September 2012

Introduction: Announcing the first Research Compendium

For more than three decades, physicians and medical professionals from Anne Arundel Medical Center have conducted clinical research studies. They have presented or published their results without fanfare, quietly contributing to medical knowledge in their fields.

The steady increase in clinical research activities by AAMC investigators led four years ago to the creation of the Anne Arundel Health System Research Institute, to facilitate and support those efforts.

Subsequently, working with the Johns Hopkins Institute for Clinical and Translational Research, we co-developed and became the first affiliate of the Johns Hopkins Clinical Research Network, which now has five affiliate health systems in three states engaged in clinical trials and research studies.

All of this was made possible by the quality and sophistication of the research work done by our physicians and hospital staff. We felt it was time that their accomplishments were acknowledged through the health system in which they work. Thus, this compendium was developed covering 2010 and 2011, the first of a series of periodic reviews of clinical research by AAMC investigators.

Beyond the recognition, the clinical results of these studies will be of interest to regional practitioners. In addition, physicians who advance medicine through research are usually on the leading edge of their areas of research interest. They can be a valuable resource for practitioners who wish to refer a patient whose specific needs fall into one of those areas.

Finally, I want to thank the staff and volunteers of the Research Institute who have worked with our investigators to help carry out those studies.

We hope you will find this compendium both interesting and useful.

Joe Moser, M.D.
Sr. VP for Medical Affairs
Anne Arundel Medical Center
**Oncology**

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## Oncology

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**Abstract**

Philadelphia chromosome (Ph)-negative myeloproliferative neoplasms (MPNs) are characterized by stem cell-derived, unrestrained clonal myeloproliferation. The World Health Organization classification system, proposed in 2008, identifies 7 distinct categories of Ph-negative MPNs including essential thrombocythemia (ET); polycythemia vera (PV); primary myelofibrosis (PMF); mastocytosis; chronic eosinophilic leukemia; chronic neutrophilic leukemia; and MPN, unclassifiable. For many years, the treatment of ET, PV, and PMF, the most frequently diagnosed Ph-negative MPNs, has been largely supportive. In recent years, that paradigm has been challenged because of the discovery of a recurrent point mutation in the Janus kinase 2 (JAK2) gene (JAK2(V617F)). This mutation can be detected in the vast majority of patients with PV and approximately half of patients with ET or PMF and serves as both a diagnostic marker as well as representing a putative molecular target for drug development. Several putative targeted agents with significant in vitro JAK2 inhibitory activity and various degrees of JAK2 specificity are currently undergoing clinical evaluation. Furthermore, other investigational non-tyrosine kinase inhibitor approaches such as immunomodulatory agents and pegylated interferon- have also shown promising results in MPNs.

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**Abstract**

The treatment of chronic myeloid leukemia (CML) drastically changed with the introduction of imatinib mesylate, a Bcr-Abl1 tyrosine kinase inhibitor (TKI), in 1998. By directly targeting this leukemogenic protein kinase, imatinib affords patients with CML sustained cytogenetic remissions, which translate into prolonged survival. However, there has been concern over the emergence of resistance to imatinib, and some patients fail to respond or are intolerant of imatinib therapy because of untoward toxicity. This has spurred interest in developing novel TKIs to overcome the mechanisms of resistance that lead to treatment failure—most importantly, Bcr-Abl1 kinase domain mutations. Two of these second-generation TKIs, nilotinib and dasatinib, are approved worldwide for the treatment of CML after imatinib failure or intolerance. Although these agents are active, they fail in many patients because of the development of highly resistant mutations such as the T315I, against which several novel agents are currently being tested in clinical trials. This review provides an account of the progress made in the field of TKI therapy for CML over the past decade.

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**Abstract**

**BACKGROUND:**

Among the well described cytogenetic abnormalities in adults with acute lymphoblastic leukemia (ALL), a translocation involving chromosomes 1 and 19 (t[1;19] [q23;p13]) occurs in a small subset but has been associated variously with an intermediate prognosis or a bad prognosis in different studies.

**METHODS:**

Adults with ALL and t(1;19) who were treated at The University of Texas M. D. Anderson Cancer Center were reviewed. Their clinical features and outcomes were compared with those of patients who had other cytogenetic abnormalities. The study endpoints included the complete remission (CR) rate, the complete response duration (CRD), and overall survival (OS).

**RESULTS:**

Of 411 adults with pre-B-cell ALL, 12 patients had t(1;19). Ten of 12 patients with t(1;19) received hyperfractionated cyclophosphamide, vincristine, doxorubicin (Adriamycin), and dexamethasone alternating with methotrexate and high-dose cytarabine (hyper-CVAD) chemotherapy; and the other 2 patients received combined vincristine, doxorubicin, and dexamethasone (VAD). All 12 patients achieved CR, and the 3-year survival rate was 73%. Patients with t(1;19) had significantly better CRD and OS compared with all other patients combined and compared individually with patients who had Philadelphia chromosome-positive, t(4;11), and lymphoma-like abnormalities (deletion 6q, addition q14q, t[11;14], and t[14;18]).

**CONCLUSIONS:**

Adults with ALL and t(1;19) had an excellent prognosis when the received the hyper-CVAD regimen.

|---------------|-----------------------------------------------------------------|-----------------------------------------------------------------|---------------------------------------------------------------------|

**Abstract**

Responses can be achieved with dasatinib or nilotinib after failure of 2 prior tyrosine kinase inhibitors (TKIs). We report on 48 chronic myeloid leukemia patients sequentially treated with 3 TKIs: 34 with dasatinib after imatinib/nilotinib failure and 14 with nilotinib after imatinib/dasatinib failure. Before the third TKI, 25 patients were in chronic phase (CP), 10 in accelerated phase (AP), and 13 in blast phase (BP). Best response to third TKI in CP was 5 major molecular responses (MMR), 3 complete cytogenetic (CCyR), 2 partial cytogenetic (PCyR), 3 minor cytogenetic (mCyR), 6 complete hematologic responses (CHR), and 6 with no response.
Abstract

The introduction of imatinib mesylate, a Bcr-Abl tyrosine kinase inhibitor (TKI), has revolutionized the treatment of chronic myeloid leukemia (CML). By directly targeting the Bcr-Abl kinase, imatinib leads to durable cytogenetic remissions and in turn improved survival. However, many patients with CML develop resistance, fail to respond, or become intolerant to imatinib due to side effects. This has spurred interest in developing second-generation TKIs to overcome the mechanisms of resistance that lead to treatment failure, specifically Bcr-Abl kinase domain mutations. Two second-generation TKIs, nilotinib and dasatinib, are approved for the treatment of CML after imatinib failure or intolerance. Unfortunately, many patients fail subsequent treatment with these agents, as they can develop highly resistant mutations such as T315I. Various other strategies are now in use to optimize the treatment of CML, including dose optimization of imatinib, combination therapy, upfront use of second-generation TKIs, and use of maintenance therapy with interferon-alpha and vaccines. This review highlights progress made in the treatment of CML in the past year.

Ravin J. Garg

Chronic myeloid leukemia in the tyrosine kinase inhibitor era: what is the "best" therapy?

Agrawal M, Garg RJ, Kantarjian H, Cortes J.

Epub 2010 Oct 4. Review

Abstract

This study was designed to investigate the molecular mechanism underlying the chemopreventive effects of methionine on benzo[a]pyrene metabolism in HepG2 cells. Methionine significantly inhibited B[a]P-DNA adduction formation in HepG2 cells. Methionine significantly decreased the cellular uptake of [(3)H]B[a]P, but increased the cellular discharge of [(3)H]B[a]P from HepG2 cells into the media. B[a]P significantly lowered total cellular glutathione (GSH) level, but co-cultured with B[a]P and methionine, gradually attenuated intracellular GSH levels was achieved higher at 20-500 μM methionine. The cellular proteins of treated cells were resolved by 2D-polyacrylamide gel electrophoresis. Proteomic profiles showed that phase II enzymes such as glutathione S-transferase (GST) omega-1, GSTM3, glyoxalase I (GLO1) and superoxide dismutase (SOD) were down-regulated by B[a]P treatment, whereas cathepsin B (CTSB), Rho GDP-dissociation inhibitor alpha (Rho-GDP-DIA), histamine N-methyltransferase (HNMT), spermidine synthase (SRM) and arginase-1 (ARG1) were up-regulated by B[a]P. B[a]P and methionine treatments, GST omega-1, GSTM3, GLO1 and SOD were significantly enhanced compared to B[a]P alone. Similarly, methionine was effective in diminishing the B[a]P-induced up-regulation of CTSB, Rho-GDP-DIA, HNMT, SRM and ARG1. Our data suggests that methionine might exert a chemoprotective effect on B[a]P-DNA adduct formation by attenuating intracellular GSH levels, blocking the uptake of B[a]P into cells, or by altering expression of proteins involved in DNA adduct formation.

Young J. Lee

Chemopreventive mechanisms of methionine on inhibition of benzo(a)pyrene-DNA adducts formation in human hepatocellular carcinoma HepG2 cells.


Abstract

This study was designed to investigate the molecular mechanism underlying the chemopreventive effects of methionine on benzo[a]pyrene metabolism in HepG2 cells. Methionine significantly inhibited B[a]P-DNA adduction formation in HepG2 cells. Methionine significantly decreased the cellular uptake of [(3)H]B[a]P, but increased the cellular discharge of [(3)H]B[a]P from HepG2 cells into the media. B[a]P significantly lowered total cellular glutathione (GSH) level, but co-cultured with B[a]P and methionine, gradually attenuated intracellular GSH levels was achieved higher at 20-500 μM methionine. The cellular proteins of treated cells were resolved by 2D-polyacrylamide gel electrophoresis. Proteomic profiles showed that phase II enzymes such as glutathione S-transferase (GST) omega-1, GSTM3, glyoxalase I (GLO1) and superoxide dismutase (SOD) were down-regulated by B[a]P treatment, whereas cathepsin B (CTSB), Rho GDP-dissociation inhibitor alpha (Rho-GDP-DIA), histamine N-methyltransferase (HNMT), spermidine synthase (SRM) and arginase-1 (ARG1) were up-regulated by B[a]P. B[a]P and methionine treatments, GST omega-1, GSTM3, GLO1 and SOD were significantly enhanced compared to B[a]P alone. Similarly, methionine was effective in diminishing the B[a]P-induced up-regulation of CTSB, Rho-GDP-DIA, HNMT, SRM and ARG1. Our data suggests that methionine might exert a chemoprotective effect on B[a]P-DNA adduct formation by attenuating intracellular GSH levels, blocking the uptake of B[a]P into cells, or by altering expression of proteins involved in DNA adduct formation.

Young J. Lee

Tnk1/Kos1: a novel tumor suppressor.

May WS, Hoare K, Hoare S, Reinhard MK, Lee YJ, Oh SP.

Toxicol Lett. 2011 Nov 25

Abstract

Tnk1/Kos1 is a non-receptor protein tyrosine kinase implicated in negative regulation of cell growth by a mechanism involving inhibition of Ras activation and requiring Tnk1/Kos1’s intrinsic catalytic activity. Tnk1/Kos1 null mice were created by homologous recombination by deleting the catalytic domain. Upon aging, both Tnk1+/− and Tnk1−/− mice develop spontaneous tumors, including lymphomas and carcinomas at high rates (i.e. 27%, and 43%, respectively), indicating that Tnk1/Kos1 is a tumor suppressor. Tissues from Tnk1/Kos1-null mice exhibit proportionally higher levels of basal and growth factor-stimulated Ras activation. Mechanistically, Tnk1/Kos1 requires either or both Y277 and Y287 sites to be intact for enzymatic activity and phosphorylation of its substrate, growth factor receptor binding protein 2 (Grb2). Data indicate that following tyrosine phosphorylation of Grb2 by Tnk1/Kos1, the Grb2-Sos1 guanine exchange factor (GEF) complex that mediates growth factor stimulated Ras activation becomes disrupted, resulting in the reversal of Ras activation. Conversely, the loss of Tnk1/Kos1 activity results in constitutive activation of Ras due to prolonged stabilization/activation of the Grb2-Sos1 GEF activity. Tnk1/Kos1 is the first tyrosine kinase discovered to have tumor suppressor activity, and the mechanism of spontaneous tumor formation involves constitutive, indirect activation of Ras. Thus, Ras may display "oncogenic activity" without undergoing "oncogenic" mutation. We now find that a cohort of patients with diffuse large B-cell lymphoma (DLBCL) display downregulation of Tnk1/Kos1 that may account for tumorigenesis in humans.

Barry Meisenberg

Phase I Clinical Trial Assessing Temozolomide and Tamoxifen With Concomitant Radiotherapy for Treatment of High-Grade Glioma

Pate1 S, Dibiasi S, Meisenberg B, Flannery T, Patel A, Dhople A, Cheston S, Amin P.

The new standard treatment of glioblastoma multiforme is concurrent radiotherapy (RT) and temozolomide. The proliferation of high-grade gliomas might be partly dependent on protein kinase C-mediated pathways. Tamoxifen has been shown in vitro to inhibit protein kinase C through estrogen receptor-independent antineoplastic effects. This Phase I trial was designed to determine the maximal tolerated dose (MTD) of tamoxifen when given with temozolomide and concurrent RT to patients with high-grade gliomas.

**METHODS AND MATERIALS:**

A total of 17 consecutive patients in four cohorts with World Health Organization Grade 3 \((n = 2)\) and 4 \((n = 15)\) gliomas were given tamoxifen twice daily during 6 weeks of concurrent RT and temozolomide. Eligibility included histologic diagnosis, age >18 years old, Karnofsky performance status \(\geq 60\), and no previous brain RT or chemotherapy. The starting dose was 50 \(mg/m^2\) divided twice daily. If no dose-limiting toxicities (DLTs) occurred in 3 patients, the dose was escalated in 25-\(mg/m^2\) increments until the MTD was reached. When \(\geq 2\) patients within a cohort experienced a DLT, the MTD had been exceeded. Temozolomide was given with RT at 75 \(mg/m^2\). A dose of 60 \(Gy\) in 2 \(Gy/d\) fractions to a partial brain field was delivered.

**RESULTS:**

A total of 6 patients in Cohort 4 had received tamoxifen at 125 \(mg/m^2\). One patient was excluded, and the fourth patient developed Grade 4 thrombocytopenia (DLT). Thus, 3 more patients needed to be enrolled. A deep venous thrombosis (DLT) occurred in the sixth patient. Thus, the MTD was 100 \(mg/m^2\).

**CONCLUSIONS:**

The MTD of tamoxifen was 100 \(mg/m^2\) when given concurrently with temozolomide 75 \(mg/m^2\) and RT. Tamoxifen might have a role in the initial treatment of high-grade gliomas and should be studied in future Phase II trials building on the newly established platform of concurrent chemoradiotherapy.

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**Abstract**

**BACKGROUND:**

Some studies (but not others) suggested that high doses are beneficial in small cell lung cancer (SCLC). We hypothesized that dose-response curve (DRC) shape reflects resistance mechanisms.

**METHODS:**

We reviewed published SCLC clinical trials and converted response rates into estimated mean tumor cell kill, assuming killing is proportional to reduction in tumor volume. Mean % cell survival was plotted versus planned dose intensity. Nonlinear and linear meta-regression analyses (weighted according to the number of patients in each study) were used to assess DRC characteristics.

**RESULTS:**

Although associations between dose and cell survival were not statistically significant, DRCs sloped downward for five of seven agents across all doses and for all seven when lowest doses were excluded. Maximum mean cell kill across all drugs and doses was approximately 90%, suggesting that there may be a maximum achievable tumor cell kill irrespective of number of agents or drug doses.

**CONCLUSIONS:**

Downward DRC slopes suggest that maintaining relatively high doses may possibly maximize palliation, although the associations between dose and slope did not achieve statistical significance, and slopes for most drugs tended to be shallow. DRC flattening at higher doses would preclude cure and would suggest that "saturable passive resistance" (deficiency of factors required for cell killing) limits maximum achievable cell kill. An example of factors that could flatten the DRC at higher doses and lead to saturable passive resistance would be presence of quiescent, noncycling cells.


**Abstract**

**BACKGROUND:**

Sentinel lymph node biopsy (SLNB) is a more sensitive and accurate nodal staging procedure than axillary lymph node dissection (ALND). Because of increased pathologic evaluation in the sentinel node era, more nodal micrometastases (MIC) (> 0.2 mm to 2 mm) and isolated tumor cells (ITC, < or = 0.2 mm) have been identified. We present the 10-year analysis of our prospective SLN study, focusing on regional axillary node status and distant metastases in patients with nodal ITC and MIC.

**STUDY DESIGN:**

From 1996 to 2005, breast cancer patients were enrolled in an Institutional Review Board-approved, multicenter study. SLNs were examined at multiple levels by hematoxylin and eosin; most (85%) hematoxylin and eosin-negative SLNs were also examined by cytokeratin immunohistochemistry. Data from 1,259 patients with invasive breast cancer and in whom an SLN was found were reviewed for this analysis.
RESULTS:
Of the 1,259 patients, 893 (71%) had negative SLNs, 25 (2%) had ITCs, 57 (5%) had MIC, and 284 (23%) had positive SLNs. None of the 13 patients with ITCs who underwent an ALND had additional positive nodes, compared with 27% (11 of 41) of patients with MIC. At a mean followup of 4.9 years, the distant recurrence rates for SLN-negative, ITC, MIC, and SLN-positive groups were 6%, 8%, 14%, and 21%, respectively. The presence of MIC in the SLN was associated with a significantly shorter disease-free interval than was SLN negativity (p < 0.02 by Cox regression model).

CONCLUSIONS:
This prospective breast cancer study found that sentinel node MIC, but not ITCs, were associated with additional positive nodes and with distant recurrence. These data suggest that ALND may be unnecessary in patients with ITCs. But ALND and more aggressive adjuvant therapy should be considered in patients with SLN micrometastases.

| **Lorraine Tafra** | **Specialists Provide More Consistent and Comprehensive ASCO-recommended Surveillance of Breast Cancer Survivors than Primary Care Physicians** | **Hollowell K, Olmsted C, Richardson AS, Pitman HK, Bellin L, Tafra L, Verbanac KM.** | **Cancer. 2010; 116(9): 2090-2098.**
Presented at ASBS 10th Annual Meeting, April 2009 |
---|---|---|---|
**Abstract**
**BACKGROUND:**
It is unclear whether it is appropriate to transfer the follow-up care of breast cancer (BrCa) survivors from cancer specialists to primary care physicians (PCPs). This contemporary study compared physician specialty and documented the long-term surveillance of survivors who underwent surgery at an American academic center.

**METHODS:**
Women in this institutional review board-approved study underwent breast surgery between 1996 and 2006. Data were collected for 270 patients with stage I to III BrCa (mean follow-up, 6 years). Charts were reviewed based on American Society of Clinical Oncology (ASCO) guidelines for recommended surveillance frequency and care.

**RESULTS:**
The majority of patients (90%; n = 242) were followed by specialists with 10% (n = 28) followed by PCPs. Patients with advanced disease and a greater risk of disease recurrence more often received specialist care. Patients followed by specialists were more often seen at ASCO-recommended intervals (eg, 89% vs 69% of patients followed by a PCP at follow-up Year 6; P < .01); however, many patients were followed inconsistently. Breast disease was often not the focus of PCP visits or mentioned in clinic notes (18% of patients). Women seen by specialists were more likely to have documented clinical examinations of the breast (93% vs 44% at Year 6), axilla (94% vs 52%), or annual mammograms (74% vs 48%; P = .001-.02).

**CONCLUSIONS:**
Consistent compliance with surveillance guidelines and chart documentation needs improvement among all providers; however, specialists more consistently met ASCO guidelines. If transfer of care to a PCP occurs, it should be formalized and include follow-up recommendations and defined physician responsibilities. Providers and patients should be educated regarding surveillance care and current guidelines incorporated into standard clinical practice.

© 2010 American Cancer Society.

| **Lorraine Tafra** | **The Relationship between Quality and Cost during the Perioperative Breast Cancer Episode of Care.** | **Landercasper J, Tafra L.** | **The Breast, August 2010, Vol 19, Issue 4, 289-96.** |
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**Abstract**
The relationship between quality and cost of care for breast cancer surgery was investigated by literature review. The guidelines, policy statements, quality measures (QM) and target goals for performance described by professional organizations were also reviewed. After review, the relationship between quality and cost of care for the components of perioperative care were assigned an inverse, direct or uncertain relationship. Identification of processes of care with an inverse relationship between quality and cost, such as performing a needle biopsy to diagnose cancer compared to an open surgical biopsy, provide opportunity to concurrently lower cost and improve quality. Other components of care, such as post-mastectomy reconstruction, demonstrate a direct relationship between quality and cost. Recognition of the variability of performance of QM’s with an inverse quality and cost relationship has the potential to lower breast cancer population healthcare expenditures, if average performance for those QM can be improved.

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**Abstract**
**BACKGROUND:**
This prospective multicenter sentinel lymph node (SLN) trial investigated whether molecular analysis would improve the detection of SLN metastases and their prognostic value. We report mammaglobin quantitative real-time polymerase chain reaction (qRT-PCR) results and clinical outcome for 547 patients (mean follow-up 7 years).

**METHODS:**
Breast cancer patients (excluding stage IV disease or palpable nodes) were enrolled from 1996 to 2005 at 16 institutional review board-approved sites. Alternate 2-mm serial sections of each SLN were examined by hematoxylin and cosin staining with or without immunohistochemistry at multiple levels or blinded and assayed by Taqman qRT-PCR according to previously established thresholds.
### RESULTS:
Mammaglobin remains a highly specific (99%), sensitive (97% primary tumor; 82% N1 SLN) marker for breast cancer. Mammaglobin SLN expression was associated with other prognostic factors, was detected in most patients with distant recurrence (48 of 79; 61%), and was associated with decreased recurrence-free survival (log rank P < 0.0001). Molecular analysis upstaged 13% (52 of 394) node-negative (N0) patients who exhibited a significantly lower distant recurrence-free survival compared to node-negative, PCR-negative patients (80 vs. 91%; P < 0.04). N0 patients with PCR-positive SLN were 3.4 times more likely to experience relapse than PCR-negative patients (odds ratio 3.4; 95% confidence interval 1.6-7.1; P = 0.001). However, molecular staging failed to predict most of the N0 patient recurrences (25 of 34) and was not a statistically significant independent predictor of distant recurrence.

### CONCLUSIONS:
To our knowledge, these data are the first to prospectively compare PCR detection of SLN metastases with long-term outcome in breast cancer patients. Molecular staging of SLN detected clinically significant disease missed by standard pathology. Further refinement and optimization of molecular staging is indicated to improve clinical utility.

PMID: 20853060
[PubMed - indexed for MEDLINE]

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| Lorraine Tafra  | "Use of Peri-operative Gabapentin (Neurontin) in Reducing Post-operative Narcotic Usage in Patients Undergoing Mastectomy and Axillary Nodal Dissection." | Cheng Z, Tafra L. Accepted for poster presentation at ASBS 10th Annual Meeting April 2009 |

Abstract
**BACKGROUND:**
Sentinel lymph node biopsy (SLNB) is a more sensitive and accurate nodal staging procedure than axillary lymph node dissection (ALND). Because of increased pathologic evaluation in the sentinel node era, more nodal micrometastases (MIC) (> 0.2 mm to 2 mm) and isolated tumor cells (ITC; < or = 0.2 mm) have been identified. We present the 10-year analysis of our prospective SLN study, focusing on regional axillary node status and distant metastases in patients with nodal ITC and MIC.

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**RESULTS:**
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**CONCLUSIONS:**
This prospective breast cancer study found that sentinel node MIC, but not ITCs, were associated with additional positive nodes and with distant recurrence. These data suggest that ALND may be unnecessary in patients with ITCs. But ALND and more aggressive adjuvant therapy should be considered in patients with SLN micrometastases.

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| Lorraine Tafra  | "Does Breast Tumor Heterogeneity Necessitate Further Immunohistochemical Staining on Surgical Specimens?" | Lauren T. Greer, M.D., Martin Rosman, M.D., Charles Mylander, Ph.D., Albert J. Kovatich, M.S., Jeffrey Hooke, M.D., Wen Liang, D.O., Robert R. Buras, M.D., FACS, Craig D. Shriver, M.D., FACS, Lorraine Tafra, M.D., FACS Submitted for Society of Surgical Oncology (SSO) meeting- accepted |

No abstract available
**Introduction:** Prognostic and predictive tumor markers (ER, PR, HER2, Ki-67) in breast cancer are most commonly performed on core needle biopsies (CNB) of the primary tumor. Because treatment recommendations are influenced by these markers, it is imperative to verify strong concordance between tumor markers derived from IHC testing on CNB specimens and the corresponding surgical specimens (SS).

**Methods:** A prospective study was performed on 132 women (151 samples) with breast cancer diagnosed from January 2009 to March 2011. Tumor type, histologic grade, and ER, PR, HER2, Ki67 activity by IHC were retrospectively analyzed in the CNB and SS. The pathologist analyzing the SS was blinded to the report on the CNB. Tumor heterogeneity was noted in the SS of 14 subjects, who then underwent multiple IHC testing on different areas of the primary tumor(s). Contingency tables and agreement modeling were performed to generate Kappa values, with corresponding Landis-Koch Agreement Grades.

**Results:** The 151 samples revealed substantial agreement between the core and surgical specimens for tumor type; moderate agreement for histologic grade, ER%, and PR%; and fair agreement for HER2 and Ki67% (see Chart). The CNB contained higher percentages of ER, PR, and Ki67 as compared with the SS. Fourteen patients (11%) had tumor heterogeneity seen on SS, which was also reflected in the IHC testing. In 3 subjects (21%), HER2 was found to be positive in an area of the SS but was negative on the CNB. No cases were seen where ER or PR were negative on CNB but became positive in the SS. However, 2 subjects with strongly ER and PR positive tumors on the CNB were negative on areas of the SS.

**Conclusion:** The heterogeneous distribution of antigens in breast cancer tumors raises concern that the CNB may not adequately represent the true biologic profile in about 11% of patients. We have demonstrated adequate concordance for histologic type, grade, ER, and PR activity between CNB and SS (although a decline is noted between the CNB and SS), however, HER2 activity does not appear to be adequately detected on CNB in patients with heterogenous tumors. We recommend that all breast cancer patients with ER, PR, or HER2 negative tumors on the CNB with evidence of tumor heterogeneity in their SS, undergo additional IHC testing on the SS in order to adequately tailor therapy.
**Abstract**

**BACKGROUND:**

Bisphosphonates are used to prevent skeletal events of bone metastases, and may exhibit antitumour effects. We aimed to evaluate whether bisphosphonates can bring a response rate (RR), progression free survival (PFS) and overall survival (OS) benefit to patients with bone metastasis from renal cell carcinoma (RCC) that is treated with sunitinib.

**METHODS:**

We performed a multicentre retrospective study of patients with bone metastases from RCC that was treated with sunitinib. The effect of bisphosphonates on RR, PFS and OS was tested with adjustment for known prognostic factors using a chi-square test from contingency table and partial likelihood test from Cox regression model.

**RESULTS:**

Between 2004 and 2011, 209 patients with metastatic RCC were treated with sunitinib, 76 had bone metastases, 35 bisphosphonates users and 41 non-users. The groups of bisphosphonates users and non-users were balanced regarding known prognostic factors. Objective response was partial response/stable disease 86% (n=30) versus 71% (n=29), and progressive disease 14% (n=5) versus 29% (n=12) (p=0.125, OR 2.48) in users versus non-users, respectively. Median PFS was 15 versus 5 months (HR=0.55, p<0.0001), and median OS was not reached (with a median follow-up time of 45 months) versus 14 months (HR=0.4, p=0.029), in favour of bisphosphonates users. In multivariate analysis of the entire patient cohort (n=76), factors associated with PFS were bisphosphonates use (HR=0.58, p=0.035), and pre-treatment neutrophil to lymphocyte ratio >3 (HR=3.5, p=0.009). Factors associated with OS were bisphosphonates use (HR=0.5, p=0.008), elevated pre-treatment alkaline phosphatase (HR=2.9, p=0.003) and sunitinib induced HTN (HR=0.63, p<0.0001).

**CONCLUSIONS:**

Bisphosphonates may improve the RR, PFS and OS of sunitinib treatment in RCC with bone metastases.

---

**RESULTS:**

Of the 2,868 subjects with invasive breast cancer, 18% had ALN metastases at diagnosis. The incidence of ALN metastases is highest in young subjects after which it declines until age 60 and then begins to increase after 70. The proportion of patients with any positive ALN metastases is significantly higher in patients > 80 (CI 18.0-30.1%) compared with those who are 60-74 (CI 8.8-17.9%) years old. In reviewing the predictive factors, tumor size mirrored the shape of percent positive ALN across different ages (see Figure). Multivariate modeling reveals tumor size as the main factor driving the increased incidence of ALN metastases, and not age. LVI was also predictive, but all other factors were insignificant.

**Conclusions:**

The incidence of ALN metastases appears to increase after age 60. When all prognostic variables are examined, tumor size and LVI are driving the increase in ALN metastasis. All other variables were insignificant on multivariate analysis. The reason for these larger tumors in older women is open for speculation.
Secondary objectives included overall tumor response rate (OR = complete response [CR] + partial response [PR]) and overall survival (OS).

RESULTS:
Of the 94 patients enrolled, 68 were evaluable for efficacy. Although no CRs were observed, 9 patients achieved PRs, for an OR of 13.2% in the evaluable population. The median TTP for the evaluable population was 10.3 weeks, and the proportion of patients free of disease progression at 6 months was 17%. The median OS was 61.6 weeks for all patients enrolled. The most common drug-related ≥ grade 3 adverse events (graded using the National Cancer Institute Common Toxicity Criteria version 2) were diarrhea, asthenia, nausea, and dehydration.

CONCLUSIONS:
The combination of UFT and leucovorin administered orally in a twice-daily regimen was found to have modest activity. Grade 3 toxicities were manageable with appropriate dose adjustments in patients with metastatic breast cancer previously treated with anthracyclines and/or taxanes.
**Vascular Surgery**


**Abstract**

**PURPOSE:**
In 1992, Centers for Medicare and Medicaid Services instituted the Resource Based Relative Value Scale (RBRVS) system to determine physician reimbursement. Relative value units (RVU) were assigned to each Current Procedure Terminology (CPT) code and intended to reflect the time and intensity of work. Little data exist correlating actual procedural and clinical time with respect to reimbursement within the RVU value system. The purpose of this study was to determine how well this system distributes payments per hour for hospital-based procedures in a single vascular practice in the state of Maryland between July 1, 2008 and June 30, 2009.

**METHODS:**
As part of an ongoing prospective outcomes program, procedural times for all vascular procedures (time into until time out of room) were recorded. Fifteen minutes were added for administrative functions on procedural day, each hospital day, and office visits during the global period. The combination of all times was reflected in the total care time (TCT) for each procedure. We recorded all physician fees collected for each procedure. This total fee collected for each procedure was then divided by the TCT to determine the procedure-specific payment per unit time. All similar procedures were grouped together and the average reimbursement per procedure was reported.

**RESULTS:**
Data was collected on all 1103 procedures performed during this period. Insurance carrier distribution was 75% Medicare and 25% private insurance. The average reimbursement was $316/hour for open procedures and $556/hour for endovascular. Higher reimbursing procedures included visceral endovascular procedures ($701/hour) and caval filters ($751/hour). Lower reimbursing procedures included lower extremity bypass ($292/hour), dialysis access ($268/hour) and lower extremity amputations ($223/hour). Striking was the difference between payment based on approach for similar conditions. Reimbursement for carotid stent vs carotid endarterectomy was $643/hour vs $383/hour, endovascular abdominal aortic aneurysm (AAA) repair vs open $593/hour vs $359/hour.

**CONCLUSION:**
This unique study demonstrates a "real world" experience of reimbursement per unit time and raises questions as to the validity of the RBRVS process. The disparity between payments for open and endovascular repair of similar conditions are typical of this inequality. These data do not reflect the intangible time of operative planning, administrative matters, or overhead, and these factors must be considered when interpreting this data. Regardless, this study suggests that capturing detailed financial data is possible and is a more accurate source for future discussions on reimbursement.


**Abstract**

**BACKGROUND:**
Carotid-artery stenting and carotid endarterectomy are both options for treating carotid-artery stenosis, an important cause of stroke.

**METHODS:**
We randomly assigned patients with symptomatic or asymptomatic carotid stenosis to undergo carotid-artery stenting or carotid endarterectomy. The primary composite end point was stroke, myocardial infarction, or death from any cause during the periprocedural period or any ipsilateral stroke within 4 years after randomization.

**RESULTS:**
For 2502 patients over a median follow-up period of 2.5 years, there was no significant difference in the estimated 4-year rates of the primary end point between the stenting group and the endarterectomy group (7.2% and 6.8%, respectively; hazard ratio with stenting, 1.11; 95% confidence interval, 0.81 to 1.51; P=0.51). There was no differential treatment effect with regard to the primary end point according to symptomatic status (P=0.84) or sex (P=0.34). The 4-year rate of stroke or death was 6.4% with stenting and 4.7% with endarterectomy (hazard ratio, 1.50; P=0.03); the rates among symptomatic patients were 8.0% and 6.4% (hazard ratio, 1.37; P=0.014), and the rates among asymptomatic patients were 4.5% and 2.7% (hazard ratio, 1.86; P=0.07), respectively. Periprocedural rates of individual components of the end points differed between the stenting group and the endarterectomy group for death (0.7% vs. 0.3%, P=0.18), for stroke (4.1% vs. 2.3%, P=0.01), and for myocardial infarction (1.1% vs. 2.3%, P=0.03). After this period, the incidences of ipsilateral stroke with stenting and with endarterectomy were similarly low (2.0% and 2.4%, respectively; P=0.85).

**CONCLUSIONS:**
Among patients with symptomatic or asymptomatic carotid stenosis, the risk of the composite primary outcome of stroke, myocardial infarction, or death did not differ significantly in the group undergoing carotid-artery stenting and the group undergoing carotid endarterectomy. During the periprocedural period, there was a higher risk of stroke with stenting and a higher risk of myocardial
John Martin
The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) – Stenting versus Carotid Endarterectomy for Carotid Disease. Stroke

Abstract
BACKGROUND AND PURPOSE:
Carotid artery stenosis causes up to 10% of all ischemic strokes. Carotid endarterectomy (CEA) was introduced as a treatment to prevent stroke in the early 1950s. Carotid stenting (CAS) was introduced as a treatment to prevent stroke in 1994.

METHODS:
The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) is a randomized trial with blinded end point adjudication. Symptomatic and asymptomatic patients were randomized to CAS or CEA. The primary end point was the composite of any stroke, myocardial infarction, or death during the periprocedural period and ipsilateral stroke thereafter, up to 4 years.

RESULTS:
There was no significant difference in the rates of the primary end point between CAS and CEA (7.2% versus 6.8%; hazard ratio, 1.11; 95% CI, 0.81 to 1.51; P=0.51). Symptomatic status and sex did not modify the treatment effect, but an interaction with age and treatment was detected (P=0.02). Outcomes were slightly better after CAS for patients aged <70 years and better after CEA for patients aged >70 years. The periprocedural end point did not differ for CAS and CEA, but there were differences in the components, CAS versus CEA (stroke 4.1% versus 2.3%, P=0.012; and myocardial infarction 1.1% versus 2.3%, P=0.032).

CONCLUSIONS:
In CREST, CAS and CEA had similar short- and longer-term outcomes. During the periprocedural period, there was higher risk of stroke with CAS and higher risk of myocardial infarction with CEA. Clinical Trial Registration-www.clinicaltrials.gov. Unique identifier: NCT00004732.

John Martin
Safety of Stenting and Endarterectomy by Symptomatic Status in the Carotid Revascularization Endarterectomy Versus Stenting Trial. Stroke

Abstract
BACKGROUND AND PURPOSE:
The safety of carotid artery stenting (CAS) and carotid endarterectomy (CEA) has varied by symptomatic status in previous trials. The Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) data were analyzed to determine safety in symptomatic and asymptomatic patients.

METHODS:
CREST is a randomized trial comparing safety and efficacy of CAS versus CEA in patients with high-grade carotid stenoses. Patients were defined as symptomatic if they had relevant symptoms within 180 days of randomization. The primary end point was stroke, myocardial infarction, or death within the periprocedural period or ipsilateral stroke up to 4 years.

RESULTS:
For 1321 symptomatic and 1181 asymptomatic patients, the periprocedural aggregate of stroke, myocardial infarction, and death did not differ between CAS and CEA (5.2% versus 4.5%; hazard ratio, 1.18; 95% CI, 0.82 to 1.68; P=0.38). The stroke and death rate was higher for CAS versus CEA (4.4% versus 2.3%; hazard ratio, 1.90; 95% CI, 1.21 to 2.98; P=0.005). For symptomatic patients, the periprocedural stroke and death rates were 6.0%±0.9% for CAS and 3.2%±0.7% for CEA (hazard ratio, 1.89; 95% CI, 1.11 to 3.21; P=0.02). For asymptomatic patients, the stroke and death rates were 2.5%±0.6% for CAS and 1.4%±0.5% for CEA (hazard ratio, 1.88; 95% CI, 0.79 to 4.42; P=0.15). Rates were lower for those aged <80 years.

CONCLUSIONS:
There were no significant differences between CAS versus CEA by symptomatic status for the primary CREST end point. Periprocedural stroke and death rates were significantly lower for CEA in symptomatic patients. However, for both CAS and CEA, stroke and death rates were below or comparable to those of previous randomized trials and were within the complication thresholds suggested in current guidelines for both symptomatic and asymptomatic patients.

John Martin
Myocardial Infarction following Carotid Stenting and Endarterectomy: Results from the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST).

Abstract
BACKGROUND:
The Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) found a higher risk of stroke after carotid artery stenting and a higher risk of myocardial infarction (MI) after carotid endarterectomy.

METHODS AND RESULTS:
Cardiac biomarkers and ECGs were performed before and 6 to 8 hours after either procedure and if there was clinical evidence of ischemia. In CREST, MI was defined as biomarker elevation plus either chest pain or ECG evidence of ischemia. An additional category of biomarker elevation with neither chest pain nor ECG abnormality was prespecified (biomarker+ only). Crude mortality was defined as symptomatic if they had relevant symptoms within 180 days of randomization. The primary end point was stroke, myocardial infarction, or death within the periprocedural period or ipsilateral stroke up to 4 years.
and risk-adjusted mortality for MI and biomarker+ only were assessed during follow-up. Among 2502 patients, 14 MIs occurred in carotid artery stenting and 28 MIs in carotid endarterectomy (hazard ratio, 0.50; 95% confidence interval, 0.26 to 0.94; P=0.032) with a median biomarker ratio of 40 times the upper limit of normal. An additional 8 carotid artery stenting and 12 carotid endarterectomy patients had biomarker+ only (hazard ratio, 0.66; 95% confidence interval, 0.27 to 1.61; P=0.36), and their median biomarker ratio was 14 times the upper limit of normal. Compared with patients without biomarker elevation, mortality was higher over 4 years for those with MI (hazard ratio, 3.40; 95% confidence interval, 1.67 to 6.92) or biomarker+ only (hazard ratio, 3.57; 95% confidence interval, 1.46 to 8.68). After adjustment for baseline risk factors, both MI and biomarker+ only remained independently associated with increased mortality.

CONCLUSIONS:
In patients randomized to carotid endarterectomy versus carotid artery stenting, both MI and biomarker+ only were more common with carotid endarterectomy. Although the levels of biomarker elevation were modest, both events were independently associated with increased future mortality and remain an important consideration in choosing the mode of carotid revascularization or medical therapy.

CLINICAL TRIAL REGISTRATION:

John Martin

Influence of sex on outcomes of stenting versus endarterectomy: Results from the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST)

BACKGROUND:
In the randomised Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), the primary endpoint did not differ between carotid artery stenting and carotid endarterectomy in patients with symptomatic and asymptomatic stenosis. A prespecified secondary aim was to examine differences by sex.

METHODS:
Patients who were asymptomatic or had had a stroke or transient ischaemic attack within 180 days before random allocation were enrolled in CREST at 117 clinical centres in the USA and Canada. The primary outcome was the composite of stroke, myocardial infarction, or death during the periprocedural period or ipsilateral stroke within 4 years. We used standard survival methods including Kaplan-Meier survival curves and sex-by-treatment interaction term to assess the relation between patient factors and risk of reaching the primary outcome. Analyses were by intention to treat. CREST is registered with ClinicalTrials.gov, NCT00004732.

FINDINGS:
Between Dec 21, 2000, and July 18, 2008, 2502 patients were randomly assigned to carotid endarterectomy (n=1240) or carotid artery stenting (n=1262), 872 (34.9%) of whom were women. Rates of the primary endpoint for carotid artery stenting compared with carotid endarterectomy were 6.2% versus 6.8% in men (hazard ratio [HR] 0.99, 95% CI 0.66-1.46) and 8.9% versus 6.7% in women (1.35, 0.82-2.23). There was no significant interaction in the primary endpoint between sexes (interaction p=0.34). Periprocedural events occurred in 35 (4.3%) of 807 men assigned to carotid artery stenting compared with 40 (4.9%) of 823 assigned to carotid endarterectomy (HR 0.90, 95% CI 0.57-1.41) and 31 (6.8%) of 455 women assigned to carotid artery stenting compared with 16 (3.8%) of 417 assigned to carotid endarterectomy (1.84, 1.01-3.37; interaction p=0.064).

INTERPRETATION:
Periprocedural risk of events seems to be higher in women who have carotid artery stenting than those who have carotid endarterectomy whereas there is little difference in men. Additional data are needed to confirm whether this differential risk should be taken into account in decisions for treatment of carotid disease in women.

FUNDING:
National Institute of Neurological Disorders and Stroke and Abbott Vascular Solutions (formerly Guidant).

John Martin

Health-Related Quality of Life after Carotid Stenting versus Carotid Endarterectomy: Results from the CREST Trial.

OBJECTIVES:
The purpose of this study was to compare health-related quality of life (HRQOL) outcomes in patients treated with carotid artery stenting (CAS) versus carotid endarterectomy (CEA).

BACKGROUND:
In CREST (Carotid Revascularization Endarterectomy versus Stenting Trial), the largest randomized trial of carotid revascularization to date, there was no significant difference in the primary composite endpoint, but rates of stroke and myocardial infarction (MI) differed between CAS and CEA. To help guide individualized clinical decision making, we compared HRQOL among patients enrolled in the CREST study. We also performed exploratory analyses to evaluate the association between periprocedural complications and HRQOL.

METHODS:
We measured HRQOL at baseline, and after 2 weeks, 1 month, and 1 year among 2,502 patients randomly assigned to either CAS or CEA in the CREST study. The HRQOL was assessed using the Medical Outcomes Study Short-Form 36 (SF-36) and 6 disease-specific scales designed to study HRQOL in patients undergoing carotid revascularization.

RESULTS:
At both 2 weeks and 1 month, CAS patients had better outcomes for multiple components of the SF-36, with large differences for role physical function, pain, and the physical component summary scale (all p < 0.01). On the disease-specific scales, CAS patients reported less difficulty with driving, eating/swallowing, neck pain, and headaches but more difficulty with walking and leg pain (all p < 0.05). However, by 1 year, there were no differences in any HRQOL measure between CAS and CEA. In the exploratory analyses, periprocedural stroke was associated with poorer 1-year HRQOL across all SF-36 domains, but periprocedural MI or cranial nerve palsy were not.

**CONCLUSIONS:**
Among patients undergoing carotid revascularization, CAS is associated with better HRQOL during the early recovery period as compared with CEA—particularly with regard to physical limitations and pain—but these differences diminish over time and are not evident after 1 year. Although CAS and CEA are associated with similar overall HRQOL at 1 year, event-specific analyses confirm that stroke has a greater and more sustained impact on HRQOL than MI. (Carotid Revascularization Endarterectomy versus Stenting Trial [CREST]; NCT00004732)

<table>
<thead>
<tr>
<th>John Martin</th>
<th>Age and Outcomes after Carotid Stenting and Endarterectomy: The Carotid Revascularization Endarterectomy Versus Stenting Trial</th>
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</table>

**Abstract**

**BACKGROUND AND PURPOSE:**
High stroke event rates among carotid artery stenting (CAS)-treated patients in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) lead-in registry generated an a priori hypothesis that age may modify the relative efficacy of CAS versus carotid endarterectomy (CEA). In the primary CREST report, we previously noted significant effect modification by age. Here we extend this investigation by examining the relative efficacy of the components of the primary end point, the treatment-specific impact of age, and contributors to the increasing risk in CAS-treated patients at older ages.

**METHODS:**
Among 2502 CREST patients with high-grade carotid stenosis, proportional hazards models were used to examine the impact of age on the CAS-to-CEA relative efficacy, and the impact of age on risk within CAS-treated and CEA-treated patients.

**RESULTS:**
Age acted as a treatment effect modifier for the primary end point (P interaction=0.02), with the efficacy of CAS and CEA approximately equal at age 70 years. For CAS, risk for the primary end point increased with age (P<0.0001) by 1.77-times (95% confidence interval, 1.38-2.28) per 10-year increment; however, there was no evidence of increased risk for CEA-treated patients (P=0.27). Stroke events were the primary contributor to the overall effect modification (P interaction=0.033), with equal risk at ≈64 years. The treatment-by-age interaction for CAS and CEA was not altered by symptomatic status (P=0.96) or by sex (P=0.45).

**CONCLUSIONS:**
Outcomes after CAS versus CEA were related to patient age, attributable to increasing risk for stroke after CAS at older ages. Patient age should be an important consideration when choosing between the 2 procedures for treating carotid stenosis.

<table>
<thead>
<tr>
<th>John Martin</th>
<th>Interventions to increase enrollment in a large multicenter phase 3 trial of carotid stenting vs. endarterectomy</th>
</tr>
</thead>
</table>

**Abstract**

**BACKGROUND:**
Randomized clinical trials often encounter slow enrollment. Failing to meet sample size requirements has scientific, financial, and ethical implications.

**AIMS:**
We report interventions used to accelerate recruitment in a large multicenter clinical trial that was not meeting prespecified enrollment commitments.

**METHODS:**
The Carotid Revascularization Endarterectomy vs. Stenting Trial began randomization in December 2000. To accelerate enrollment, multiple recruitment tactics were initiated, which included expanding the number of sites, hiring a recruitment director (May 2003), broadening eligibility criteria (April 2005), branding with a study logo, Web site, and recruitment materials, increasing site visits by study leadership, sending e-mails to the site teams after every enrollment, distributing electronic newsletters, and implementing investigator and coordinator conferences.

**RESULTS:**
From December 2000 through May 2003, 14 sites became active (54 patients randomized), from June 2003 through April 2005, 44 sites were added (404 patients randomized), and from May 2005 through July 2008, 54 sites were added (2044 patients randomized). During these time intervals, the number of patients enrolled per site per year was 1-5, 3-6, and 5-6. For the single years 2004 to 2008, the mean monthly randomization rates per year were 19.7, 38.1, 56.4, 53.0, and 54.7 (annualized), respectively. Enrollment was highest after recruitment tactics were implemented: 677 patients in 2006, 636 in 2007, and 657 in 2008 (annualized). The prespecified sample size of 2502 patients, 47% asymptomatic, was accomplished on July 2008.

**CONCLUSIONS:**
Aggressive recruitment tactics and investment in a full-time recruitment director who can lead implementation may be effective in accelerating recruitment in multicenter trials.
Abstract
PURPOSE:
In 1992, Centers for Medicare and Medicaid Services instituted the Resource Based Relative Value Scale (RBRVS) system to determine physician reimbursement. Relative value units (RVU) were assigned to each Current Procedure Terminology (CPT) code and intended to reflect the time and intensity of work. Little data exist correlating actual procedural and clinical time with respect to reimbursement within the RVU value system. The purpose of this study was to determine how well this system distributes payments per hour for hospital-based procedures in a single vascular practice in the state of Maryland between July 1, 2008 and June 30, 2009.

METHODS:
As part of an ongoing prospective outcomes program, procedural times for all vascular procedures (time into until time out of room) were recorded. Fifteen minutes were added for administrative functions on procedural day, each hospital day, and office visits during the global period. The combination of all times was reflected in the total care time (TCT) for each procedure. We recorded all physician fees collected for each procedure. This total fee collected for each procedure was then divided by the TCT to determine the procedure-specific payment per unit time. All similar procedures were grouped together and the average reimbursement per procedure was reported.

RESULTS:
Data was collected on all 1103 procedures performed during this period. Insurance carrier distribution was 75% Medicare and 25% private insurance. The average reimbursement was $316/hour for open procedures and $556/hour for endovascular. Higher reimbursing procedures included visceral endovascular procedures ($701/hour) and caval filters ($751/hour). Lower reimbursing procedures included lower extremity bypass ($292/hour), dialysis access ($268/hour) and lower extremity amputations ($223/hour). Striking was the difference between payment based on approach for similar conditions. Reimbursement for carotid stent vs carotid endarterectomy was $643/hour vs $383/hour, endovascular abdominal aortic aneurysm (AAA) repair vs open $593/hour vs $359/hour.

CONCLUSION:
This unique study demonstrates a "real world" experience of reimbursement per unit time and raises questions as to the validity of the RBRVS process. The disparity between payments for open and endovascular repair of similar conditions are typical of this inequality. These data do not reflect the intangible time of operative planning, administrative matters, or overhead, and these factors must be considered when interpreting this data. Regardless, this study suggests that capturing detailed financial data is possible and is a more accurate source for future discussions on reimbursement.
### Surgery

<table>
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<th>Name</th>
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<tr>
<td></td>
<td>Abstract</td>
<td>BACKGROUND:</td>
<td>Survival outcomes of never smokers with non-small cell lung cancer (NSCLC) who undergo surgery are poorly characterized. This investigation compared surgical outcomes of never and current smokers with NSCLC. METHODS:</td>
<td>This investigation was a single-institution retrospective study of never and current smokers with NSCLC from 1975 to 2004. From an analytic cohort of 4,546 patients with NSCLC, we identified 724 never smokers and 3,822 current smokers. Overall, 1,142 patients underwent surgery with curative intent. For survival analysis by smoking status, hazard ratios (HRs) were estimated using Cox proportional hazard modeling and then further adjusted by other covariates. RESULTS:</td>
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<tr>
<td></td>
<td>Abstract</td>
<td>OBJECTIVE:</td>
<td>We hypothesized that most relapses in patients with esophageal cancer having neoadjuvant chemoradiation therapy would occur outside of the surgical and radiation fields. METHODS:</td>
<td>Recurrence patterns, time to recurrence, and median survival were examined in 267 patients who had esophagectomy after neoadjuvant chemoradiation therapy at Johns Hopkins over 19 years. RESULTS:</td>
</tr>
</tbody>
</table>
Abstract
Cardiac allotransplantation is subject to a number of chronic complications that may limit graft survival. These include allograft coronary artery disease, renal dysfunction, hypertension, and malignancy, which are largely due to the immuno-modulatory and adverse effects of transplant medications. Reoperation for native allograft disease progression is a rarer phenomenon. We report a case of aortic valve replacement for bicuspid aortic valve stenosis that occurred in a patient more than ten years after cardiac transplantation.

Orthopedics

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<th>Name</th>
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Abstract
Patellar instability is a generic term that is used to describe patellar dislocation, patellar subluxation, and general symptomatic instability. Patellofemoral instability is a relatively difficult condition to treat; accurate management of the condition should take into account the anatomy of the joint and its stabilizing structures. The goal of any treatment should be to restore the normal anatomy of the joint. It is important to understand the basic anatomy and biomechanics of this condition, the classification of different types of patellar instability, varying presentations, and diagnostic techniques and criteria, including the types of imaging studies that can be useful in determining the ultimate course of treatment.

Cardiovascular

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Abstract
Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit production of prostaglandins by acting on cyclooxygenase (COX) isoenzymes 1 and 2. Nonselective NSAIDs inhibit both COX 1 and 2 isoenzymes (eg, ibuprofen and naproxen). Selective NSAIDs act on COX-1 (eg, aspirin) or COX-2 (eg, celecoxib) isoenzymes, respectively. Prostaglandins are produced in platelets and gastric
mucosal cells through constitutively expressed COX-1 isoenzyme. They are involved in the regulation of hemostasis, functional integrity of the gastrointestinal and renal tracts, platelet function, and macrophage differentiation. Inhibition of COX-1 isoenzymes impedes platelet aggregation, impairs maintenance of protective gastric mucosal barrier, and affects renal function. Prostaglandin production in inflamed tissue results from de novo induction of COX-2 expression by inflammatory cytokines and other noxious stimuli. Thus, COX-2 isoenzyme inhibition either selectively or nonselectively helps in reducing inflammation in the setting of musculoskeletal disorders. Safety and efficacy of NSAIDs are related to their relative actions on COX-1 or COX-2 inhibition. Given the multisystem (gastrointestinal, hematopoietic, and renal) adverse effect profile of COX-1 inhibition, formulation of NSAIDs with relative COX-2 selectivity became a highly desirable target during the 90’s. However, studies in the first half of this decade revealed adverse effects of COX-2 inhibition on the cardiovascular system, including increased risks of myocardial infarction, exacerbation of stable congestive heart failure, and worsening high blood pressure. Randomized trials and meta-analyses confirmed these findings, which led to withdrawal of some of the COX-2 inhibitors from the market by the federal Food and Drug Administration a few years ago. Here, we review the effects of COX-2 isoenzyme inhibitors on the cardiovascular system to provide a safe strategy for prescribing these agents in patients with existing cardiovascular disease. We did not find adequate long-term randomized controlled trials appropriately powered to evaluate cardiovascular outcomes. Potentially, all NSAIDs possess a fair risk of adverse effects on gastrointestinal, cardiovascular, and renal systems. Until more evidence for safety via randomized trials is available, we recommend caution in prescribing COX-1 and 2 inhibitors for musculoskeletal disorders in patients with existing gastrointestinal or cardiovascular conditions.

**Medicine**

<table>
<thead>
<tr>
<th>Jim Welker</th>
<th>A Randomized Controlled Trial of Physician Alerts to Prevent Symptomatic Venous thromboembolism after Hospital Discharge</th>
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<tbody>
<tr>
<td>Gregory Piazza, MD, Frederick A. Anderson, PhD, Thomas L. Ortel, MD, PhD, Michael J. Cox, MD, David J. Rosenberg, MD, MPH, Shahram Rahimian, MD, PhD, William J. Pendergast, MD, Gordon D. McLaren, MD, James A. Welker, DO, Jan J. Akus, MD, Scott M. Stevens, MD, C. Gregory Elliott, MD, Andrew L. Freeman, MD, William F. Patton, MD, Ousama Dabbagh, MD, Allison Wyman, MS, Wei Huang, MS, Amanda F. Rao, BS, and Samuel Z. Goldhaber, MD</td>
<td>Presented at the American Hospital Association (November 2011)</td>
</tr>
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</table>

**Abstract**

**BACKGROUND:**
Venous thromboembolism (VTE) prophylaxis remains underused among hospitalized patients. We designed and carried out a large, multicenter, randomized controlled trial to test the hypothesis that an alert from a hospital staff member to the attending physician will reduce the rate of symptomatic VTE among high-risk patients not receiving prophylaxis.

**METHODS AND RESULTS:**
We enrolled patients using a validated point score system to detect hospitalized patients at high risk for symptomatic VTE who were not receiving prophylaxis. We randomized 2493 patients (82% on Medical Services) from 25 study sites to the intervention group (n=1238), in which the responsible physician was alerted by another hospital staff member, or the control group (n=1255), in which no alert was issued. The primary end point was symptomatic, objectively confirmed VTE within 90 days. Patients whose physicians were alerted were more than twice as likely to receive VTE prophylaxis as control subjects (46.0% versus 20.6%; P<0.0001). The symptomatic VTE rate was lower in the intervention group (2.7% versus 3.4%; hazard ratio, 0.79; 95% CI, 0.50 to 1.25), but the difference did not achieve statistical significance. The rate of major bleeding at 30 days in the alert group was similar to that in the control group (2.1% versus 2.3%; P=0.68).

**CONCLUSIONS:**
A strategy of direct notification of the physician by a staff member increases prophylaxis use and leads to a reduction in the rate of symptomatic VTE in hospitalized patients. However, VTE prophylaxis continues to be underused even after physician notification, especially among Medical Service patients.

<table>
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<tr>
<th>James Welker</th>
<th>Toxin assay is more reliable than ICD-9 data and less time-consuming than chart review for public reporting of Clostridium difficile hospital case rates.</th>
</tr>
</thead>
</table>

**Abstract**

**OBJECTIVE:**
Clostridium difficile-associated disease (CDAD) is common and has a 6.1% mortality. Governmental agencies have recommended surveillance, but reporting increases health care costs. We sought to identify a reliable method of reporting CDAD that will not significantly increase health care costs.

**METHODS:**
Patients were identified via database query for International Statistical Classification of Diseases and Related Health Problems, 9th Edition (ICD-9) codes and C. difficile toxin positivity. All identified patients underwent a chart review, which was used to determine...
the accuracy of the database query methods. Methods of determining whether CDAD was acquired at the reporting institution were studied, and time required to perform each method was measured.

**RESULTS:**
The toxin assay reported 96.1% (369/384) of cases and had a positive predictive value of 100%. No difference was found in comparison of the toxin assay case rate of 15.7 per 1000 discharged patients to the rate of 16.3 identified by chart review (P = 0.44); 95% confidence interval [CI], 14.1-17.4), whereas the ICD-9 method was found to be significantly different by reporting 116.1% (446/384) of cases for a case rate of 19.0 per 1000 discharges (P = 0.001; 95% CI, 17.3-20.8). The time for data extraction via the toxin assay method required only 842 minutes, while the chart review method consumed 21,899 minutes.

**CONCLUSION:**
A positive C. difficile toxin assay accurately reports the institutional incidence of disease and is more reliable than ICD-9 query. This process can be instituted at a fraction of the cost of the standard chart review, and enables governmental agencies to inexpensively add CDAD to their list of reportable diseases.

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**Abstract**

**BACKGROUND:**
Treatment of pulmonary embolism with low-molecular-weight heparin and vitamin K antagonists, such as warfarin, is not ideal. We aimed to assess non-inferiority of idrabiotaparinux, a reversible longlasting indirect inhibitor of activated factor X, to warfarin in patients with acute symptomatic pulmonary embolism.

**METHODS:**
In our randomised, double-blind, double-dummy, non-inferiority trial, we enrolled adults with objectively documented acute symptomatic pulmonary embolism attending 291 centres in 37 countries. We excluded patients who were pregnant, had active bleeding, kidney failure, or malignant hypertension, or were at high risk of death, bleeding, or adverse reactions to study drugs. We randomly allocated patients to receive 5-10 days’ enoxaparin 1·0 mg/kg twice daily followed by subcutaneous idrabiotaparinux (starting dose 3·0 mg) or adjusted-dose warfarin (target international normalised ratio 2·0-3·0); regimens lasted 3 months or 6 months dependent on clinical presentation. Block randomisation was done with a central interactive computerised system, stratified by study centre and intended treatment duration. The primary efficacy outcome was recurrent venous thromboembolism at 99 days after randomisation. We estimated the odds ratio and 95% CI with a Mantel-Haenzsel $\chi^2$ analysis (non-inferiority margin 2·0) in the intention-to-treat population. The main safety outcome was clinically relevant bleeding (major or non-major) in all patients at day 99. This study is registered with ClinicalTrials.gov, number NCT00345618.

**RESULTS:**
Between Aug 1, 2006, and Jan 31, 2010, we enrolled 3202 patients aged 18-96 years. 34 (2%) of 1599 patients randomly allocated to receive enoxaparin-iradrabiotaparinux and 43 (3%) of 1603 patients randomly allocated to receive enoxaparin-warfarin had recurrent venous thromboembolism (odds ratio 0·79, 95% CI 0·50-1·25; p(non-inferiority)=0·0001). 72 (5%) of 1599 patients in the enoxaparin-iradrabiotaparinux group and 106 (7%) of 1603 patients in the enoxaparin-warfarin group had clinically relevant bleeding (0·67, 0·49-0·91; p(superiority)=0·0098). We noted similar differences in outcomes in those patients treated to 6 months.

**CONCLUSION:**
Iдрабиотапаринус could provide an alternative to warfarin for the long-term treatment of pulmonary embolism, and seems to be associated with reduced bleeding.

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**Abstract**

**BACKGROUND:**
The efficacy and safety of prolonging prophylaxis for venous thromboembolism in medically ill patients beyond hospital discharge remain uncertain. We hypothesized that extended prophylaxis with apixaban would be safe and more effective than short-term prophylaxis with enoxaparin.

**METHODS:**
In this double-blind, double-dummy, placebo-controlled trial, we randomly assigned acutely ill patients who had congestive heart failure or respiratory failure or other medical disorders and at least one additional risk factor for venous thromboembolism and who were hospitalized with an expected stay of at least 3 days to receive apixaban, administered orally at a dose of 2·5 mg twice daily for 30 days, or enoxaparin, administered subcutaneously at a dose of 40 mg once daily for 6 to 14 days. The primary efficacy outcome was the 30-day composite of death related to venous thromboembolism, pulmonary embolism, symptomatic deep-vein thrombosis, or asymptomatic proximal-leg deep-vein thrombosis, as detected with the use of systematic bilateral compression ultrasonography on day 30. The primary safety outcome was bleeding. All efficacy and safety outcomes were independently adjudicated.

**RESULTS:**
A total of 6528 subjects underwent randomization, 4495 of whom could be evaluated for the primary efficacy outcome—2211 in the apixaban group and 2284 in the enoxaparin group. Among the patients who could be evaluated, 2.71% in the apixaban group (60 patients) and 3.06% in the enoxaparin group (70 patients) met the criteria for the primary efficacy outcome (relative risk with apixaban, 0.87; 95% confidence interval [CI], 0.62 to 1.23; P=0.44). By day 30, major bleeding had occurred in 0.47% of the patients in the apixaban group (15 of 3184 patients) and in 0.19% of the patients in the enoxaparin group (6 of 3217 patients) (relative risk, 2.58; 95% CI, 1.02 to 7.24; P=0.04).
CONCLUSIONS:
In medically ill patients, an extended course of thromboprophylaxis with apixaban was not superior to a shorter course with enoxaparin. Apixaban was associated with significantly more major bleeding events than was enoxaparin. (Funded by Bristol-Myers Squibb and Pfizer; ClinicalTrials.gov number, NCT00457002).


**Abstract**
**BACKGROUND:** Vitamin K antagonists are highly effective in preventing stroke in patients with atrial fibrillation but have several limitations. Apixaban is a novel oral direct factor Xa inhibitor that has been shown to reduce the risk of stroke in a similar population in comparison with aspirin.

**METHODS:** In this randomized, double-blind trial, we compared apixaban (at a dose of 5 mg twice daily) with warfarin (target international normalized ratio, 2.0 to 3.0) in 18,201 patients with atrial fibrillation and at least one additional risk factor for stroke. The primary outcome was ischemic or hemorrhagic stroke or systemic embolism. The trial was designed to test for noninferiority, with key secondary objectives of testing for superiority with respect to the primary outcome and to the rates of major bleeding and death from any cause.

**RESULTS:**
The median duration of follow-up was 1.8 years. The rate of the primary outcome was 1.27% per year in the apixaban group, as compared with 1.60% per year in the warfarin group (hazard ratio with apixaban, 0.79; 95% confidence interval [CI], 0.66 to 0.95; P<0.001 for noninferiority; P=0.01 for superiority). The rate of major bleeding was 2.13% per year in the apixaban group, as compared with 3.09% per year in the warfarin group (hazard ratio, 0.69; 95% CI, 0.60 to 0.80; P<0.001), and the rates of death from any cause were 3.52% and 3.94%, respectively (hazard ratio, 0.89; 95% CI, 0.80 to 0.99; P=0.047). The rate of hemorrhagic stroke was 0.24% per year in the apixaban group, as compared with 0.47% per year in the warfarin group (hazard ratio, 0.51; 95% CI, 0.35 to 0.75; P<0.001), and the rate of ischemic or uncertain type of stroke was 0.97% per year in the apixaban group and 1.05% per year in the warfarin group (hazard ratio, 0.92; 95% CI, 0.74 to 1.13; P=0.42).

**CONCLUSIONS:** In patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality. (Funded by Bristol-Myers Squibb and Pfizer; ARISTOTLE ClinicalTrials.gov number, NCT00412984.)


**Abstract**
**BACKGROUND:** Chronic kidney disease (CKD) associated with type 2 diabetes is the leading cause of kidney failure, with both inflammation and oxidative stress contributing to disease progression. Bardoxolone methyl, an oral antioxidant inflammation modulator, has shown efficacy in patients with CKD and type 2 diabetes in short-term studies, but longer-term effects and dose response have not been determined.

**METHODS:** In this phase 2, double-blind, randomized, placebo-controlled trial, we assigned 227 adults with CKD (defined as an estimated glomerular filtration rate [GFR] of 20 to 45 ml per minute per 1.73 m² of body-surface area) in a 1:1:1:1 ratio to receive placebo or bardoxolone methyl at a target dose of 25, 75, or 150 mg once daily. The primary outcome was the change from baseline in the estimated GFR with bardoxolone methyl, as compared with placebo, at 24 weeks; a secondary outcome was the change at 52 weeks.

**RESULTS:** Patients receiving bardoxolone methyl had significant increases in the mean (±SD) estimated GFR, as compared with placebo, at 24 weeks (with between-group differences per minute per 1.73 m² of body-surface area) in a 1:1:1:1 ratio to receive placebo or bardoxolone methyl at a target dose of 25, 75, or 150 mg once daily. The primary outcome was the change from baseline in the estimated GFR with bardoxolone methyl, as compared with placebo, at 24 weeks; a secondary outcome was the change at 52 weeks.

**RESULTS:**

**CONCLUSIONS:**
Bardoxolone methyl was associated with improvement in the estimated GFR in patients with advanced CKD and type 2 diabetes at 24 weeks. The improvement persisted at 52 weeks, suggesting that bardoxolone methyl may have promise for the treatment of CKD. (Funded by Reata Pharmaceuticals; BEAM ClinicalTrials.gov number, NCT00811889).

**Jim Welker**
**Focus 1 randomized double blinded. multicentre, phase III trial of the efficacy and safety of ceftaroline**

**Abstract**

**OBJECTIVES:**
Ceftaroline (active form of the prodruk ceftaroline fosamil) is a novel cephalosporin with activity against pathogens commonly associated with community-acquired pneumonia (CAP), including Streptococcus pneumoniae and Gram-negative pathogens. This randomized, double-blind, Phase III study evaluated the efficacy and safety of ceftaroline fosamil in treating patients with CAP. The primary objective was to determine non-inferiority [lower limit of 95% confidence interval (CI) ≥ -10%] of clinical cure rates achieved with ceftaroline fosamil compared with those achieved with ceftriaxone in the clinically evaluable (CE) and modified intent-to-treat (MITTE) populations.

**METHODS:**
Patients hospitalized in a non-intensive care unit setting with CAP of Pneumonia Outcomes Research Team (PORT) risk class III or IV requiring intravenous (iv) therapy were randomized (1:1) to receive 600 mg of ceftaroline fosamil iv every 12 h or 1 g of ceftriaxone iv every 24 h. Clinical cure, microbiological response, adverse events (AEs) and laboratory tests were assessed. FOCUS 2 registration number NCT00509106 (http://clinicaltrials.gov/ct2/show/NCT00509106).

**RESULTS:**
The study enrolled 627 patients, 315 of whom received ceftaroline fosamil and 307 of whom received ceftriaxone. Patients in both treatment groups had comparable baseline characteristics. Clinical cure rates were as follows: CE population, 82.1% (193/235) for ceftaroline fosamil and 77.2% (166/215) for ceftriaxone [difference (95% CI), 4.9% (-2.5, 12.5)]; and MITTE population, 81.3% (235/289) for ceftaroline fosamil and 75.5% (206/273) for ceftriaxone [difference (95% CI), 5.9% (-1.0, 12.7)]. Clinical cure rates for extended-duration enoxaparin thromboprophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial

**Jim Welker**
**Extended duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility: a randomized trial**

**Abstract**

**OBJECTIVE:**
To evaluate the efficacy and safety of extended-duration enoxaparin thromboprophylaxis in acutely ill medical patients.

**DESIGN:**
Randomized, parallel, placebo-controlled trial. Randomization was computer-generated. Allocation was centralized. Patients, caregivers, and outcome assessors were blinded to group assignment. (ClinicalTrials.gov registration number: NCT00077753)

**SETTING:**
370 sites in 20 countries across North and South America, Europe, and Asia.

**PATIENTS:**
Acutely ill medical patients 40 years or older with recently reduced mobility (bed rest or sedentary without [level 1] or with [level 2] bathroom privileges). Eligibility criteria for patients with level 2 immobility were amended to include only those who had additional VTE risk factors (age >75 years, history of VTE, or active or previous cancer) after interim analyses suggested lower-than-expected VTE rates.

**INTERVENTION:**
Enoxaparin, 40 mg/d subcutaneously (2975 patients), or placebo (2988 patients), for 28 +/- 4 days after receiving open-label enoxaparin for an initial 10 +/- 4 days.

**MEASUREMENTS:**
Incidence of VTE up to day 28 and of major bleeding events up to 48 hours after the last study treatment dose. RESULTS: Extended-duration enoxaparin reduced VTE incidence compared with placebo (2.5% vs. 4%; absolute risk difference favoring enoxaparin, -1.53% [95.8% CI, -2.54% to -0.52%]). Enoxaparin increased major bleeding events (0.8% vs. 0.3%; absolute risk difference favoring placebo, 0.51% [95% CI, 0.12% to 0.89%]). The benefits of extended-duration enoxaparin seemed to be restricted
to women, patients older than 75 years, and those with level 1 immobility.

**LIMITATION:**
Estimates of efficacy and safety for the overall trial population are difficult to interpret because of the change in eligibility criteria during the trial.

**CONCLUSION:**
Use of extended-duration enoxaparin reduces VTE more than it increases major bleeding events in acutely ill medical patients with level 1 immobility, those older than 75 years, and women.


**Abstract**

**BACKGROUND:**
Despite contemporary therapies for acute coronary syndrome (ACS), morbidity and mortality remain high. Low levels of high-density lipoprotein (HDL) cholesterol are common among patients with ACS and may contribute to ongoing risk. Strategies that raise levels of HDL cholesterol, such as inhibition of cholesterol ester transfer protein (CETP), might reduce risk after ACS. Dal-OUTCOMES is a multicenter, randomized, double-blind, placebo-controlled trial designed to test the hypothesis that CETP inhibition with dalcetrapib reduces cardiovascular morbidity and mortality in patients with recent ACS.

**DESIGN:**
The study will randomize approximately 15,600 patients to receive daily doses of dalcetrapib 600 mg or matching placebo, beginning 4 to 12 weeks after an index ACS event. There are no prespecified boundaries for HDL cholesterol levels at entry. Other elements of care, including management of low-density lipoprotein cholesterol, are to follow best evidence-based practice. The primary efficacy measure is time to first occurrence of coronary heart disease death, nonfatal acute myocardial infarction, unstable angina requiring hospital admission, resuscitated cardiac arrest, or atherothrombotic stroke. The trial will continue until 1,600 primary end point events have occurred, all evaluable subjects have been followed for at least 2 years, and 80% of evaluable subjects have been followed for at least 2.5 years.

**SUMMARY:**
Dal-OUTCOMES will determine whether CETP inhibition with dalcetrapib, added to current evidence-based care, reduces cardiovascular morbidity and mortality after ACS.
Part of the Johns Hopkins Clinical Research Network, an integrated network of academic and community-based clinical researchers established within the Johns Hopkins Institute for Clinical and Translational Research. The purpose of the JHCRN is to accelerate the transfer of new diagnostic, treatment, and disease prevention advances from the research arena into patient care. This bridge between Hopkins and select community hospitals creates a collaborative system that ensures a seamless platform for conducting clinical research and a broader and more diverse pool of clinical investigators and patients for studies. More at: http://ictr.johnshopkins.edu/JHCRN/