Managing hemoglobin levels might improve outcome in patients with heart failure

Although evidence suggests that anemia is common in patients with heart failure (HF) and is linked with increases in mortality and morbidity, the underlying mechanism of action is unclear. In addition, it is not evident whether changes in hemoglobin over time are related to the occurrence of adverse events.

In this retrospective analysis of data from the Valsartan Heart Failure Trial, patients with the largest average decrease in hemoglobin over 12 months (from 142 g/l to 126 g/l) had a significantly greater risk of hospitalization, morbid events and death than the quartile of patients who showed little change in hemoglobin ($P \leq 0.01$ for all). Decrease in hemoglobin levels was independently associated with increased risk of death even in those patients who were not anemic at baseline. Interestingly, lack of anemia at baseline and increases in hemoglobin over 12 months were not associated with improved cardiac function. A range of factors, including serum albumin, glomerular filtration rate, blood pressure and C-reactive protein, were independently associated with hemoglobin levels at baseline and over time, suggesting multiple causes of anemia in patients with HF.

The link between changes in hemoglobin levels and mortality and morbidity seen in this study suggests that there might be potential benefits in managing anemia in patients with moderate to severe HF. What constitutes the optimal hemoglobin level and the best way to achieve this level remains to be addressed.

Carol Lovegrove

Original article Anand IS *et al.* (2005) Anemia and change in hemoglobin over time related to mortality and morbidity in patients with chronic heart failure: results from Val-HeFT. *Circulation* **112:** 1121–1127

PCI-CLARITY: is clopidogrel pretreatment before PCI beneficial?

Following percutaneous coronary intervention (PCI), antiplatelet therapy in the form of aspirin alone or dual therapy with aspirin and clopidogrel can lower the risk of adverse thrombotic and ischemic events. Whether treatment with clopidogrel before PCI prevents more complications than clopidogrel administered at the time of PCI in patients with ST-segment elevation myocardial infarction (STEMI) who have received fibrinolytic therapy is, however, unclear.

The PCI–Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY) study was a prospective substudy of patients with STEMI who underwent PCI following initial fibrinolytic pharmacotherapy in the CLARITY–Thrombolysis in Myocardial Infarction (TIMI) 28 study. Patients were randomly assigned placebo or a loading dose of 300 mg clopidogrel administered in the 45 min after fibrinolysis followed by 75 mg clopidogrel daily.

Of the 1,863 patients who underwent PCI, 933 received clopidogrel and 930 received placebo. On the basis of intention to treat, the overall occurrence of stroke, recurrent myocardial infarction or cardiovascular-related mortality, from randomization to 30-day follow-up, was significantly lower in patients who had received clopidogrel pretreatment than in patients who received placebo (70 versus 112; number needed to treat 23, odds ratio 0.59, 95% CI 0.43–0.81; $P = 0.001$). Importantly, clopidogrel pretreatment did not raise the risk of bleeding complications.

The authors conclude that clopidogrel should be administered before PCI in patients with STEMI treated with fibrinolytic therapy.

Hannah Camm

Original article Sabatine MS *et al.* (2005) Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI–CLARITY study. *JAMA* **294:** 1224–1232

Concentric remodeling and myocardial dysfunction

Concentric remodeling is generally thought to be a compensatory response to increased cardiac afterload, but the way in which it develops into myocardial dysfunction and congestive heart failure is unclear. To examine the relationship between concentric remodeling and regional left ventricular failure, Rosen and colleagues used quantitative analysis of tagged MRI to look at regional myocardial function in a cross-sectional study of individuals with no previous history of heart disease who were participants in the Multi-Ethnic Study of Atherosclerosis (MESA).

Peak systolic midwall circumferential strain (Ecc) was analyzed in 441 consecutive patients, using the HARP® harmonic phase tool (Johns Hopkins University, Baltimore, MD), to determine global and regional left ventricular function. Peak Ecc was found to correlate with the extent of concentric remodeling. A gradual decline in peak global Ecc with increasing left ventricular mass to end-diastolic volume ratio (M:V) was seen in men. In women, this association held true only for those with a more-severe degree of concentric remodeling; remodeling resulted in a gradual increase in M:V for the first three quartiles, followed by evidence of dysfunction in the fourth quartile. There might, therefore, be a difference between the sexes in adaptation to increased cardiac afterload.

Increased concentric remodeling was associated with decreased myocardial function. The relationship between lower Ecc and increasing M:V ratio was most pronounced in the left anterior descending coronary artery region; the authors suggest that this might be an indication of local transition to myocardial dysfunction.

Carol Lovegrove

Original article Rosen BD *et al.* (2005) Left ventricular concentric remodeling is associated with decreased global and regional systolic function. *Circulation* **112:** 984–991

Contrast echocardiography for risk stratification of patients with cardiac chest pain

When patients present to an emergency department with cardiac chest pain and a nondiagnostic electrocardiogram, it can be difficult to distinguish between those who can be discharged safely and those with a high risk of an adverse outcome. Although Thrombolysis in Myocardial Infarction (TIMI) scores are useful for risk stratification, troponin levels are not always known at presentation.

Tong *et al*. compared the diagnostic and prognostic accuracy of regional function and myocardial perfusion on contrast echocardiography with that of TIMI scores for 957 individuals with suspected cardiac chest pain and no ST-segment elevation on the electrocardiogram. All patients underwent myocardial contrast echocardiography within 12 h of symptom onset. Modified TIMI risk scores were initially calculated from six clinical variables, but were adjusted later to incorporate troponin levels.

Participants were followed up for primary (death and myocardial infarction) or secondary (unstable angina and revascularization) events at three time points—early (within 24 h), intermediate (up to 30 days), and late (more than 30 days).

Data analysis revealed that contrast echocardiography classified patients as at high or low risk of adverse events more accurately than modified TIMI scores. A model that incorporated assessment of regional function and myocardial perfusion, together with initial clinical variables, provided the best prognostic information and was not improved further with the addition of troponin data.

According to the authors, implementation of this approach in the emergency department could improve risk assessment of patients with cardiac chest pain, and reduce hospital costs.

Claire Braybrook

Original article Tong KL *et al.* (2005) Myocardial contrast echocardiography versus Thrombolysis in Myocardial Infarction score in patients presenting to the emergency department with chest pain and a nondiagnostic electrocardiogram. *JACC* **46:** 920–927

Late-enhancement signal in MRI as a tool for myocardial viability assessment

Early clinical studies have shown that the late-enhancement (LE) signal in contrast-enhanced MRI can help identify regions of nonviable myocardium with excellent short-term reproducibility in patients with coronary artery disease (CAD). Bülow *et al.* have evaluated contrast-enhanced MRI as a tool for myocardial viability assessment by investigating whether the LE signal has long-term stability and whether it can be quantified reliably.

In this study, 33 patients with CAD and left ventricular dysfunction underwent two contrast-enhanced MRI procedures within 3–15 months. MRI results were analyzed by two independent observers who delineated and quantified the LE signals in different sections of the myocardium and who also assessed the degree of regional wall motion.

Fifteen patients had no interventions between the two MRI investigations, whereas 18 patients underwent revascularization after the first MRI.

Changes in the LE signal between the first and second MRIs were investigated in both groups, and variation in signal measurements between the observers was also determined.

The results showed that, in patients with chronic CAD and impaired left ventricular function, LE signals in myocardial segments can be quantified and localized in a highly reproducible manner over an extended time. Furthermore, the researchers noted that LE signals were stable when patients had undergone revascularization, and there was little variation between measurements recorded by different observers.

The authors conclude that their study provides further evidence that contrast-enhanced MRI is a useful tool for assessment of myocardial viability.

Claire Braybrook

Original article Bülow H *et al.* (2005) Cardiac magnetic resonance imaging: long term reproducibility of the late enhancement signal in patients with chronic coronary artery disease. *Heart* **91:** 1158–1163

Coronary calcium measurement predicts coronary heart disease

Coronary artery calcium (CAC) is linked to an increased risk of coronary heart disease (CHD), but the degree to which detection of CAC provides incremental risk prediction beyond contemporary measure is controversial.

In this cohort study, 2,000 healthy male and female US Army personnel aged 45–50 years were evaluated using measured coronary risk variables and CAC detected by electron-beam tomography.

The incidences of acute coronary syndromes and sudden cardiac death were recorded over a mean follow-up period of 3 ± 1.4 years. Coronary calcium was detected in 22.4% of men and 7.9% of women and was associated with an 11.8-fold increased risk of CHD in men. The study was not powered to detect a relationship between CAC and CHD in women. Overall, at a mean age of 46 years, 1.95% of men with CAC suffered from acute cardiac events compared with 0.16% of those without CAC ($P<0.0001$). The risk of coronary events increased incrementally with the degree of CAC. A family history of premature CHD was also predictive of incident events.

The marginal cost-effectiveness of introducing screening for CAC into a conventional risk-prediction assessment was projected to be US$37,633 per quality-adjusted life year, assuming 30% improvement in survival.

The authors conclude that, in young, asymptomatic men, "the presence of CAC provides substantial, cost-effective, independent prognostic value in predicting CHD." Further studies including women and various ethnic groups are needed to extend these data.

Carol Lovegrove

Original article Taylor AJ *et al.* (2005) Coronary calcium independently predicts incident premature coronary heart disease over measured cardiovascular risk factors. *J Am Coll Cardiol* **46:** 807–814

Low public awareness of heart failure in Europe and health-care funding

Levels of community awareness of heart failure (HF) in Europe are low and might affect public demands for appropriate funding of health care and research, according to the first reported findings of the Study of Heart failure Awareness and Perception in Europe (SHAPE).

Data were obtained from a sample of 7,958 randomly selected individuals from nine European countries who completed a 32-question survey covering recognition, impact on health, prevalence and severity, treatment and costs of HF.

Although 86% of participants had heard of HF, only 3% were able to identify the condition from its clinical description, compared with 31% who correctly identified angina and 51% who identified stroke. Only 29% of participants considered breathlessness, tiredness and swollen ankles to be 'a severe complaint', although 86% said they would seek medical attention if they had these symptoms. Overall, participants tended to underestimate the prevalence of HF, the effect of HF on mortality relative to other diseases, the ability of drugs to prevent HF, and the degree of health-care expenditure related to HF. In general, responses across Europe were similar, although recognition of the term HF, the perceived benefits of therapy, knowledge of the need for lifestyle changes resulting from HF, and preferred sources of information, varied between countries.

Given these clear misconceptions, strategies to improve public awareness of the importance of HF are needed. The authors suggest

that improved understanding of HF in the community could lead to increased funding of both HF healthcare and of research into this major public health problem.

Carol Lovegrove

Original article Remme WJ *et al.* (2005) Public awareness of heart failure in Europe: first results from SHAPE. *Eur Heart J* [doi: 10.1093/eurheartj/ehi447]

Dual growth-factor treatment can regenerate infarcted myocardial tissue

Growth factors can activate cardiac stem cells in mice with infarcted hearts, leading to regeneration of the myocardium, US researchers have shown.

The human heart has been found to harbor cardiac stem cells and early committed cells (CSCs–ECCs). Researchers have, therefore, been trying to promote the survival and proliferation of these cells. Urbanek *et al*. investigated whether a combination of insulin-like growth factor 1 (IGF1) and hepatocyte growth factor (HGF) could stimulate migration and growth of cardiac stem cells.

The researchers identified replicating CSCs–ECCs in the atrioventricular groove of the mouse heart and labeled these cells using enhanced green fluorescence protein. Mice with infarcted myocardial tissue were then treated with IGF1 and HGF and the degree of death, survival and growth of CSCs–ECCs were evaluated by confocal microscopy at regular time points over 4 months.

Sixteen days after growth-factor treatment, new myocardium-containing arterioles, capillaries and contractile myocytes had developed at the site of infarction. Although the area of ischemic heart tissue was generally larger in growth-factor-treated mice than in controls, the former had a higher chance of survival as the newly formed myocardium led to improved ventricular function.

These findings show that CSCs–ECCs can respond to local administration of IGF1 and HGF by migrating to sites of ischemic injury and developing into functional myocardial tissue.

Claire Braybrook

Original article Urbanek K *et al.* (2005) Cardiac stem cells possess growth factor-receptor systems that after activation regenerate the infarcted myocardium, improving ventricular function and long-term survival. *Circ Res* **97:** 663–673

Anti-huHSP60 linked with adverse 1-year prognosis in patients with cardiac chest pain

Previous studies have shown that titers of antibodies to human heat shock protein 60 (anti-huHSP60) or mycobacterial heat shock protein 65 (anti-mHSP65) are linked with progression of carotid atherosclerosis and clinical outcomes. In what is claimed to be the first study to assess the prognostic implications of anti-huHSP60 titers in a population of patients with unstable angina, Birnie *et al.* have now investigated whether titers of anti-huHSP60 and anti-mHSP65 can predict adverse clinical outcome in patients with acute chest pain of suspected cardiac ischemic origin.

In this prospective study, venous blood samples were obtained from 588 participants, and their titers of anti-mHSP65 and anti-huHSP60 measured. Patients were followed up for a mean period of 304 days and the following endpoint outcomes were recorded: coronary heart disease death; nonfatal myocardial infarction; coronary artery bypass grafting; percutaneous transluminal coronary angioplasty; angiogram; and readmission with further cardiac chest pain.

The risk of an adverse 1-year prognosis increased by about 50% for patients with titers of anti-huHSP60 greater than 16 U/l compared with those with lower titers. This trend was still evident after adjustment for the established cardiovascular risk factors of age, hypertension, diabetes and smoking. Titers of anti-mHSP65, however, did not correlate significantly with 1-year clinical outcomes.

The authors conclude that elevated titers of anti-huHSP60 are associated with increased risk of an adverse 1-year prognosis in patients presenting with acute chest pain.

Claire Braybrook

Original article Birnie *et al.* (2005). Increased titres of anti-human heat shock protein 60 predict an adverse one year prognosis in patients with acute cardiac chest pain *Heart* **91:** 1148–1153

Early initiation of statins after ACS improves vascular endothelium function

Cholesterol lowering using statin regimens initiated soon after acute coronary syndromes (ACS) has been shown to improve endothelial

function, although the time course of the improvement is unknown and the effect of treatment intensity has not been established. Dupuis *et al.* have reported the results of the Brachial Artery Vascular Endothelium Reactivity (BRAVER) study to elucidate these factors.

Patients ($n = 50$) who had been hospitalized following ACS (myocardial infarction or high-risk angina) underwent evaluation of endothelium-dependent, flow-mediated dilation (FMD) and endothelium-independent, sublingual nitroglycerin-mediated dilation (NMD) by high-resolution brachial ultrasound, at baseline, 48 h, and at 1 and 4 months after initiation of either pravastatin or atorvastatin. LDL cholesterol decreased by 32% after 4 months in patients treated with atorvastatin; levels were not different from baseline in the pravastatin group. For statin-naive patients, FMD and NMD increased significantly after 4 months, by 27% and 24%, respectively ($P < 0.05$), with no difference between treatment groups. Improvement in vascular reactivity with statin therapy was, therefore, suggested to be independent of the degree of cholesterol lowering. There was no significant change in FMD or NMD in patients who had previously used statin therapy, which implies that new statin therapy needs to be initiated in these patients for improvements in vascular reactivity following ACS.

Rapid initiation of statin therapy following ACS was thereby shown to be associated with improvements in vascular reactivity, endothelial function and endothelium-independent vasodilation after 4 months.

Carol Lovegrove

Original article Dupuis J *et al.* (2005) Intensity of lipid lowering with statins and brachial artery vascular endothelium reactivity after acute coronary syndromes (from the BRAVER trial). *Am J Cardiol* [doi: 10.1016/j.amjcard.2005.06.057]

Neurosurgical clipping versus endovascular coiling to treat ruptured intracranial aneurysm

A recent paper published in *The Lancet* has compared neurosurgical clipping with endovascular coiling in patients with ruptured intracranial aneurysm. Of the two treatments, endovascular coiling was associated with the lowest risk of death or dependency at 1 year.

The International Subarachnoid Aneurysm Trial (ISAT) included 2,143 patients at 42 neurosurgical centers. All patients had subarachnoid hemorrhage due to intracranial aneurysm and were randomized to endovascular detachable-coil treatment ($n = 1,073$) or neurosurgical clipping ($n = 1,070$). In 2002, an interim analysis showed that patients treated with endovascular coiling were more likely to achieve independent survival at 1 year; the latest results confirm these findings and provide information on subgroup analyses and secondary outcomes.

After the first procedure, the endovascular group showed a highly significant reduction in seizures when compared with the neurosurgery group (relative risk 0.52; 95% CI 0.37–0.74). During the first year after treatment, death or dependency was reported in 23.5% of patients randomized to endovascular coiling, compared with 30.9% of those in the neurosurgical clipping group. This corresponded to an absolute risk reduction of 7.4% (95% CI 3.6–11.2%; $P = 0.0001$) in the endovascular treatment group. Although follow-up continues, the data available thus far suggest that the survival benefit might persist for up to 7 years.

Ruth Kirby

Original article Molyneux AJ *et al.* (2005) International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *Lancet* **366:** 809–817

Cognitive decline after CABG related to underlying cerebrovascular disease

Coronary artery bypass grafting (CABG) is commonly thought to cause a decline in the postoperative cognitive functioning of patients. McKhann and colleagues, however, have recently reported results of a study that casts doubt on this claim.

The four-arm, prospective study investigated CABG patients ($n = 140$), patients undergoing off-pump coronary surgery ($n = 72$), nonsurgical cardiac controls with diagnosed coronary artery disease ($n = 99$), and heart-healthy controls with no cardiac risk factors ($n = 69$). Participants underwent a series of neuropsychological tests at baseline (before surgery), 3 months and 12 months. Scores

from the tests were combined to form eight cognitive domain scores for cognitive abilities such as verbal memory and psychomotor speed.

Baseline performances of heart-healthy controls were found to be higher than those of the other three groups for all cognitive domains. For six of the domains, the difference between the performances of the healthy controls and the two surgical groups was significant ($P<0.01$). All groups showed a similar degree of improvement in intrasubject scores from baseline to 3 months, and from 3 to 12 months. At 12 months all groups were performing at or above their baseline levels.

Concluding that there was no evidence that CABG patients' cognitive performance was worse than that of control patients with coronary artery disease over a 12-month follow-up period, the authors suggest that, in general, patients with long-standing coronary artery disease have an element of cognitive impairment caused by cerebrovascular disease, and that this is present before they undergo surgery.

Christine Kyme

Original article McKhann GM *et al.* (2005) Is there cognitive decline 1 year after CABG? *Neurology* **65:** 991–999

Benefits of abciximab for patients with ischemic stroke

Abciximab could have beneficial effects on neurological status and size of ischemic lesions in patients with ischemic stroke, an MRI-guided trial has shown.

Abciximab is a glycoprotein IIb/IIIa receptor antagonist previously shown to induce thrombolysis and restore vessel patency in patients with acute coronary syndromes who receive coronary stents.

Mitsias and colleagues recruited 29 patients with supratentorial stroke to take part in a single-center, open-label trial. Trial participants received abciximab therapy within 3–24 h of stroke onset. Following treatment, patients were monitored for bleeding and changes in hemoglobin levels, hematocrit and platelet count. Neurological deterioration was also measured at regular intervals using the NATIONAL INSTITUTES OF HEALTH STROKE SCALE (NIHSS). Post-treatment primary outcome measures were changes in NIHSS scores at 48–72 hours and ischemic lesion size on diffusion-weighted imaging at 24-hour follow-up.

NIHSS scores decreased for most patients after abciximab therapy, indicating that their neurological status had improved. Furthermore, there was a reduction in the size of ischemic lesions in 27% of patients. No treatment-related deaths, symptomatic intracranial hemorrhages or major systemic hemorrhages were observed.

Despite the small number of patients and uncontrolled nature of this study, the authors conclude that abciximab is relatively safe when used to treat patients with ischemic stroke within a 3–24-hour window, and that the drug could attenuate both neurological deterioration and ischemic lesion growth.

Claire Braybrook

Original article Mitsias PD *et al.* (2005) MRI-guided, open trial of abciximab for ischemic stroke within a 3- to 24-hour window. *Neurology* **65:** 612–615

GLOSSARY

NATIONAL INSTITUTES OF HEALTH STROKE SCALE (NIHSS)
A structured, clinician-rated scale incorporating physical examination, pre-set questions, and language assessment to quantify neurological deficits following stroke