Inter-arm differences in blood pressure: A brief summary

Cardiovascular disease is the primary cause of death globally and elevated blood pressure (hypertension) is a major contributing, and potentially avoidable, risk factor. International hypertension guidelines encourage assessment of risk markers associated with target organ damage (TOD) and utilisation of cardiovascular risk scores to identify individuals with elevated cardiovascular risk. Preventative treatment, such as initiation of anti-hypertensive medication, can thus be recommended to individuals who can most benefit by reducing their risks of cardiovascular events (Williams et al, 2018; NICE, 2019).

Although useful in identifying individuals at elevated cardiovascular risk, many markers of TOD require specialised equipment and skills. Some markers of TOD (e.g. pulse pressure in the elderly or renal function) are readily measured, whereas others, such as carotid ultrasound, pulse-wave velocity or echocardiography, require specialised equipment and trained personnel which are not practical or readily available, or likely to become so, in primary care. Recognition of novel cardiovascular risk markers that can be easily assessed in primary care to refine risk prediction and stratify treatment priorities is, therefore, desirable.

A difference in systolic blood pressure between arms (inter-arm difference; IAD) is one risk marker that is easily measured clinically with no additional equipment and appears acceptable to patients. Different measurements between arms can cause errors in blood pressure interpretation and management when not recognised, thus exposing individuals to avoidable risk through sub-optimal blood pressure control. An IAD is commonly encountered, with systolic differences of ≥10 mmHg prevalent in 11% of hypertensive subjects, 7% of people with diabetes and 4% of the general population (Clark et al, 2016).

National and international guidelines have long advised measuring blood pressure in both arms during initial hypertension assessment to standardise future blood pressure measurements and assess impacts of treatment on the higher-reading arm. The guidelines do not specify in detail how or why blood pressure in both arms should be measured. The 2018 European Society of Cardiology and European Society of Hypertension (ESC/ESH) guidelines, and forthcoming NICE guidelines, now acknowledge the association of a systolic IAD ≥15 mmHg with increased risk of cardiovascular events (Williams et al, 2018; NICE, 2019).

In fact, cross-sectional studies have associated a smaller systolic IAD of ≥10 mmHg with diabetic nephropathy (Okada et al, 2013) and a systolic IAD of ≥15 mmHg with retinopathy (Clark et al, 2014). Whilst competing explanations for the aetiology of an IAD exist, the association of IAD with arterial stiffness and/or increased pulse-wave velocity suggests arterial stiffening as a probable cause for the observed IAD and its sequelae (Clark and Aboyans, 2015). Prospectively, study-level meta-analyses have associated a systolic IAD ≥15 mmHg (Clark et al, 2012) and, more recently, ≥10 mmHg with cardiovascular and all-cause mortality (Cao et al, 2015).

Historically, guidance to measure both arms when assessing hypertension may not have been followed by the majority of clinicians. Uptake of bilateral blood pressure measurement may now be increasing (Mejzner et al, 2017). However, this is hampered both by a lack of clarity for practitioners regarding the importance of detecting an IAD and by a lack of knowledge as to how detection of an IAD should influence management.

Differences in systolic blood pressure between arms have been observed for over a century. Prevalence differs based on the population under investigation and the measurement method. Blood pressure can be measured sequentially in both arms by clinicians in typical primary and secondary care settings, with no additional equipment needed. Simultaneous measurement

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using specialised automated oscillometric devices results in lower observed prevalence of IAD than the sequential method and is regarded as the "gold standard" method for research (Clark et al, 2016). Observed IADs with sequential measurement methods can, in part, be accounted for by a white coat effect (Schwartz et al, 2017); however, the weight of evidence to associate sequentially measured IAD with mortality suggests that these observations cannot be entirely dismissed as artefacts of measurement (Kleefstra et al, 2007).

To provide robust evidence for clinicians measuring blood pressure, a prospective individual participant data (IPD) meta-analysis was recently completed. Known as INTERPRESS-IPD (the INTER-arm blood PRESSure difference-IPD Collaboration), it combines data from 24 cohorts totalling 57 000 participants. Pooled data originating from Europe, East Asia, the USA and sub-Saharan Africa (Clark et al, 2018) indicated that IAD remains a significant predictor of cardiovascular and all-cause mortality, after adjustment in a validated multivariable model incorporating age, sex, ethnicity, smoking status, systolic blood pressure, and diagnoses of hypertension and/or diabetes. A new lower systolic IAD cut-off of ≥5 mmHg was observed as a threshold for increased all-cause mortality (hazard ratio, 1.07 [95% confidence interval, 1.01–1.14]), and rising hazards were associated with greater magnitudes of IAD (Clark et al, 2018). Of relevance to clinicians, the IADs in the study were predominantly obtained by sequential measurement, reflecting everyday clinical practice. The Primary Care Research Group at the University of Exeter Medical School and INTERPRESS colleagues demonstrated that systolic IADs also predict additional risk for cardiovascular events after adjustment for current cardiovascular risk scores, with every 1-mmHg increment in systolic IAD representing a 1–2% increase in 10-year risk using Framingham, ASCVD and QRISK2 scores.

Further work is needed, including medical imaging, to confirm the precise underlying mechanisms of observed IADs and their relationship to cardiovascular risk. At present, there are no recommendations for managing individuals on the basis of their IAD. Our findings suggest that estimates of cardiovascular risk could be adjusted, according to observed IAD, to discuss blood-pressure-lowering and/or lipid-lowering treatment when individuals cross risk thresholds set out by current guidelines (Clark and McDonagh, 2019). We have found that this approach is feasible in the primary care setting (McDonagh et al, 2019), although no outcome studies for interventions based on assessment of IAD yet exist. With this proviso in mind, we believe that there is sufficient evidence to at least take IAD into account when assessing and discussing cardiovascular risk with our patients. ■

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