Trends-in-Medicine

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By Lynne Peterson

SUMMARY

The news also was good for Guidant, with the COMPANION trial confirming the value of CRT and, even more, CRT-D. However, CMS' lack of decision on reimbursement for ICDs using the MADIT-II indication continues to overhang the field. BNP testing is increasing, and doctors generally don't care which test is used – BNP or pro-BNP. With the entry of new BNP tests, BNP testing appears poised to move from point-of-care to analyzer testing, though a niche market is expected to remain in the ER and ICU. This is bad news for Biosite, but good news for Roche as well as Abbott and Dade-Behring, which also have BNP analyzer tests in development

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AMERICAN COLLEGE OF CARDIOLOGY: NON-STENT DEVICES

Chicago, Illinois
March 28 – April 2, 2003

Attention at this meeting was focused primarily on drugs and drug-eluting stents, but there were some devices that also deserve mention.

APPROVA MEDICAL'S PLAATO

PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion). During AF, the LAA is believed to be a source of dislodged blood clots that can travel to the brain and result in a stroke. The PLAATO procedure is a minimally invasive, endovascular therapy that occludes the LAA, site where blood clots are prone to form. PLAATO is intended to be a one-time therapy that provides a mechanical alternative to anticoagulation medication. It is placed with the use of a thin, flexible catheter, eliminating the need for open-heart surgery. An 87-patient study looked at permanent placement of this small occlusion device in atrial fibrillation patients at high risk of stroke. The study found the device and procedure safe, and a researcher concluded that it "may be an alternative for AF patients who cannot or will not take warfarin."

GUIDANT'S COMPANION TRIAL

The negative news about the Vision stent being recalled in Europe was offset somewhat by the positive news from the open label COMPANION trial, which compared optimal pharmacological therapy (OPT) with cardiac resynchronization therapy (CRT) and with a CRT+ICD (CRT-D). The trial had been stopped by the DSMB for efficacy. The figures presented were preliminary, but researchers believe they are likely an accurate representation of the final outcomes.

Preliminary Results from COMPANION Trial *

Measurement	Optimal Pharmacological Therapy (OPT)	OPT+CRT	OPT+CRT-D
Success rate	---	88.3%	92.0%
Implant time	----	200 minutes	213 minutes
Primary endpoint: Time to all cause death or all cause hospitalization	N/A	35.8% reduction vs. OPT (p=0.015)	39.5% reduction vs. OPT (p=0.005)
Secondary endpoint: All cause mortality	19%	23.9% reduction vs. OPT (nss)	43.4% reduction vs. OPT (p=0.002)

* All p-values are nominal and unadjusted.

Among the findings:

- The treatment effect was uniform across all subgroups.
- 55% of patients were ischemic, and 45% non-ischemic. There was a similar treatment effect in both groups.
- Mean follow-up was 16 months, and 13% of patients withdrew prior to the end of the trial.

Asked which device he would recommend, an investigator said, "The data is not completely analyzed, but I think at the end of the day, it will come down to a personal issue involving individual patients. We have clinical trial data that show probabilities, but individual patients have individual characteristics. For example, CRT clearly reduces hospitalizations and improves quality of life, but CRT-D provides a greater effect on mortality – but not all patients want to live longer, some just want to feel better. Ultimately, it will come down to an estimate of subgroup modifiers."

A Guidant official said the estimate is for tacky market growth this year to be 15%-25%, with a similar growth next year. He said, "A negative CMS coverage decision would put that at the low end…It would be very bad news." He said CMS would make a decision within 60 days of circulating the minutes of the MedPAC meeting, which he thought was imminent. However, CMS may wait longer, perhaps for the results of the SCD-HeFT trial, though that is unlikely to be conclusive either. In addition, some sources indicated that CMS already might be starting to crack down on doctors who implant ICDs by MADIT-II criteria. A source said some colleagues in New York had gotten warning letters advising them that CMS considers it Medicare/Medicaid fraud to use MADIT-II indications for ICD implantation. Another source said his hospital was using MADIT-II criteria for ICD use, and getting reimbursed, but he was concerned that they would lose that reimbursement soon.

JOHNSON & JOHNSON'S Noga System

Doctors at the Texas Heart Institute are investigating stem cell research for heart failure and end-stage heart disease. They are looking at delivering the stem cells percutaneously, using the Noga electromechanical mapping system. A tiny incision is made in the groin, a catheter is threaded into the left ventricle, electrical and motion capabilities of the heart are measured, and damaged or weakened areas of the heart muscle are mapped. The same catheter then is used to deliver stem cells to those damaged areas.

BNP TESTING

Two tests are currently available – Roche's proBNP and Biosite's Triage BNP – but Bayer is expected to launch its analyzer-based BNP test in May 2003, and Abbott hopes to launch its analyzer-based BNP test later this year. Dade-Behring also has a proBNP test in development. Last year, Biosite got a lot of attention at ACC, including inclusion in an ACC-sponsored press conference. This year, Roche's proBNP test got the spotlight – including participation in an ACC press conference.

Roche was strongly pushing its pro-BNP test. Pricing is $17-18 per test, and is not expected, as some have speculated, to drop as low as $7 any time in the foreseeable future. Roche officials claim their test is more stable, lab-based and more precise than Biosite's Triage test. Roche currently has 7,000 Elecsys machines installed world-wide, and an official claims the company has sold 100 new machines since the proBNP test was approved, and he said those sales were due to the test. He said, "Sales have greatly exceeded our expectations."

The outlook for Biosite's Triage point-of-care test continues to deteriorate. Even a big Triage advocate admitted that the device is likely to become only a nice product used in the ER and ICU. He was telling other doctors that Roche's analyzer test is cheaper than Triage, and it appears it is since Triage costs about $21-$24. Most doctors interviewed said their hospitals want an analyzer test – Roche, Bayer or Abbott, whichever the hospital already uses.

Most sources didn't care which test was used, BNP or proBNP; they considered the choice mostly a marketing issue. Most doctors also said they wanted the test available through their central lab, but there were still some strong advocates of point-of-care testing. A doctor who has been a big advocate of point-of-care testing was telling other doctors thinking of starting BNP testing that it is cheaper to do on an analyzer. He predicted that point-of-care testing would become a niche use, restricted mostly to the ED and ICU. A heart failure specialist said, "I think we are on downside of the adoption curve."

A cardiologist explained how his hospital uses BNP testing: "If a patient is doing poorly but has a low BNP (say, 140), there is no change in our plan to admit the patient. If another patient is doing well, but has a higher BNP (say, 710), the BNP might change the plan and cause the patient to be admitted…In most cases, we continue to rely on a history and physical. We don't get BNP on all patients, and I'm not sure we should. But in some circumstances plasma BNP is very useful, especially when the clinical diagnosis is ambiguous...BNP is a very useful test, but for most cases, I would continue to urge you to rely on your clinical skills…This test is indeed important and very useful, but the irrational exuberance is over, and now use will be more rational." At this hospital 44% of BNP tests are done in the ER, 30% in the central lab, 11% in the ICU and 15% in the heart failure clinic.

BNP test advocates suggested that in the future BNP may be used to help diagnose and screen for many diseases. A

speaker said, "BNP is a prognostic for MI, ACS, heart failure and dyspnea." Another commented, "Can we use it to guide therapy? We probably don't have data to do that." BNP testing is being considered to:

- Guide therapy:
  - Natrecor treatment.
  - CHF outpatient management. An expert said, "BNP predicts adverse events in ACS. Any movement of BNP off the reference value (by 20-40 pg/dl) predicts an impending event."
- Screen for:
  - Left ventricular dysfunction. A 183-patient sub-study of the LIFE trial found that proBNP can predict cardiovascular events in patients with hypertension and left ventricular hypertrophy. A researcher concluded, "Future investigation may test the use of proBNP to select patients in need of more aggressive blood pressure reduction...and to monitor anti-hypertensive therapy."
  - Transplant rejection. While BNP screening for heart failure may not be cost-effective, BNP does appear to be useful in evaluating patients heart transplant patients. A researcher said, "In Scotland, that is something we want to implement in the near future."
  - Athletes.
- Determine risk of death. Patients with the highest BNP have a greater risk of death, independent of troponin elevation.
- Predict patients with acute pulmonary embolism.
- Diagnose diastolic dysfunction. A speaker said, "That is where I think this technology will really come into play."
- Aid in hospital discharge decisions. A speaker said that a BNP >500 pg/dL on discharge predicts rehospitalization, and a BNP <250 predicts event-free survival and successful outpatient management. He commented, "CRP cannot separate survival curves to the extent BNP can."

There are a number of unanswered questions besides which test to use or where to do the test. These include:

1. How much should BNP be lowered?
2. How frequently should BNP be monitored?
3. What is the full effect of drugs on BNP levels?
4. Do BNP levels need to be adjusted for age and gender?

Other tests also are being explored that could be even better predictors than BNP. One is plasma CNP. A speaker said, "CNP is not elevated in stable CHF. CNP has a short circulatory half-life, and it seems to be far more specific than BNP. CNP may be an important new mediator in the heart." A pilot study in 10 patients, using BNP as the control, found that there is a statistically significant relationship between CNP and PCWP and CNP may be "an important new local autocrine and/or endocrine mediator." Another expert said, "CNP might have value, but it won't be developed as a test…In plasma, the circulating level drops too quickly and is too low to be a diagnostic tool, but levels in the urine are higher than ANP or BNP, and a urine dip-stick test might be able to be developed. Data will follow on that."

A Cleveland Clinic researcher found some symptomatic patients with systolic heart failure have plasma BNP levels in the normal range (<100 pg) despite their disease. He did a retrospective chart review of 662 consecutive heart failure patients at his hospital between November 2002 and February 2003 all of whom had BNP measured with Biosite's Triage, and 30% had BNP measurements in the normal range.

Measurement	Number
Consecutive patients	662
Eligible patients	558
Plasma BNP ≥100	392 (70%)

The normal BNPs were not due to lab errors, he said, adding, "Up to 60% of normal BNPs values were rechecked within two hours, and all were within 10% of the same number…Sixty-four percent of patients with normal BNP levels remained symptomatic…Non-ischemic cardiomyopathy predominates in this normal BNP cohort. Further studies are needed to understand the heterogeneity of BNP generation, which may affect the interpretation of plasma BNP levels…We assume that there is a linear relationship between filling pressure and BNP release, but maybe there are other unknown factors that make BNP somewhat independent…It could be the etiology of the heart failure or something specific to viral infection…There are many factors that could influence the finding." A Pennsylvania doctor commented, "This shows you can't send home all the patients who have low BNP…This basically highlights that a clinical exam is still key, and the (BNP) test is an aid to diagnosis."

Another speaker suggested that the FDA may be considering the use of BNP measures as a surrogate for NYHA functional class, "The FDA likes the idea of including this as in inclusion for clinical trials and perhaps as a surrogate endpoint."

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