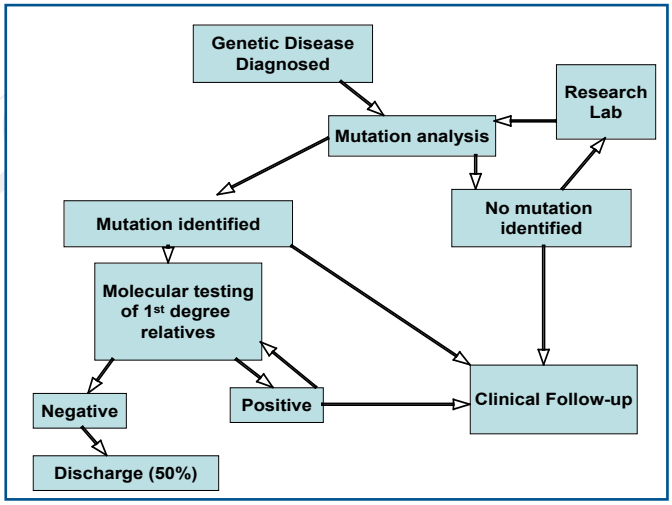
Influence of Mutation Analysis on Management

How is mutation analysis applied in clinical practice? Prof. McKenna described a pathway for testing that involves carrying out mutation analysis on first-degree relatives when a mutation is detected in an individual (Figure 1). "If a mutation is found, you know that serial follow-up has merit," he said. If no mutation is found, the patient is discharged. Genetic counseling should be offered when testing demonstrates troponin I or beta-myosin heavy chain mutations. Perhaps the most important illustration of how knowledge of a specific mutation influences management is the identification of an individual with a troponin T mutation and being able to avoid premature sudden death with an implantable defibrillator.

Figure 1. Molecular Diagnostics in Clinic.



Advantages and Disadvantages of Mutation Analysis

Determining a molecular diagnosis of familial HCM has many advantages as well as some disadvantages, said Prof. McKenna. The targeted management allowed by a molecular diagnosis is cost-effective, as serial follow-up is done only when warranted by risk. Diagnostic uncertainty and false-negative clinical evaluations are also avoided, leading to better psychological well-being for patients. The primary disadvantage is related to the complexity of testing. For example, genetic data are difficult to interpret, an individual may have more than one disease-causing gene, and evaluation of entire families is needed. In addition, the approach requires that cardiologists work with genetic counselors and other specialists. "We will need new models of care," he said.

Raising HDL: Is It a Good Idea?

A low level of high-density lipoprotein cholesterol (HDL-C) has been considered to be a cardiovascular (CV) risk factor. In fact, a 1% increase in HDL-C leads to a 2-3% decrease in the risk of coronary artery disease (CAD), said Sergio Nabais-Araujo, MD, Hospital S. Marcos, Braga, Portugal.

Prof. Nabais-Araujo presented study findings in which the association between HDL-C level and outcomes was evaluated in 944 patients with acute coronary syndrome (ACS). The patients were assigned to one of two groups based on their baseline HDL-C level (within 24 hours of admission to the coronary care unit). High HDL-C was defined as ≥40 mg/dL for men and ≥45 mg/dL for women; low HDL-C was defined as <40 mg/dL for men and <45 mg/dL in women. High HDL-C level was associated with a lower rate of the composite endpoint of death, MI, and recurrent ischemia at 6 months (18.6% vs 24.3%; p=0.037). However, mortality at 30 days and 6 months was similar for the two groups of patients.

The cardioprotection conferred by an elevated level of HDL-C is thought to be related to anti-inflammatory effects. In a hypothesis-generating study presented by Demosthenes Panagiotakos, MD, University of Athens, Greece, the relationship between HDL-C and several anti-inflammatory markers was evaluated in a population of 2,282 men and women who were free of cardiovascular disease. Prof. Panagiotakos reported that there was a significant inverse correlation between levels of HDL-C and levels of high-sensitivity C-reactive protein (p=0.001) and homocysteine (p=0.036), after adjustments were made for several demographic variables. No significant relationship was found between HDL-C levels and interleukin-6 and serum amyloid A levels.

Another marker of CV risk is the ratio of total cholesterol (TC) to HDL-C; a ratio of 4 or more has been associated with increased risk for ACS. Deepu Nair, MD, Cleveland Clinic, Ohio, and colleagues assessed the association between the TC/HDL-C ratio and evidence of disease in the proximal coronary arteries (the site of most atherosclerotic ruptures) on multislice computed tomography. Dr. Nair reported that in 281 individuals with documented CAD, the prevalence of proximal plaque was significantly higher in individuals with a TC/HDL-C ratio of 4 or more (62% vs 48%; p=0.02). The prevalence of proximal stenosis was also significantly higher in this group of patients (20% vs 8%; p=0.003). He suggested that an

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The study population included 11,140 patients (mean age 66 years; mean SBP 145 mmHg) who were randomly assigned to receive combination perindopril/indapamide 2.0mg/0.625mg for 3 months followed by 4.0mg/1.25mg thereafter (n=5,569) or placebo (n=5,571). Patients received ancillary treatment at the discretion of the treating physician. The primary study outcomes were macrovascular (nonfatal stroke or MI or death from any cardiovascular cause) and microvascular events (new or worsening nephropathy or diabetic eye disease).

Baseline patient characteristics were similar between groups. Average patient follow-up was 4.3 years at which point 73% of those receiving active therapy and 74% of those receiving placebo remained on therapy. Mean systolic and diastolic blood pressure (DBP) declined by 5.6 and 2.2 mmHg, respectively, in patients receiving combination perindopril/indapamide vs placebo (p<0.001 for both systolic and DBP). Blood pressure dropped from 145/81 mmHg at baseline to 135/75 mmHg in the treatment arm and 140/77 mmHg in the control group.

In patients receiving combination perindopril/indapamide there was a significant relative risk reduction (RRR) of 14% in all-cause mortality (p=0.025) which was driven primarily by an 18% RRR in cardiovascular deaths (p=0.027).

The overall RRR of a macrovascular or microvascular event was 9% (p=0.041).

Additional secondary endpoint analyses showed a 14% reduction (8.4% vs 9.6%, p=0.020) in the risk for coronary heart disease and a 21% reduction (22.3% vs 26.9%, p<0.0001) in all renal events. There was no difference in cerebrovascular or diabetic eye events. Similar benefits were achieved for those with or without hypertension and in the presence or absence of treatment with other blood pressure lowering drugs, statins, or anti-platelet drugs (Table 1).

Table 1. Relative Risk Reduction by Subgroup.

Subgroup	Perindopril/ Indapamide n=5569	Placebo n=5571	Relative Risk Reduction (95% CI)
History of hypertension			
No	121 (12.7%)	136 (13.8%)	9% (-1.7, 29)
Yes	740 (16.0%)	802 (17.5%)	9% (0, 18)
Any blood pressure lowering therapy			
No	177 (12.6%)	183 (13.3%)	6% (-15, 24)
Yes	684 (16.4%)	755 (18.0%)	10% (0, 19)
Statin therapy			
No	638 (15.8%)	687 (17.3%)	10% (0, 19)
Yes	223 (14.5%)	251 (15.6%)	8% (-10, 23)
Anti-platelet therapy			
No	408 (13.7%)	454 (15.3%	11% (-2, 22)
Yes	453 (17.4%	484 (18.6%)	7% (-5, 18)

Source: ADVANCE Collaboration Group. *Lancet* 2007. Published Online September 2, 2007

Prof. MacMahon called for routine blood pressure reduction for all patients with type 2 diabetes. "In absolute terms", said Prof. MacMahon, "one death would be avoided for every 78 patients treated with the fixed combination of perindopril and indapamide over 5 years. Lowering blood pressure is what counts, not the way by which it is lowered"

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The importance of monitoring weight in patients with HF was reinforced by the findings of a study in which weight loss and leanness simultaneously predicted poor prognosis in a broad spectrum of HF patients. The study was carried out by Joanna Dobson, MD, London School of Hygiene, UK, who reports that weight loss at 6 months predicted poor prognosis in the long-term. In the study, for every 1% weight loss, there was an 11.2% increase in mortality hazard. Prof. Dobson advocates for more intense monitoring of weight loss as well as optimizing treatment when weight loss is detected.

Patient Education

According to the Study group on Heart failure Awareness and Perception in Europe (SHAPE) study, only 3% of 7,958 respondents to a European survey could correctly identify HF from a description of typical signs and symptoms [Remme WJ et al. *Eur Heart J* 2005]. This was much lower than the rates for recognition of any other cardiovascular disease. To address this knowledge gap, the Heart Failure Association of the ESC developed the website www.heartfailurematters.org. "The website is designed to empower patients to know what they can do to help themselves," says Prof. Dickstein. It offers a description of HF and its treatment in simple language and features an optional narrative guide to help older visitors to the site. Prof. Dickstein encouraged physicians to tell their patients about the website as a way to improve patient compliance with treatment and lifestyle changes that can help enhance their quality of life and improve survival.

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elevated TC/HDL-C ratio defines a group of patients at higher risk for ACS.

The results of these studies indicate that enhanced efforts to increase the HDL-C level and to decrease the TC/HDL-C ratio may be of benefit, especially in individuals with ACS or at high risk for the disease; the cardioprotection offered by HDL-C stemming from its direct relationship with anti-inflammatory markers.