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Patient stratification and treatment effects in diseases with disturbed cardiac function

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Akademisk avhandling

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Title
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Abstract
Cardiovascular disease characteristics are often measured using a combination of different measurement modalities. By combining information from these modalities using statistical modelling we can gain additional knowledge about these diseases.

Patients with transthyretin amyloidosis (ATTR) often present with heart rate disturbances and cardiac enlargements and can be misdiagnosed as having other diseases, e.g. hypertrophic cardiomyopathy (HCM). Children with hereditary long QT syndrome (LQTs) carry the risk of lethal cardiac events linked to increased sympathetic activity which could be assessed by analysis of heart rate variability (HRV). Statins is the most common pharmaceutical treatment for atherosclerosis. However, the effect of statins on coronary calcification has shown mixed results between studies.

The overall aim of this thesis was to use statistically rigorous methodology to explore stratification of subgroups of patients and estimate treatment effects in diseases with cardiac involvement. The specific aims were: to evaluate discriminating features between ATTRv amyloidosis- and HCM patients; to explore similarities and differences between these patient groups; to evaluate the longitudinal growth pattern in HRV in children with LQTs; and, to estimate the short- and long-term treatment effects of statin treatment on coronary calcification.

Classification trees was used in order to differentiate between ATTRv amyloidosis HCM based on features derived from echocardiography (echo) and ECG. K-means clustering and Random forest models was used in order to investigate similarities and differences in echo and HRV features between ATTRv amyloidosis patients, HCM patients and healthy controls. Gender and treatment dependent age trends was estimated for spectral HRV features children with LQTs. Data from two large clinical trials, was combined to estimate the short- and long-term treatment effects of statin treatment on coronary calcification.

Data from our studies could be used for differentiating HCM- and ATTRv amyloidosis patients. A combination of ECG and echocardiography provided the best separation between HCM and ATTRv amyloidosis. We found that HRV could be used for discriminating between these diseases and that abnormalities in HRV are related on ATTRv fibril type but uncommon in HCM. Our data do not support evidence for a different age trend in HRV parameters in children with LQTs compared to controls of similar age. We found that high dose statin treatment resulted in a dose dependent increase in calcium score. Taken together, the results and methods from this thesis may be used for future support in clinical decisions regarding patient stratification and knowledge of treatment effects.

Keywords
Patient stratification, decision trees, heart rate variability, echocardiography, machine learning, biostatistics

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