A Bi-Center Cardiovascular Magnetic Resonance Prognosis Study Focusing on Dobutamine Wall Motion and Late Gadolinium Enhancement in 3,138 Consecutive Patients

To the Editor: In the present study we sought to investigate the predictive value of resting and inducible wall motion abnormalities (WMA) and of late gadolinium enhancement (LGE) for hard cardiac outcomes and for revascularization procedures in 3,138 patients undergoing dobutamine cardiac magnetic resonance (DCMR) in 2 tertiary centers (University Hospital Heidelberg; and German Heart Institute, Berlin) and during a long-term follow-up.

From January 2000 through June 2008, consecutive patients who were referred for clinically indicated DCMR due to suspected or known coronary artery disease were prospectively enrolled. Our patient cohort consisted of 1,369 patients enrolled in Berlin and 1,493 patients enrolled in Heidelberg who were reported in previous studies (1,2). Additional patients (n = 276) were added in the present analysis, resulting in 3,138 patients in the analysis population. Patients were examined in clinical 1.5-T whole-body cardiac magnetic resonance scanners. Wall motion and LGE imaging were performed and interpreted as described previously (1,2). Patient preparation, imaging and analysis for DCMR amounted to approximately 30 to 40 min.

Cardiac death and nonfatal myocardial infarction were registered as hard cardiac events. Other events included clinically indicated revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). Because the results of the magnetic resonance examination might have triggered revascularization procedures, patients with "early" revascularization procedures within 3 months after DCMR were censored. A separate analysis was performed in this patient subgroup, to investigate the effect of early revascularization procedures on subsequent cardiac events.

Data were collected in 3,138 patients during a 3.3 ± 1.7-year (range 0.5 to 9.7-year) follow-up period. Hard cardiac events occurred in 183 (5.8%) patients, including 80 (2.5%) cardiac deaths (n = 44 due to intractable heart failure, n = 21 due to infarction, and n = 15 who died suddenly) and 103 (3.3%) nonfatal myocardial infarctions. In 520 (16.6%) patients early revascularization was performed within 90 days after the magnetic resonance examination (450 by PCI, and 70 by CABG), and 257 (8.2%) patients underwent late revascularization (203 by PCI, and 54 by CABG). Noncardiac death was recorded in 43 (1.4%) patients.

By multivariable analysis, inducible WMA, LGE, and resting WMA were independent predictors of hard cardiac events (hazard ratio [HR]: 6.5, 95% confidence interval [CI]: 4.6 to 9.3; HR: 2.2, 95% CI: 1.2 to 4.1; and HR: 1.6, 95% CI: 1.2 to 2.3, respectively, p < 0.001 for all). With a series of Cox proportional hazards models, resting and inducible WMA exhibited incremental value beyond clinical parameters for the prediction of outcome (Fig. 1A). In patients where LGE was additionally performed, resting WMA, LGE, and inducible WMA exhibited incremental value (Fig. 1B). With integrated discrimination improvement analysis, inducible WMA exhibited incremental value in the first model, whereas LGE and inducible WMA showed incremental value in the second model (Figs. 1A and 1B).

Patients with inducible WMA experienced a significantly higher rate of hard cardiac events (Fig. 1C), whereas patients with LGE exhibited a higher rate of subsequent hard cardiac events compared with those without LGE (Fig. 1D). In the absence of inducible ischemia by DCMR, clinical outcomes were not influenced either by PCI or CABG (Fig. 1E). Conversely, patients with inducible WMA equally profited from PCI and CABG compared with those continued on medical treatment (Fig. 1F).

Within the first 3 years of follow-up excellent outcomes were recorded for patients without inducible ischemia with regard to hard cardiac events and late revascularization procedures (annual hard event rate of 0.6%, and revascularization rate of 1.6%). Between the third and fourth year, however, hard cardiac event rates increased by 2-fold (from 0.9% to 2.0%). Over the third and sixth year, annual event rates rose for both hard events and revascularization to 1.6% and 3.2%, respectively.

Our DCMR findings in 3,138 patients demonstrate that:

1. The presence of inducible WMA and LGE independently identify patients at increased risk for subsequent cardiac events;
2. Only patients with inducible ischemia benefit from revascularization procedures (PCI and CABG);
3. Excellent risk prediction extends up to 3 years after the initial diagnostic procedure, whereas repeated testing might be warranted after this time period due to a subsequent rise (2-fold rise between the third and fourth year) in the annual event rates.

The assessment of myocardial perfusion during vasodilator stress with adenosine or dipyridamole was shown to be a strong predictor of hard cardiac events in several studies, which included patients with stable angina (3–8). A number of further studies demonstrated the value of wall motion assessment during inotropic stimulation with dobutamine for the prediction of cardiac events (1,2,4,9,10). Hereby, it should be noted that the mean follow-up duration was lower in previous studies (2.2 years vs. 3.3 years in our study), whereas the total number of hard cardiac events was lower than that observed in our population (142 in all previous studies vs. 183 in our study). Furthermore, although the complementary value...
of LGE was previously demonstrated for myocardial perfusion analysis during vasodilator stress (8), no published report investigated the role of LGE with DCMR in this context so far.

In our study, we demonstrate the incremental value of LGE and inducible WMA for the assessment of long-term prognosis in the largest patient cohort thus far. Inducible WMA and LGE provided the highest HRs for future hard cardiac events, surpassing that provided by clinical parameters. Patients without inducible ischemia (IDI), clinical outcomes were not influenced either by percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) (E). Conversely, patients with inducible WMA profited from PCI and CABG compared with those continued on medical treatment (F).

Figure 1  Cox Proportional Hazards Models and Survival Analysis
In a series of Cox models evaluated for the prediction of hard cardiac events clinical risk factors, resting, and inducible wall motion abnormality (WMA), each offered incremental prognostic information to the model (A). In patients where late gadolinium enhancement (LGE) was performed, LGE exhibited incremental value beyond clinical parameters and resting WMA for the prediction of outcome (B). Patients with inducible WMA exhibited a significantly higher rate of hard cardiac events (C), whereas patients with LGE showed a higher rate of subsequent hard cardiac events (D). In the absence of inducible ischemia (IDI), clinical outcomes were not influenced either by percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) (E). Conversely, patients with inducible WMA profited from PCI and CABG compared with those continued on medical treatment (F).
However, the annual event rate rose after the first 3 years, indicating that in patients with persistent or recurrent stable chest pain syndrome and initially negative stress testing, repeated DCMR diagnostic procedures might be warranted.

Furthermore, early revascularization either by PCI or CABG both improved clinical outcome only in patients with inducible WMA by DCMR, whereas patients who underwent revascularization in the absence of inducible ischemia showed no significant benefit from invasive treatment. This is in agreement with recent randomized multicenter trials, where only patients with ischemia benefited from invasive procedures (11,12).

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Letters to the Editor

Long-Term Survival of Young Patients With Coronary Artery Disease Is Best Realized Through Surgical Revascularization With Mammary Arteries

In a recent issue of the Journal, Flather et al. (1) reported a subgroup analysis of individual patient data from 10 randomized trials comparing percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) for multivessel coronary disease. Their analysis showed that there was a significant treatment-by age interaction for 10-year mortality (p < 0.001). Strikingly enough, in the youngest group of patients (≤56.2 years of age), there was no difference in mortality (hazard ratio [HR] for PCI: 1.23; 95% CI: 0.95 to 1.59), whereas the HR shifted toward a significant benefit of CABG over PCI in older patients (≥65.2 years of age) (HR: 0.79; 95% CI: 0.67 to 0.94).

Although the data from these trials are compelling, the trials were not performed according to the “all-comers” design, and it is therefore likely that there was a severe selection bias in the inclusion of patients. Young patients were probably those with low lesion complexity, and it is known that CABG does not offer a survival benefit in these patients (2). In contrast, even though the

REFERENCES