NIH Heart Failure Network Annual Clinical Skills Core Retreat
October 30, 2009
Mortimer J. Buckley Conference Room
Massachusetts General Hospital

The meeting was called to order by Dr. Dec at 12:31 PM.

Attendees included: Dr. Kenneth Baughman, Dr. William Dec, Ms. Kim Brooks, Dr. Eugene Braunwald, Susan Anello, Dr. Garrick Stewart, Dr. Stephanie Moore, Ms. Sally Keck, Ms. Coral Haggan, Ms. Diane Cocca-Spofford, Ms. Joan Doody, Dr. William Carlson, Dr. Lynne Stevenson, Dr. Pat Campbell, Ms. Dottie Sullivan, Ms. Kathryn Gonczarek, Dr. Kimberley Parks, Dr. Ravi Shah, Dr. Anju Nohria, Dr. Akshay Desai, Dr. Maya Guglin, Dr. Neal Lakdawala, Dr. Michael Givertz, Dr. Christine Seidman, and Dr. Mary Keebler.

The agenda was reviewed (see attachment 1). Drs. Dec and Baughman welcomed all participants to the Third Annual Clinical Skills Core Retreat. Introductions were undertaken and each individual's role within the Heart Failure Network was reviewed. Dr. Dec then invited Dr. Eugene Braunwald to provide an overview of the NIH Heart Failure Network.

Dr. Braunwald indicated that 9 sites currently comprised the national network. He then reviewed a variety of studies that are currently being completed within the network. He first reviewed the DOSE-AFH trial. This study is evaluating high versus low-dose diuretic therapy for acute decompensated heart failure. High-dose treatment includes loop diuretic at 2.5 times the oral maintenance dose administered intravenously. The low-dose treatment administers a maintenance dose of loop diuretic intravenously. A second component of this trial is an evaluation of continuous intravenous infusion versus bolus therapy. The primary endpoint is change in serum creatinine at 72 hours. A secondary endpoint includes clinical efficacy based on change in symptoms using the visual analogue scale. Over 300 patients have been enrolled and the enrollment will be closing out within the next few weeks. The study has enrolled more than the expected number of patients.

Dr. Braunwald then reviewed the CARESS-HF trial. This study is designed to evaluate the use of ultrafiltration in the treatment of cardiorenal syndrome

in acute decompensated heart failure. Dr. Braunwald emphasized the importance of NIH-sponsored research for such trials that evaluate generic therapy such as furosemide since industry would generally not sponsor such important mechanistic studies. The primary endpoint of the study is a bivariate endpoint looking at change in weight and change in renal function. Enrollment has been slow because of the complex study design; 75 patients have been enrolled. Dr. Braunwald made a strong plea to aggressively complete enrollment.

The next study reviewed was the RELAX trial. This study evaluates the use of phosphodiesterase 5 inhibition to improve clinical status and exercise capacity in diastolic heart failure. The primary end-point is changing peak oxygen uptake at 24 weeks. Secondary end-points include change in submaximal exercise capacity at 12 and 24 weeks by 6 minute walk test and a composite scale of several clinical parameters. Dr. Braunwald made a point of the importance of the Harvard site, particularly the work of Dr. Greg Lewis in establishing a core cardiopulmonary exercise laboratory and setting rigorous standards so that national data can be combined.

Dr. Braunwald then reviewed the EXACT-HF trial. This study evaluates the use of the xanthine oxidase inhibitor, allopurinol, in patients with heart failure and elevated uric acid levels. Approximately 25% of the heart failure population falls into this category. Dr. Michael Givertz is leading this effort. Planned enrollment is to include 200 patients. Dr. Seidman raised the issue of whether genotyping should be undertaken as part of this since altered uric acid metabolism may influence the results of the study. This issue will be further evaluated.

The ROSE-HF trial looks at renal optimization strategies in acute heart failure. Patients will be randomized to low-dose dopamine (2 mcg/kg/min) therapy, diuretics alone, or low-dose nesiritide (0.005 mcg/kg/min) plus diuretic therapy. The primary endpoints will be change in serum cystatin C at 72 hours and change in urinary volume.

Dr. Braunwald concluded with some general remarks based on his experience as Network chairman. He indicated the strengths of the network: 1) it tackles key questions that would not be investigated by other funding sources. 2) it has developed a high quality group of heart failure investigators pursuing a common set of scientific goals. The weakness of the network is that it has too many committees and takes too long to develop

proposals and get them implemented. He suggested a series of parallel structures to evaluate and modify proposals rather than considering the studies in series.

Dr. Lynne Stevenson next spoke and reviewed the status of the Harvard site. She indicated that enrollment had generally been very good initially but has been slow in CARESS. We have been one of the leading sites in enrollment in the RELAX trial. The topic of renewal of the grant was discussed. Dr. Stevenson indicated that the plan was to add another site – namely, the West Roxbury VA. This would increase the size of the Harvard network and also improve demographics for enrollment. Dr. Neal Lakdawala and Dr. Jacob Joseph, Director of the Heart Failure Program at West Roxbury VA, will be involved in site enrollment. Dr. Stevenson then reviewed the timeline for network renewal. Notification of the review process will be sent from NIH in November 2009. In December and January, potential new network protocols will be evaluated. February will lead to selection of protocols. The establishment of the VA site and confirmation of other sites should be completed by the end of February 2010. By March 30th, an outline of the renewal including current site performance, planned changes, new protocols, training grant renewal, budgets, and outlines of progress will need to be ready. By April 1st, budgets will need to be submitted to CNG. A first draft of the grant application is due by April 30th and a second draft, by May 30th. The anticipated deadline for submission of the final grant will be July 30, 2010.

The fellows' presentations followed. The first presentation was by Dr. Neal Lakdawala. He spoke about a study that he has been completing with Dr. Carolyn Ho on the preclinical recognition of hypertrophic cardiomyopathy using electrocardiographic findings. Patients who are genotype positive but without evidence for left ventricular hypertrophy on echocardiography were studied. The majority of patients with preclinical hypertrophic cardiomyopathy was found to have normal electrocardiograms. Thus, this test could not be relied upon with adequate sensitivity or specificity for early disease detection. In a second study, a subgroup of patients with preclinical disease underwent gadolinium-enhanced cardiac MRI. No preclinical patient had evidence for gadolinium uptake.

In a second study, he discussed a unique D230N alpha tropomyosin mutation in dilated cardiomyopathy. This was identified in several families and had different presentations in adults versus children. Although many

infants and children presented with sudden death, a significant number also developed acute heart failure and some had spontaneous recovery of function. This led to a general discussion about the genetic basis of dilated cardiomyopathy and environmental triggers such as myocarditis.

Dr. Ravi Shah next presented several of his research projects. His initial discussion revolved around the role of the biomarker ST2. This was found to be a marker of cellular matrix turnover and was found to be a to ligand for interleukin-33. Using retrospective data from the PRIDE study of 599 patients with acute dyspnea presenting to the emergency room, ST 2 correlated weakly positively with ejection fraction with an r-value of 0.37. When evaluating outcomes, ST 2 was found to be useful as a prognostic factor for patients in the lowest quartile with 4 year mortality was 30% compared to > 60% for patients in the highest quartile. He discussed the uncertainties regarding the source of ST 2 in the blood. Prior studies did not show any increase in gradient between the coronary sinus and the atrium, suggesting a non-myocardial source. He finished his discussion by discussing a new study that will be done in collaboration with the University of Utah looking at the role of serum ST 2 in detecting acute cardiac allograft cellular rejection.

The next speaker was Dr. Garrick Stewart. Dr. Stewart described his ongoing research in two areas: 1): devices in heart failure; he is pursuing studies with Dr. Lynne Stevenson employing the INTERMACS mechanical circulatory support database. 2) viral cardiomyopathy, particularly circulating cardiodepressant autoantibodies. He presented an elegant discussion of the literature regarding autoantibodies and the use of immunoadsorption for removing these myocardial depressant factors. It appears that the most common autoantibody in this class is an IgG3 subtype. He is looking at a study of the epidemiology of circulating cardiodepressant antibodies in patients with dilated cardiomyopathy versus controls. Ultimately, the hope is to employ immunoadsorption to treat this condition. Small studies have been performed in Germany which suggest that this approach has merit but they have yet to be replicated in the United States.

Drs. Dec and Baughman reviewed the current status of the Clinical Skills Core. The purpose of the Core is to train future leaders in the field of heart failure, both clinical care and scientific investigation. Annual events include enrollment in the Clinical Effectiveness Program for fellows who wish that training, attendance at national meetings including the Heart Failure Society

of America, Gordon Conferences, the International Society of Heart/Lung Transplantation, ACC, and AHA. Travel for fellows is funded through the grant. In addition, a Heart Failure Champions series occurs every year. Past speakers have included Drs. Margaret Redfield, Douglas Mann, and John Burnett. The upcoming speaker for 2010 is Dr. Gary Francis. Speakers spend 2 days lecturing and meeting with fellows and junior faculty to discuss their career development and research interests. These visiting expert series have been highly effective. An Advisory Committee also meets yearly with each fellow to review their progress. In addition, ongoing meetings occur between the trainee and his/her advisor on a regular basis. The goal is to develop clinician-investigators who can pursue independent funding for heart failure investigation. The fellowship is advertised through the web site as well as through advertisements that are run yearly in major journals. A summary is provided each year of progress for the grant. To date, core fellows have included Drs. Gregory Lewis, Neal Lakdawala, Garrick Stewart, and Ravi Shah. All fellows have impressive records of publications and several are in the process of obtaining funding. Dr. Lewis is now on the faculty at MGH and has an American Heart Association Fellow-to-Faculty Transition Award. Dr. Stewart has an MIT CITP award. Dr. Ravi Shah is currently a first year clinical fellow but will be applying for grants next year. A web site re-design is currently underway to enhance access to the elements of the Clinical Skills Core including its multiple opportunities for research conferences, Cardiology Grand Rounds, and other educational conferences.

Dr. Kimberley Parks then presented an update on ongoing Network Trials. Since the majority of this material had been previously covered by Dr. Braunwald, her focus was on providing demographics of ongoing studies, enrollment performance, and substudies that are underway. She began by reviewing the DOSE trial and indicated that enrollment was 100% complete. Other interesting features of the patient demographics included the fact that 25% of patients enrolled had normal ejection fraction and 40% of patients had 2 or more heart failure hospitalizations. The primary results of the trial will be presented at ACC 2010 (late-breaking clinical trials) session.

She next discussed the CARESS trial. Difficulties in enrollment were discussed with the coordinators as well as key investigators. Difficulties in obtaining venous access, as well as staffing for ultrafiltration appear common at both sites. Criteria regarding recent creatinine measurement has also limited enrollment. With the completion of the DOSE trial, it is hoped

enrollment in CARESS will increase. Dr. Stevenson indicated that enrollment is one of the key metrics that will be assessed by NIH in the selection of sites for renewal. She pointed out that the SMART trial has already terminated prematurely due to lack of enrollment. She strongly urged that all investigators and staff focus on CARESS so that a second study does not have to be terminated. One of the key ancillary studies includes the collection of urinary biomarkers to evaluate renal injury during diuresis. KIM-1, NGAL, sodium albumin, and NAG samples will all be collected and analyzed. The hypothesis is that elevated urinary biomarkers at baseline will predict the development of worsening renal function during diuretic treatment. A second hypothesis to be tested is that those patients who have biomarker evidence for renal injury at baseline may do better with ultrafiltration treatment than loop diuretic therapy.

Dr. Parks then summarized several RELAX substudies. The enrollment goal for the trial is 190 patients. A series of studies will be looking at pulmonary vascular response to exercise in heart failure patients and in normal controls. Exercise-induced ventilatory oscillation will be studied with a hypothesis that treatment with a phosphodiesterase inhibitor will improve this abnormality. An earlier pilot study suggested that this beneficial effect could be observed with the positive inotrope, milrinone. Studies are also underway to evaluate the ergoreflex and its effects on exercise capacity in heart failure.

Dr. Desai raised the issue of how site investigators, particularly heart failure fellows, can gain access to data for analysis from the trials. Although the primary endpoints in studies certainly will be reported by the senior Principal Investigators, it was felt that fellows need to be able to submit proposals to analyze data as part of their training and participation in the Trial Network. Dr. Stevenson indicated that it was important for this academic activity to be pursued as there has been no clear mechanism for this to be implemented up to now; it will be especially important as studies reach their conclusions and data sets are “locked in”.

Dr. Givertz finished the discussion for the day. He indicated that previous speakers had already covered most of the key results for ongoing studies. He summarized two trials that are being implemented but not yet actively enrolling. 1) the first trial evaluates the role of xanthine oxidase inhibitor in decreasing oxidative stress in heart failure. This will be a randomized, double-blind, placebo-controlled, 26 week trial of allopurinol. Although

earlier studies did not suggest a benefit, the patients were not stratified for the presence of increased uric acid levels. This trial will do just that. Enrollment should begin in the Winter or Spring of 2010. 2) a second study, AGEDD, is a project that will supplement an RO1 grant entitled "Advanced Glycation End-Products in Human Myocardium" that was recently awarded to Dr. Martin LeWinter at the University of Vermont and Dr. Michael Zile at the Medical College of South Carolina. This study is complex and will involve endomyocardial biopsy as well as surgical myocardial specimens taken from patients at the time of coronary revascularization. The logistics of obtaining myocardial specimens was discussed as well as the importance of the Harvard site participating actively in this study. Additional details will be circulated as the study reaches the implementation stage.

There was a general discussion regarding the accomplishments of the network during the past year as well as the challenges of enrolling patients in an increasing number of complex studies with limited personnel. The investigators thanked the nurses and coordinators for their dedicated work in making sure that patients were screened and entered into appropriate studies. The meeting was adjourned at 4:25 PM after this discussion.