basal podocyte glycocalyx, and only a bit more is known about factors influencing that of the endothelial glycocalyx. Our present concept of the GBM may also be much too static, and perhaps cells anchored to the GBM (i.e., endothelial cells, mesangial cells, and podocytes) can acutely influence the arrangement of the molecular components of the GBM and thereby its size-selective properties. Inside-out and outside-in cell-matrix signaling through integrins can influence the podocyte cytoskeleton, which in turn affects the GFB. Similar considerations may apply to the distinct glycocalyx layers. For example, both the glycocalyx of the capillary luminal endothelia and the free urinary space podocyte surface contain N-acetyl glucosamines, whereas the glycocalyx at the base of podocyte foot processes contains nonreducing N-acetyl-D-galactosamine.[9] Future experiments to address the respective contribution of the endothelial and podocyte glycocalyx to glomerular permselectivity will not only have to employ cell-specific (endothelial vs. podocyte) modulation of genes involved in the generation of glycocalyx, but should also focus on genes encoding for the specific enzymes involved in the generation of either N-acetyl glucosamines or N-acetyl-D-galactosamine. Similar considerations apply to disease-associated changes in glycocalyx, such as those observed in diabetic nephropathy, as these may occur in 1 or both layers. Certainly future research will be required to determine whether and how cell-cell and cell-matrix signaling pathways may influence the permselectivity of the basal podocyte glycocalyx and of the GBM. Elucidation of these signaling pathways as potentially "druggable" targets may yet prove to be a worthwhile endeavor for future treatment of proteinuric kidney diseases.

DISCLOSURE

All the authors declared no competing interests.

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hypertension

How low can you go? Achieved blood pressure and cardiovascular outcomes

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The benefits of controlling blood pressure to levels < 140/90 mm Hg are well established, but the risks and benefits of further reductions in blood pressure are less clear. A recent observational study using pooled data from 2 large randomized trials of renin-angiotensin system blockers suggested no added benefit and some increased risk of cardiovascular events with achieved blood pressures < 120 mm Hg systolic or 70 mm Hg diastolic. Caveats of observational studies notwithstanding, these results add to the ongoing controversy over the optimal blood pressure target for high-risk individuals.

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Randomized clinical trials across diverse patient populations have established the benefits of lowering blood pressure to <140/90 mm Hg. Whether further reductions in blood pressure provide additional benefit or cause potential harm among individuals at high risk for cardiovascular disease remains less clear. In 2015, the Systolic Blood Pressure Intervention Trial (SPRINT) investigators reported significant reductions in a composite cardiovascular endpoint and all-cause mortality in older adults without diabetes but with high cardiovascular risk who were randomized to a target systolic blood pressure <120 mm Hg, compared with those randomized to a target <140 mm Hg.[1] Together with the results of recent meta-analyses of clinical trials comparing intensive versus standard blood pressure control,[2,3] the SPRINT results have challenged the field to reconsider current blood pressure targets for individuals at high cardiovascular risk.

As with many interventions, intensive blood pressure control comes with a price. The increased pill burden may be associated with poor adherence or with drug-drug interactions, whereas lower blood pressure itself may be associated with an increased incidence of symptomatic hypotension and other symptoms. Some previous observational studies have also suggested a J-curve relationship between blood pressure and clinical outcomes including cardiovascular events and all-cause mortality, although other observational studies have failed to observe this effect.[3–5] The threshold blood pressure for this effect has also varied across studies, leading some experts to speculate that blood pressure below these thresholds may have adverse consequences in some patient populations and for some clinical outcomes, but not for others.[3]

In a recent issue of the *Lancet*, Böhm and colleagues reported the results of a pooled observational analysis from 2 large randomized controlled trials of renin-angiotensin inhibitors in participants with established atherosclerotic cardiovascular disease or diabetes with end-organ damage.[6] The ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and the Telmisartan Randomised AssessmeNt Study in ACE iNtolerant participants with cardiovascular Disease (TRANSCEND) were designed to evaluate the impact of renin-angiotensin blockade on cardiovascular outcomes. The 2 trials enrolled in parallel using the same entry criteria, with angiotensin-converting enzyme–intolerant participants enrolled in TRANSCEND and all other eligible participants enrolled in ONTARGET. Eligible participants were 55 years of age or older and had established cardiovascular disease (coronary artery disease, peripheral artery disease, or cerebrovascular disease) or diabetes with end-organ damage. Relevant exclusion criteria included congestive heart failure or valvular disease, uncontrolled hypertension (blood pressure >160/100 mm Hg), significant renal artery stenosis, and serum creatinine >3 mg/dl. Because of the inclusion of a placebo arm, otherwise eligible participants with significant proteinuria were excluded from TRANSCEND. At enrollment, estimated glomerular filtration rate was <60 ml/min/1.73 m^2 in 24% of ONTARGET participants and in 28% of TRANSCEND participants, similar to the representation of patients with chronic kidney disease in SPRINT.[1] The primary results of ONTARGET and TRANSCEND supported the benefits of renin-angiotensin blockade and the equivalency of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for the reduction of cardiovascular events. ONTARGET also demonstrated an increased risk of adverse outcomes with combined therapy.

The current analysis focused on the association between baseline and achieved blood pressure and cardiovascular events during follow-up in ONTARGET and TRANSCEND.[6] It should be emphasized that these 2 trials did not target specific blood pressure levels. The pooled analysis included 30,937 (98%) participants from the 2 trials, excluding those with missing data for blood pressure or key covariates. Mean on-study blood pressure (average of 8 measurements) was categorized into 4 strata for systolic blood pressure, ranging from <120 mm Hg to >160 mm Hg, and 5 strata for diastolic blood pressure, ranging from <70 mm Hg to >90 mm Hg. Mean achieved blood pressures between 120 and 139 mm Hg systolic and 70 and 79 mm Hg diastolic were associated with the lowest risk of the primary composite outcome of cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure, and with the lowest all-cause mortality. Achieved blood pressures ≥160 mm Hg systolic or ≥90 mm Hg diastolic were associated with the greatest risk of the primary outcome; however, both the highest and lowest strata of achieved