

β遮断薬は腎機能障害を有する患者であっても死亡率を低下させる

BB-meta HF試験：心不全および中等度腎機能障害を有する患者においてベータ遮断薬は死亡率を減らす

BB-meta HF: Beta-blockers reduce death in patients with heart failure and moderate renal impairment

駆出率の低下した洞調律の心不全(HFrEF)において、β遮断薬はたとえ腎機能障害を有していても死亡率を予防するために有効である、とESC Congress 2019のHot Line Sessionで発表された。追跡期間中央値1.3年の間、腎機能障害は高死亡率と独立して関連があり、腎機能障害が重度であるほど心不全の進行が死亡原因である頻度が高かった。洞調律の患者13,861人において、中等度から中等度-重度の腎障害を有する患者であっても、β遮断薬は死亡率を有意に低下させた。補正後、β遮断薬はプラセボと比較し、死亡リスクをそれぞれ27%および29%低下させた。

Full Text

Beta-blockers remain effective for preventing death in heart failure with reduced ejection fraction (HFrEF) and sinus rhythm, even in patients with moderate or moderately-severe kidney dysfunction, according to late breaking research presented in a Hot Line Session at ESC Congress 2019 together with the World Congress of Cardiology.

It is estimated that up to half of heart failure patients have renal impairment according to their estimated glomerular filtration rate (eGFR). ESC 2016 heart failure guidelines state that "there is lack of evidence-based therapies" in patients with kidney dysfunction. In almost every section of the guidelines, clinicians are warned that caution should be exercised when heart failure drugs are used in patients with impaired renal function.

Principal investigator of the study, Dr. Dipak Kotecha of the University of Birmingham, UK said: "Although there is no clear contraindication for most patients, it is not surprising that treatment initiation or up titration of life- saving heart failure therapies is quite low in patients with coexisting renal dysfunction. Ironically, heart failure patients with impaired kidney function are at the highest risk of adverse outcomes and have potentially the most to gain from therapy."

The efficacy and safety of HFrEF treatment is unknown in those with moderate renal dysfunction (eGFR 45–59 mL/min/1.73m2) or moderately-severe renal dysfunction (30–44 mL/min/1.73m2). Prior analyses have not had sufficient power, and randomized trials tend to exclude these patients (either actively or subconsciously).

In this analysis, individual patient data were meticulously combined from landmark, double-blind, placebo- controlled randomized trials to answer key clinical questions: 1) do beta-blockers reduce mortality in patients with moderate or moderately-severe kidney dysfunction, and 2) does therapy lead to reduction in renal function over time or higher rates of adverse events that could limit clinical value? The analysis was conducted by the multinational Beta-blockers in Heart Failure Collaborative Group (BB-meta-HF).

The primary endpoint was all-cause mortality. Beta-blocker efficacy in patients with left ventricular ejection fraction less than 50% was determined according to eGFR at baseline. Results were stratified by heart rhythm since BB-meta-HF previously found a significant interaction comparing sinus rhythm and atrial fibrillation.

A total of 16,740 patients with HFrEF were included from ten trials. The median age was 65 years and 23% were women. During a median follow-up of 1.3 years, renal dysfunction was independently associated with higher mortality, and cause of death was more often due to progressive heart failure in patients with more severe renal impairment.

In 13,861 patients in sinus rhythm, beta-blockers significantly reduced mortality, even in those with moderate or moderately-severe kidney dysfunction. After adjustment, beta-blockers were associated with a 27% and 29% lower risk of death, respectively, compared to placebo. In those with eGFR 30–44 mL/min/1.73m2, the lowest range tested in large placebo-controlled trials, the absolute risk reduction from beta-blockers for all-cause mortality was 4.7%, with only 21 patients requiring treatment for a year to save a life. In patients with renal impairment, beta-blockers did not lead to any deterioration in eGFR, there was no increase in adverse events compared to placebo, and most achieved reasonable doses in these blinded trials.

Dr. Kotecha said: "In patients with HFrEF and sinus rhythm, these drugs work as effectively at an eGFR of 40 as they do at an eGFR of 90. We show conclusively that moderate or moderately-severe kidney dysfunction should not be a barrier to beta-blocker initiation or up titration. Unfortunately, data is lacking on patients with severe kidney disease (eGFR less than 30) and we were unable to make any definitive statements on the efficacy or safety of beta-blockers in this group."

In the 2,879 patients with atrial fibrillation at baseline, there was no significant reduction in mortality associated with beta-blockers in any category of eGFR, but also no harm identified. Dr. Kotecha said: "Patients with HFrEF and atrial fibrillation are another high-risk group and we know treatments are less effective when these conditions are combined. Prevention of atrial fibrillation in HFrEF is always best – using guideline- recommended heart failure therapy at appropriate dosages in all patients can substantially reduce the risk of developing atrial fibrillation."

Worsening renal function of 20% or greater during follow-up was associated with a 28% increase in subsequent death overall, and a 46% increase in patients with moderate or moderately-severe renal impairment. "In our study, worsening renal function did not appear to be caused by beta-blocker therapy and all patients were already on ACE inhibitors. Nonetheless, worsening renal function was linked to poor outcomes and this highlights the importance of preserving kidney function by working with renal specialists," said Dr. Kotecha.

Regarding the implications for clinical practice, Dr. Kotecha said HFrEF patients in sinus rhythm with moderate or moderately-severe renal dysfunction should not be restricted from receiving beta-blockers. "This will save lives," he said. "Aim for good doses and inform patients that in blinded trials there was no difference in withdrawal of therapy due to adverse events compared to placebo."

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