Prescription bias in the treatment of chronic systolic heart failure impacts outcome

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Background: There is evidence that medical therapy with beta-blockers (BB) and renin-angiotensin-system-inhibitors, uptitrated to target dosage (TD) decreases mortality and hospitalizations in HFrEF. However, physicians seemingly do not sufficiently follow the guidelines and a great number of patients do not receive recommended dosages. As humans are visually deceivable, it might be that absolute numerical values of equipotent recommended TD and the "milligram-based" subjective weighting of tolerability by the individual physician influences the maximal prescribed dosage.

Purpose: We sought to assess whether different numerical TD of equipotent medications affect prescription patterns, potentially biases uptitration and impacts outcome.

Methods: 3737 HFrEF outpatients were identified from a prospective registry. Maximal achieved dosages of BB, ACEi and ARB after one year of repeated visits for uptitration were assessed. BB, ACEi and ARB with largest numerical differences in TD (10mg/d bisoprolol/nebivolol vs 200mg/d metoprolol; 10mg/d ramipril vs 40mg/d lisinopril/enalapril/fosinopril; and 32mg/d candesartan vs 320mg/d valsartan) were compared using the individually achieved dose as percentage of the defined TD at one year of FUP. The association of maximal achieved TD with HF hospitalization and overall survival were determined.

Results: Median age was 65 years (IQR: 55–74), 2720 patients (73%) were male. Within the whole study population, 1434 patients (38%) received bisoprolol/nebivolol, 280 (8%) metoprolol. Ramipril was prescribed in 599 (16%) patients, lisinopril/enalapril/fosinopril in 1138 (30%). 409 patients (11%) were on candesartan, 173 (5%) on valsartan. Significant differences at baseline were not clinically meaningful and there were no contraindications for uptitration in all subgroups. After one year aiming for up-titration dosages increased significantly in all medication-groups ($p<0.001$ for all). However, significantly less patients were treated with the TD when TD was numerically higher (BB: metoprolol (57 (20%)) vs bisoprolol/nebivolol (446 (31%), $p<0.001$); ACEi: lisinopril/enalapril/fosinopril (231 (20%) vs ramipril (313 (52%), $p<0.001$); ARB: valsartan (45 (26%) vs candesartan (166 (41%), $p<0.001$)). At 45 (IQR: 32–68) months of FUP, 859 (23%) of the patients were hospitalized for HF or died. Achievement of TD significantly improved outcome (Fig. 1A-C) and showed association with mortality and HF-hospitalization (BB: adj.HR=0.87, 95% CI: 0.79–0.95, $p<0.001$; ACEi: adj.HR=0.89, 95% CI: 0.81–0.97, p=0.023; ARB: adj.HR=0.74, 95% CI: 0.69–0.91, p=0.009).

Conclusion: The present analysis described the influence of the numerical values of recommended TD of equipotent drugs on the prescription behavior of the treating physician and on outcome. This psychological phenomenon was identified a substantial confounder at least partly responsible for the underuse of BB, ACEi and ARB in HF. Moreover, it was never shown that this cognitive illusion based on risk aversion is linked to outcome.

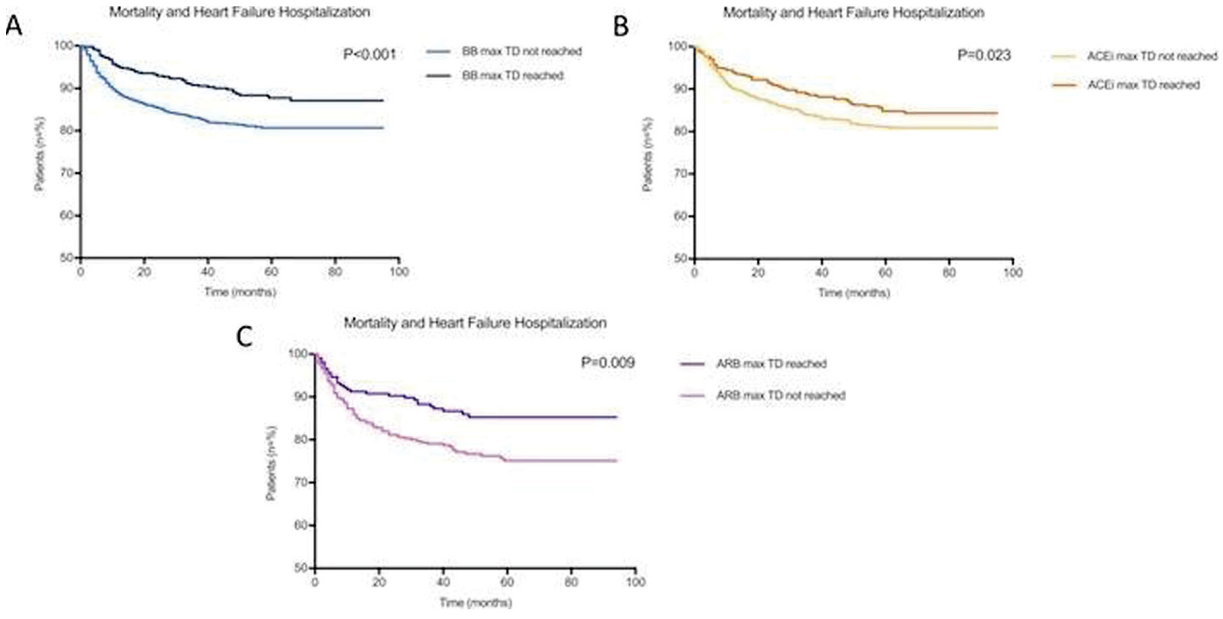

Figure 1