Hot Topics in Nephrology: A Debate

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Editorial Perspective

The Low Down on Down Low

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Perhaps it has to do with the chronic kidney disease (CKD) patients referred to me, but I do not recall ever managing to get anyone's blood pressure down to <130/80 mm Hg irrespective of what treatments I prescribed. Or perhaps I just do not have the medical talent for the job. Two experts, Raj Agarwal and Bob Toto, square off and debate the issue. Neither of them mentions the difficulties in getting the pressure down that I encountered and how many preparations it may take.

Agarwal rests his case solely on randomized prospective trials that have tested the issue. He found three such studies. Sigmund Freud might term this an 'anal approach'. In the African American Study of Kidney Disease (AASK) study, patients were assigned to two mean blood pressure goals: 102–107 mm Hg or ≤92 mm Hg. The lower blood pressure group reached the goal (128/78 mm Hg), compared to 141/85 mm Hg in the higher pressure group. The lower blood pressure did not protect from the progression of renal disease. The Modification of Diet in Renal Disease (MDRD) Study also tangentially addressed the blood pressure question. In that study, the low blood pressure group also did not appear to benefit. The Ramipril Efficacy in Nephropathy (REIN-2) Study also could not document an additional benefit from blood pressure lowering in terms of renal disease progression. Nor was protection from cardiovascular events documented in any of these studies, although they were not designed with that purpose in mind. Agarwal underscores the fact that in dialysis patients, in whom disease progression has already run its course, we have no data on whether or not lowering blood pressure to <130/80 mm Hg is helpful.

Toto rests his compelling arguments on epidemiological and observational studies and meta-analyses as well as arguments about risk within the 120–139 mm Hg range that was also addressed by the joint national committee. His strategy is strictly 'Id' by Freudian standards. Toto points out that in AASK, patients with heavy proteinuria benefited from lower blood pressures, compared to those with higher pressures. Toto draws into the argument several other studies on diabetic patients, including the Irbesartan Diabetic Nephropathy Trial (IDNT) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study. In IDNT, those patients who achieved systolic blood pressures of 120 mm Hg had a better outcome. In ACCORD, lowering systolic blood pressure to 120 mm Hg accrued no advantage. However, the lower blood pressure group in that trial had fewer strokes – so much for secondary analyses!

Agarwal argues for tailored therapy with the cliché that, 'one size does not fit all'. An extension of that idea is that our therapy could be doing some people in. Messerli et al. [1] have explored this issue. They performed a secondary analysis from the International Verapamil-Trandolapril Study (INVEST). The drugs need not concern us here. They found that the relationship between blood pressure and all-cause death, and myocardial infarction was J-shaped, particularly for diastolic pressure, with a nadir at 119/84 mm Hg. The myocardial infarction-stroke ratio remained constant over a wide blood pressure range, but at a lower diastolic blood pressure, there were substantially more myocardial infarctions than strokes. Particularly, low diastolic pressure was associated with a

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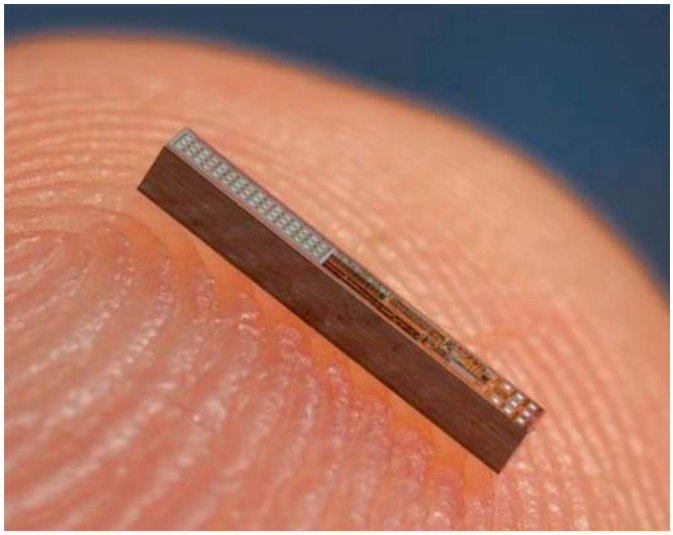

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Fig. 1. HYPER-IMS, a tiny implantable wireless pressure monitor, shown here on a fingertip.

relatively lower risk for the primary outcome in patients with revascularization than in those without revascularization. Those attending the American Society of Nephrology annual meeting will recall the presentation of the not-yet-published prevention of microalbuminuria in type 2 diabetes (ROADMAP) trial [com. by Haller et al., 'late breaking session', ASN 2009]. The ROADMAP study tested whether or not olmesartan prevents or delays the time-to-first occurrence of microalbuminuria. As a matter of fact, it did. Unfortunately, a higher cardiovascular mortality was observed in patients with pre-existing coronary heart disease. Contrary to what my cardiologist son tells me, 'we cannot cath them all'. The ROADMAP investigators concluded that pre-existing coronary heart disease (not unheard of in CKD patients) could be a particular risk with the advent of hypotensive events.

Both combatants call for more randomized controlled trials of this issue. I demur. I believe throwing further money at this issue is a futile endeavor. Besides, those who live from trials (I exclude lawyers for a change), always call for more trials. In my view, we do not have the technical expertise to test the issue. We have improved somewhat over the techniques introduced by Frederick Mohamed, the Pakistani immigrant to Britain, who first measured blood pressure in a consistent fashion. However, we are no better than Scipione Riva-Rocci, who measured blood pressure largely as we do 100 years ago. Why is it that I can measure blood pressure beat-by-beat in any (>20 g body weight) mouse for the life of the animal and cannot do that with my 100 kg patients? I teach my patients to measure their blood pressures at home, as Agarwal espouses (he is correct of course), and trust them to bring me the data. I do not have to trust my mice; I know what they are doing. As an alternative, I can hang Riva-Rocci's device around the patients, now and then, and record the information over the course of 24 h (once or twice at best).

Blood pressure variability (rather than a systolic or diastolic value per se), has been suggested as important for cardiovascular endpoints [2, 3]. A PubMed search on 'blood pressure variability' produced 8,000 'hits'. The same search for animal models yielded 28 citations. In reviewing studies that would have any relevance to human investigations cited here, I came up with none (zero). The question immediately arises, 'why not?'

The situation will improve. Novel systems are being developed to measure in humans what we now can do routinely in mice. Novel sensors, either within or around blood vessels are being developed. A currently utilized sensor, which has a diameter of about 1 mm, including the casing, measures the patient's blood pressure 30 times per second (fig. 1). The sensor is connected via a flexible micro-cable to a transponder unit, which is likewise implanted under the skin. Fear not; this contraption will not bother your defibrillator. The unit digitizes and encodes the data coming from the micro-sensor and transmits them to an external reading device that patients can wear like a cell phone on their belt. From there, the readings can be forwarded to a monitoring station and analyzed by the physician investigator. The micro-implants are supplied with electricity wirelessly via coils. The system is currently being studied in large animals (Dr. Hoc Khiem Trieu, personal communications). Telemetric, beat-by-beat long-term blood pressure monitoring in man is coming. Such approaches, coupled with animal investigations, should answer the questions of blood pressure variability and its mechanisms regarding cardiovascular risk in the near future. Until we have it, I would suggest not throwing any more money away on this issue.

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