new laboratory VISTA* and *TSH Reference Range Changes* in last month's *Laboratory Bulletin*), there will be changes in a few laboratory reference ranges. The improved sensitivity of the VISTA's troponin

The table below shows all reference range changes accompanying the migration to the new (Dade Vista) chemistry analyzer. For tests not listed, there will be no change in the reference range.

Reference Range Changes - VISTA

Test	Old	New
Albumin	3.5 - 5.0 g/dL	3.4 - 5.0 g/dL
AST	15 - 40 U/L	15 - 37 U/L
BUN	male: 10 - 20, female: 8 - 20 mg/dL	7 - 18 mg/dL (M/F)
Calcium	8.5 - 10.5 mg/dL	8.5 - 10.1 mg/dL
Carbamazepine	8.0 - 12.0 mcg/mL	4.0 - 12.0 mcg/mL
CK	30 - 120 U/L	male: 35-232 U/L, female: 21-215 U/L
Creatinine	0.4 - 1.5 mg/dL	0.6 - 1.3 mg/dL
Direct Bilirubin	0.0 - 0.3 mg/dL	0.0 - 0.2 mg/dL
Ferritin	male: 20 - 244, female 11 - 146 mcg/dL	male: 28 - 365, female: 5 -148 mcg/dL
Free T4	0.77 - 1.61 ng/dL	0.76 - 1.46 ng/dL
Glucose tolerance > 2hr	70 - 115 mg/dl	65-99 mg/dL
Hgb A1C	3.9 - 6.1%	4.8 - 6.0%
Iron	50 - 150 mcg/dL (M/F)	male: 50 - 170, female: 65 - 175 mcg/dL
Lipase	11 - 29 U/dL	114 - 286 U/L
Magnesium	1.5 - 2.1 mg/dL	1.8 - 2.4 mg/dL
Phosphorus	2.5 - 4.8 mg/dL	2.5 - 4.9 mg/dL
Potassium	3.5 - 5.0 mmol/L	3.5 - 5.1 mmol/L
Prealbumin	18.0 - 35.7 mg/dL	20 - 40 mg/dL
Protein, Total	6.0 - 8.0 g/dL	6.4 - 8.2 g/dL
Sodium	135 - 145 mmol/L	136 - 145 mmol/L
T3 free	1.8 - 4.2 pg/mL	2.18 - 3.98 pg/mL
T3 total	84.0 - 172.0 ng/dL	0.97 - 1.67 ng/ml
Troponin-I	0 - 0.09 ng/mL	0 - 0.045 ng/mL
TSH	0.34 - 4.82 uIU/ml	0.358 - 3.740 mIU/L

Change in Units

Clinically significant change in reference range

Change in Units/Clinically significant reference range change

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assay will produce yet another decrease in the troponin reference range, and allow Rex Laboratory to comply with recently published guidelines for laboratory markers of myocardial injury.

As discussed in a previous Lab Bulletin, a revised definition of acute myocardial infarct (AMI) was proposed several years ago by joint consensus of American and European cardiologists.[1,2] The "revised" clinical definition for AMI is a "typical rise and gradual fall (troponin) or rapid rise and fall (CK-MB) with at least one of the following:

- ischemic symptoms;
- development of pathologic Q waves on ECG;
- ST segment elevation or depression on ECG; or
- coronary artery intervention (e.g. coronary angioplasty).[2]

The Committee further recommended that an increased troponin or CK-MB should be defined as a value that exceeds the 99th percentile of the reference control population, and that laboratory imprecision at this level should have a coefficient of variation (CV) ≤10%. When we revised our troponin range last year, we did not adopt the 99th percentile cut-off as the precision at that level was > 10%.[1]

The new (Dade Vista®) chemistry analyzer has a "third generation" troponin assay, where the CV is < 10 percent at the 99th percentile of the reference control population. As a result, we will revise the troponin reference range to reflect the improved sensitivity and precision and comply with the above recommendations. (The Vista® CK-MB assay is basically unchanged from the previous chemistry analyzer, so we will not revise this reference range.)

Recently a second consensus document was issued by a group of laboratory scientists and cardiologists, building upon the earlier document.[3,4] Recommendations from this group included the following, (in addition to others quite similar to those given above) :

- Troponin is the preferred marker for the diagnosis of AMI. CK-MB (by mass assay, rather than enzyme activity) is an acceptable alternative when troponin is not available.
- Serial sampling is necessary for accurate diagnosis. For most patients, blood should be obtained at presentation and 6 - 9 hours later.
- In the presence of appropriate clinical history, a cardiac troponin exceeding the 99th percentile of reference range (with precision defined by CV < 10 percent) on at least one occasion during the first 24 hours is considered indicative of myocardial necrosis c/w AMI.[3,4]

The committee recommended abandoning the 2-level decision limit (one level for myocardial injury and another for myocardial infarct) employed by many assays/laboratories ever since troponin was first introduced.[1,5] As a result, with the implementation of the Vista® in the days to come, troponin values > 0.045 ng/mL will be considered elevated, and suggestive of myocardial injury. (Previously we had reported values between 0.1 - 0.59 ng/mL suggested myocardial injury while values > 0.59 ng/mL suggested myocardial infarct.)

It is understood by both of these groups that not all elevated troponins are indicative of AMI. Note that the definitions of AMI refer to use of the test in the appropriate clinical context. The pitfalls of applying a sensitive test to a group of patients with a low prevalence of disease have been discussed at length in previous lab bulletins.[1,6]

John D. Benson, M.D.

References

1. *Benson J.D. Revised troponin reference range. Rex Laboratory Bulletin. Issue 117, July 2006.*
2. *Alpert JS et al. Myocardial infarction redefined: a consensus document of the Joint European Society of Cardiology/American Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 36:959-69, 2000.*
3. *Apple FS et al. National Academy of Clinical Biochemistry and IFCC Committee for standardization of markers of cardiac damage laboratory medicine practice guidelines: Analytical issues for biochemical markers of acute coronary syndromes. Clinical Chemistry 53:547-51, 2007.*
4. *Morrow D.A. et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Clinical characteristics and utilization of biochemical markers in acute coronary syndromes. Clinical Chemistry 53:552-74, 2007.*
5. *Benson J.D., Johnson J. Cardiac enzymology update. Rex Laboratory Bulletin. Issue 46, March 2000.*
6. *Benson J.D. Significance of borderline elevated troponin-I results in ED patients. Rex Laboratory Bulletin. Issue 121, December 2006.*

Warfarin Sensitivity Genotype

Introduction: Warfarin is used extensively as anticoagulant therapy for the prevention and treatment of thrombophilic states. Warfarin therapy has one of the highest rates of severe adverse drug reactions. The goal of therapy is to prevent thrombosis without overmedicating and increasing the risk for serious hemorrhage. The drug has a narrow therapeutic window and requires laboratory monitoring with a prothrombin time (PT) and the calculated international normalized ration (INR). It is well known that there is significant variability in response to warfarin as a result of age, weight, drug interaction and diet. More recently individual inherited variations in metabolism of warfarin and Vitamin K have been shown to affect blood levels and anticoagulation effect.

Warfarin metabolism: Warfarin is a Vitamin K antagonist and is metabolized in the liver in the cytochrome P450 system. Because this pathway is also utilized by many other drugs, drug interactions result in either increased or decreased breakdown of warfarin. Warfarin is inactivated in the liver by an enzyme that converts the more active isomer S-warfarin to inactive products. Alterations in the gene (CYP2C9) that encodes for the enzyme result in reduced enzyme activity, higher warfarin blood levels, and a higher degree of anticoagulation than expected.

Vitamin K metabolism: Unexpected excess anticoagulation may also occur due to decreased synthesis of Vitamin K. Vitamin K synthesis requires the enzyme "Vitamin K epoxide reductase". The gene responsible for formation of this enzyme is VKORC1. A genetic change in this gene (polymorphism) results in decreased enzyme activity and ultimately less production of Vitamin K. Accordingly, a reduced warfarin dose is required to compensate for the effects of the VKORC1 alteration in order to maintain the target INR.

Vitamin K and Warfarin genotypes: Genetic testing for both VKORC1 and CYP2C9 genes may be helpful to predict the anticoagulant effect of warfarin. Polymorphisms in the genes indicate whether the patient is more sensitive to warfarin than average. The VKORC1 genotype estimates the patient's sensitivity to warfarin. Those with the usual genotype (referred to as the GG genotype) tend to have a normal response to warfarin. Patients who have the sensitive genotype (AA or GA genotype) typically require a lower dose than average. Asians tend to have the AA genotype (more sensitive to warfarin).

VKORC1 genotype sensitivity

VKORC1	Change	Enzyme activity
-1639G->G	-1639G->A	reduced

The CYP2C9 genotype predicts the rate of metabolism (breaking down) of warfarin. Patients with a polymorphism in the gene will metabolize warfarin more slowly than usual. These patients will continue to accumulate warfarin the blood over a longer period of time and will take longer to reach a stable level. Therefore, slower metabolizers typically require a lower dose to reach a stable therapeutic INR.

A number of specific polymorphisms of the CYP2C9 gene result in enzymatic deficiencies. The following chart outlines the relationship between the polymorphisms detected in the assay and the effect of the activity of the enzyme encoded by that allele:

CYP2C9 genotype sensitivity

CYP2C9	Change	Enzyme activity
*1	none	normal
*2	430C->T	reduced
*3	1075A->C	reduced
*4	1076T->C	reduced
*5	1080C->G	reduced
*6	818delA	no activity

Who should be tested? There is no consensus on the clinical usefulness of warfarin genotype analysis. However, relative indications are as follows:

1. Patients who have previously been prescribed warfarin and required multiple dosing adjustments to maintain the INR in the target range
2. Patients with a history of thrombosis or bleeding when previously taking warfarin
3. Patient being started on a first prescription for warfarin

Is genetic testing necessary? Some clinicians question whether genetic testing adds significantly to the management of the patient. Most clinicians take age, weight, underlying disease state, current medications and other factors into consideration when anticoagulating a patient. The pattern of response of the INR to warfarin and subsequent dosage adjustments may provide insight into the genotype of the patient. A genotype analysis may be helpful but is no substitute for careful monitoring of the INR.

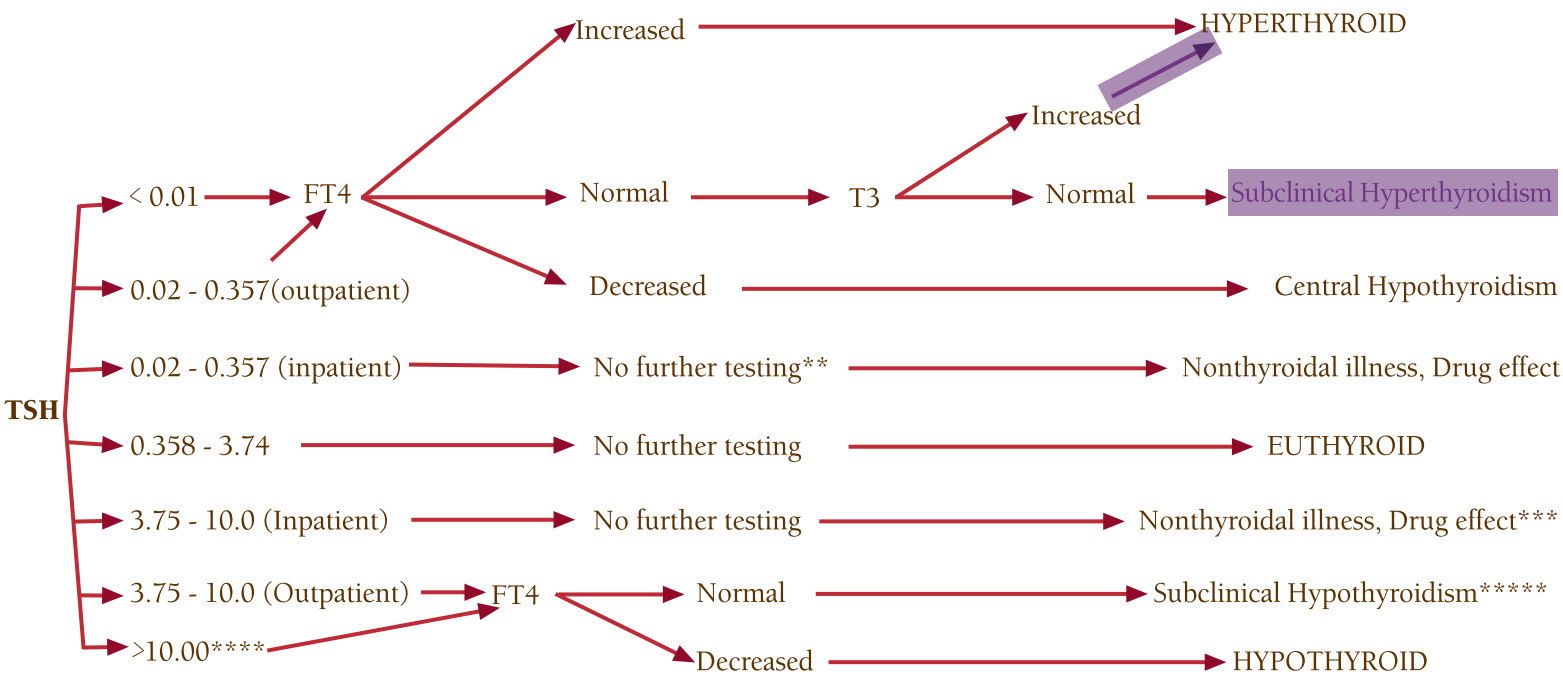
Specimen required: Order a Warfarin Sensitivity, Genotype (#89033) to Mayo Reference Laboratory. Three milliliters of EDTA (lavender-top) tube refrigerated in original tube is required. The test costs approximately $250.00 and is available Monday through Friday. The results include an interpretive report.

Summary: Genetic testing for warfarin sensitivity may be of value in certain clinical settings. However, more clinical outcome data showing a definite benefit is necessary before the test can be recommended for routine use.

Stephen V. Chiavetta, MD

References:
1. *Mayo Medical Laboratories Test Catalog, Warfarin Sensitivity, Genotype, test ID #89033, 2007.*
2. *Warfarin sensitivity genotype, #89033, Mayo Medical Laboratories Test Announcement, Volume 32, No. 7, July 2007.*
3. *Sconce, E. et al. The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristic upon warfarin dose requirements: proposal for a new dosing regimen. Blood, October 2005, Vol. 106, No.7, pp.:2329 - 2333.*
4. *Bussey, H. et al. Genetic testing for Warfarin (coumadin) dosing? - Not yet ready for prime time. ClotCare Online Resource September 27, 2007. http://www.clotcare.com/clotcare/warfaringenetictesting.aspx.*

Corrected TSH Algorithm *



* *Not applicable for patients suspected of having pituitary disease*
** *Perform FT4 only if concerned about central (pituitary, hypothalamic) hypothyroidism or symptoms suggesting hyperthyroidism*
*** *Repeat TSH after patient stabilizes as an outpatient*
**** *For inpatients, consider substituting 20.00*
***** *Controversial. Some endocrinologists favor treatment in some clinical scenarios. Determine TPO status and follow TSH annually*

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*The changes highlighted above were recognized by the (not-so-alert) editor following publication of last month's bulletin.

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