Since the discovery of propranolol, β-blockers (βB) have been prescribed to treat hypertension for more than 40 years. Based on decreased cardiovascular mortality and increase quality of life in hypertension patients, β-blockers have been recommended as first-line therapy by the “Management of Hypertension Guidelines” from Societies of Cardiology worldwide, including China. Administration of βBs is particularly effective in patients with heart failure or coronary heart disease.1 However, a series of meta-analysis on βB effectiveness showed that βBs were less effective in prevention of major cardiovascular composite events (including stroke, myocardial infarction, death) than other antihypertensive medicines.2-4 NICE (National Institute for Health and Clinical Excellence) Guidelines had suggested that beta-blockers should not be a preferred initial treatment for hypertension since 2006.5 Thus, the application of β-blockers in hypertension has been hotly debated among experts worldwide. As the controversy continues, there have been differences between guidelines from Europe and America. The former still considrs βB as the first-line treatment. Whereas, the latter, the eighth report of the Joint National Committee (JNC 8), denied its first-line treatment status due to a decade of controversial studies.6,7 The lack of clarity paints an unclear picture for clinicians. Should βB be the initial treatment of choice for hypertension?

The concerns of βB usage mainly stem from the results of Medical Research Council (MRC), Losartan Intervention for Endpoint (LIFE) reduction in hypertension study and the meta-analysis performed by Lindholm et al.2,8,9 Those studies showed βB treatment results in greater risk of stroke and death compared to other antihypertensive drugs. Lindholm et al. believe that traditional βB treatment increased central systolic and pulse pressure, which is attributable to increased pressure wave reflection from distal reflection sites. And it is remarkable that central blood pressure better predicts cardiovascular events.10 The effect might explain the increased risk for stroke seen in clinical trials. Meanwhile, unfavorable metabolic effects also have a negative influence in long-term βB treatment. However, these evidences do not completely deny β-blockers. Large heterogeneities are demonstrated among β-blockers.11 βBs represent a heterogeneous group of agents possessing several pharmacological properties, including β1/β2 selectivity, intrinsic sympathomimetic activity, lipophilicity, half-life, vasodilation property etc. that differentiate them and this might have a significant effect on clinical end points.11 For example, only three βBs (Bisoprolol, Metoprolol and Carvedilol) have showed prognostic benefit in preventing heart failure. βB are also heterogeneous for the treatment of hypertension. Metoprolol Atherosclerosis Prevention in Hypertension (MAPHY) trial, compared thiazide diuretic therapy against treatment with metoprolol, metoprolol significantly reduced all-cause mortality by 22% and cardiovascular mortality by 26% in a 4.2-year median follow-up.12 In addition, a limited meta-analysis suggests that increased risk was driven by beta-blockers other than atenolol. The risk of stroke for non-atenolol β-blockers compared with other agents did not reach statistical significance in the elderly. Non-atenolol β-blockers are effective in reducing cardiovascular end points for hypertension without compelling indications in the elderly by Kuyper et al.13 Neutel et al. showed that atenolol taken once daily, leaves the patient unprotected in the last 6 hours of a 24-hour period.14 It is possible that this short duration of action of atenolol may have contributed to increased risk of stroke or transient ischemic attack in clinical trials.

Results from recently meta-analysis shows that initial therapy of hypertension with β-blockers is not associated with reduced all-cause mortality but is associated with modest reductions in cardiovascular events compared with placebo or no treatment.15 In spite of not taking age into account, there are actually no trials in blood pressure management stratified by age to support age-related divergent pathological mechanisms.16 The blood pressure lowering treatment trialsists' collaboration meta-analysis has shown the reduction in the risk of total major cardiovascular events was connected with a larger decrease in blood pressure.17 From this standpoint, relatively inexpensive antihypertensive drugs (e.g. diuretics and β-blockers) play an important role in reducing risk of cardiovascular events for patients in low-income developing countries. Moreover, the LIFE study (an only reference cited by JNC8) could not entirely negate the effectiveness of β-blockers. Most patients used diuretics combined with βB at the end of
study. Therefore, it was inappropriate to attribute the negative effects solely to \( \beta_B \). And the results had eventually transformed to comparison between new combination regimens (ARB + Diuretics) and traditional combination regimens (\( \beta_B \) + Diuretics). Interestingly, according to results ofValsartan Antihypertensive Long-term Use Evaluation (VALUE) study, LIFE study as well as previous observational study, heart rate is a predictor of cardiac event in hypertension patients, which implies the importance of \( \beta \)-blockers.\(^{18-20}\) At last, sympathetic activation is an important mechanism of hypertension. \( \beta_B \) can reduce neurotransmitter release and sympathetic activity. Therefore, non-vasodilator \( \beta \)-blockers can be effective in the treatment of hypertension, especially in young hypertension patients with sympathetic activation in theory. As the third generation \( \beta \)-blockers (carvedilol, labetalol, nebivolol), with vasodilating properties mediated by \( \alpha \)-adrenoreceptor blockade or through Nitric Oxide (NO) release, further investigations are required to confirm whether vasodilating properties will actually translate into additional benefits in terms of hard end points.

Considering the results of the studies presented here and currently available clinical evidences, much work remains to be done to provide high-quality decisive data on the role of \( \beta \)-blockers in hypertension therapy. It is inappropriate to discontinue \( \beta_B \) treatment completely. Individuation should be emphasized during the treatment of hypertension.

REFERENCES