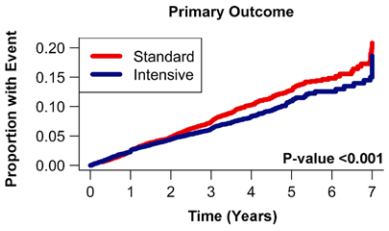
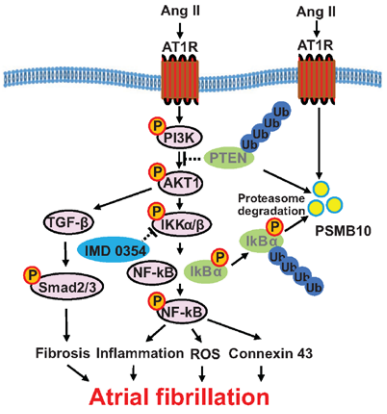
A Pooled Individual Patient Data Analysis of Intensive BP Targets (p 833)



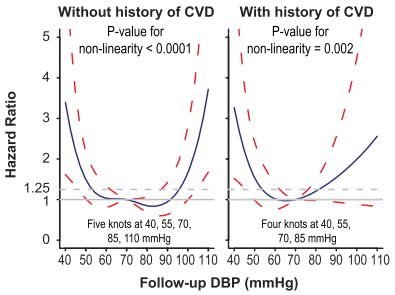
Blood pressure (BP) targets have recently become a subject of significant controversy. The ACCORD trial (Action to Control Cardiovascular Risk in Diabetes) investigated an intensive systolic BP target of <120 mm Hg in a diabetic population. ACCORD did not demonstrate a reduction in major cardiovascular events, although there was significant concern about the trial's power. Later, SPRINT (Systolic Blood Pressure Intervention Trial) demonstrated a significant cardiovascular risk reduction with a <120 mm Hg BP target in nondiabetic patients. These conflicting results have led to uncertainty about optimal BP targets in the general population. Our study, which pooled individual patient data from both trials, investigated whether the ACCORD and SPRINT patients reacted differently to intensive BP targets, and whether the combined population benefited from a target of <120 mm Hg. Our results demonstrated that a <120 mm Hg systolic BP target reduced cardiovascular events (a composite of stroke, myocardial infarction, cardiovascular mortality, and heart failure) in the pooled population. This reduction was independent of diabetes mellitus status, suggesting that the ACCORD diabetic patients reacted similarly to the nondiabetic patients of SPRINT. We also found that the benefits of intensive BP control held regardless of age, sex, race, cardiovascular disease history, and baseline BP. These cardiovascular benefits came at the increased risk of adverse events (ie, syncope events). Our results add to the growing evidence base suggesting that ACCORD's and SPRINT's results are concordant, and that intensive BP control provides cardiovascular benefits for a broader group of patients than described previously.

Immunosubunit PSMB10 Regulates Atrial Fibrillation (p 866)



Atrial fibrillation (AF) is a common arrhythmia associated with increased risk of stroke and death. Inflammation is associated with pathogenesis of AF. The immunoproteasome system plays an important role in inflammatory responses by regulating specific intracellular signaling pathways including NF-κB (nuclear factor-κB). Thus, identifying specific targets in this system is crucial for development of new therapeutic strategies against AF. PSMB10 (proteasome subunit beta-10) is an immunoproteasome subunit that has trypsin-like activity leading to protein degradation. In this study, we discovered that serum PSMB10 concentration and trypsin-like activity are increased in patients with AF. Moreover, angiotensin II (Ang II)–induced AF, atrial fibrosis, reactive oxygen species production and inflammation are significantly attenuated in PSMB10-deficient mice and are aggravated by PSMB10 overexpression. Interestingly, inhibition of the NF-κB pathway using the agent IMD 0354 blocks Ang II–induced inflammation and AF. Mechanistically, we defined a pathway involving PTEN (phosphatase and tensin homolog deleted on chromosome ten) degradation, AKT1 activation, and TGF-β (transforming growth factor-β)-Samd2/3 and IKKβ (inhibitor of nuclear factor kappa-B kinase beta)–NF-κB signaling, which leads to cardiac fibrosis, inflammation, and AF. Thus, we have discovered a previously unknown role of the immunoproteasome in AF and have defined downstream signals that are potential therapeutic targets to prevent its untoward clinical effects.

Intensive Blood Pressure Lowering in the SPRINT Trial: How Low Is Too Low? (p 840)



Systolic and diastolic blood pressure thresholds, below which cardiovascular events increase, are widely debated. Using data from SPRINT (Systolic Blood Pressure Intervention Trial), we evaluated the relationship between systolic and diastolic pressure on cardiovascular events among 1519 participants with and 7574 without prior cardiovascular disease randomized to intensive (<120 mm Hg) versus standard (<140 mm Hg) systolic pressure. After a mean of 3.1 follow-up years, a J-shaped relationship with diastolic pressure was observed in both intensive and standard groups in patients with or without cardiovascular disease. When diastolic pressure fell <55 mm Hg, the hazards were at least 25% higher relative to 70 mm Hg (P=0.29). The hazard ratios (95% confidence intervals) of diastolic pressure <55 mm Hg versus 55 to 90 mm Hg were 1.68 (1.16–2.43), P=0.006 and 1.52 (0.99–2.34), P=0.06 in patients without and with prior cardiovascular disease, respectively. Although the observed J-shaped relationship might be because of reverse causality, we advise that clinicians should use caution when trying to achieve SPRINT intensive targets, especially among those at risk including men, older patients, those with cardiovascular disease, and those with low baseline diastolic pressure. These data also suggest that there is a group of patients with cardiovascular disease, perhaps those with effective myocardial reperfusion, in whom diastolic blood pressure lowering does not produce a greater risk than people without cardiovascular disease when diastolic blood pressure is measured as <60 mm Hg using unattended, fully automated blood pressure devices with proper measurement technique.

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