Only people with increased plasma concentrations of natriuretic peptides should be included in outcome trials of diabetes, cardiovascular and kidney disease; implications for clinical practice

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Pabon et al report that the PARAGON-HF trial, comparing the effects of sacubitril-valsartan with valsartan on hospitalisations for heart failure and cardiovascular death, would have been 'positive' if it had only included patients with an elevated plasma concentration of amino-terminal pro-B-type natriuretic peptide (NT-proBNP). They propose that all future trials of patients with a preserved left ventricular ejection fraction (LVEF) and heart failure (HFpEF) should have such a requirement (1). This is an excellent suggestion; an elevated plasma NT-proBNP provides objective evidence of a high likelihood of both cardiac dysfunction and congestion and, at least in the setting of chronic disease, is a strong predictor of prognosis (2). But why limit this proposal to trials of HFpEF? Why not all trials where the primary objective is to reduce cardiovascular morbidity and mortality, including trials in hypertension, diabetes, ischaemic heart disease, or chronic kidney disease. This might apply especially when patients are not otherwise known to have cardiac dysfunction. In each of these contexts, and more, NT-proBNP has proved to be one of the strongest predictors of outcome (2-7). Patients with any of the above conditions who have a normal NT-proBNP have an excellent prognosis. NT-proBNP is highly stable in-vitro, making sample collection easy for trials and in clinical practice. The cost per test should be low, and often is.

Clinical outcome trials for conditions such hypertension, diabetes and chronic kidney disease are large because event rates are low and the impact of treatment modest. Patients with these conditions who have a normal plasma NT-proBNP will have few events in the following 5 years and little to get from participating in a clinical trial other than side-effects, which could be serious. Restricting enrolment to patients with an elevated NT-proBNP would reduce trial size substantially and avoid exposing patients to unnecessary risk.

However, perhaps an increased plasma concentration of natriuretic peptides should constitute evidence that the patient already has heart failure (2). The diagnosis of heart failure is usually missed by those who are not actively looking for it (2). Its diagnosis is seldom easy, particularly at an early stage when heart failure may be most responsive to treatments to prevent progression. The fundamental problem is that the current diagnostic criteria for heart failure requires symptoms or signs but patients and clinicians have very different opinions on what severity of symptoms and signs should be considered abnormal (8, 9). Everyone gets breathless if they exert themselves enough. Reduced exercise capacity will often be due to obesity, being unfit or having lung disease, but many such patients will also have cardiac dysfunction. Many people, and their physicians, may think that worsening exertional breathlessness is just due to ageing. Patients learn to avoid exertion to prevent breathlessness. Consequently, and unfortunately, the diagnosis of heart failure is usually delayed until symptoms are so severe that the patient needs to be hospitalised, with a mortality in the ensuing year exceeding 20% (10). Indeed, whether a diagnosis of heart failure is ever made will depend on the speciality of the doctor looking after them (11).

Relying on symptoms and signs for a diagnosis is currently a key impediment to good care. NT-proBNP identifies people at high risk of having cardiac dysfunction, provides early warning of increased cardiac wall stress and/or congestion and indicates a higher risk of events. Critics might point out that an elevated NT-proBNP may reflect renal rather than cardiac dysfunction. However, congestion is a cardio-renal problem (2). For those who need confirmation that the heart is indeed beginning to fail, an enlarged left atrium is the most sensitive measure (12). A normal atrial volume and NT-proBNP in the presence of ventricular disease indicates a compensated state (lack of congestion) and a good prognosis

(2). The development of congestion indicates increasing risk and the need to intensify management to prevent or reverse progression (2).

Trials of heart failure with a reduced LVEF (HFrEF) have had more successes than trials of HFpEF. Is this because a reduced LVEF is a surrogate for a raised NT-proBNP? Could NT-proBNP, or the congestion it reflects, be the true pathophysiological target for most of the effective treatments for HFrEF? We should be cautious; some treatments, such as beta-blockers, may target myocardial dysfunction rather than congestion. Also, patients with a grossly elevated NT-proBNP may fail to respond to some interventions (13) (14, 15); the disease may have passed the point of no return, beyond which the treatment being considered is ineffective. Patients need to be sick enough to benefit from an intervention but not so sick that they are no longer able to respond. There is a 'sweet spot' for every therapeutic intervention, although it may be very different for an ACE inhibitor compared to a left ventricular assist device. NT-proBNP can provide a "therapeutic window" to exclude patients too well to benefit from further treatment and too sick to respond to it (13) (14, 15).

The prognosis of heart failure depends more on the severity of congestion than on the ventricular phenotype. For a given plasma concentration of NT-proBNP, patients with an LVEF of 30%, 40%, 50% and 60% have a similar prognosis (2). An elevated NT-proBNP not only predicts an increased risk of developing heart failure or dying but also an increased risk of myocardial infarction, stroke and arrhythmias (2). When NT-proBNP is increased, it is a cry for help; the patient has a serious problem, which deserves investigation, diagnosis and management, or inclusion in a clinical trial to find a better treatment!

What constitutes a normal NT-proBNP needs to be carefully considered (2). It will usually not be 125ng/L. It should be much lower for a patient aged <60 years (perhaps <50ng/L for a man and <75ng/L for a woman). On average, NT-proBNP increases with age, but this may reflect the development of occult disease, declining cardiac diastolic performance and renal dysfunction. Correcting NT-proBNP for age may just be a method for rationing (16), although practically necessary because otherwise health services might not be able cope. Some will contend that there is an obese phenotype of HFpEF with lower plasma concentrations of NTproBNP that might be overlooked. However, NT-proBNP is rarely truly normal in obese patients with heart failure and, when it is, event rates are low suggesting that the symptoms might often be due to obesity itself (2). Atrial fibrillation and renal dysfunction will cause NT-proBNP to increase but both are associated with a poor prognosis when NT-proBNP is elevated and often require treatments that are rather like those mandated for heart failure, such as beta-blockers, mineralocorticoid antagonists or sodium glucose co-transporter inhibitors.

The rising costs of healthcare are an enormous global challenge. Targeting effective interventions at patients with moderate to high-risk, whilst deferring treatment and monitoring those at low risk for events, provides an opportunity for population-based, precision-medicine. In clinical practice, most patients with hypertension, diabetes or coronary artery disease will have an NT-proBNP <75 ng/L. Many of these patients will need treatments, such as statins, aimed at reducing the development of atherosclerosis. However, other treatments for cardiovascular disease and diabetes might be deferred when NT-proBNP is not elevated. Instead, NTproBNP could be monitored periodically (every few years depending on the level of risk) with management restricted to life-style advice (for instance, reduced salt intake for hypertension) unless and until NT-proBNP becomes elevated. This

precision-medicine approach could have enormous cost-savings for health services and for patients. We should also consider the planet. Reducing medical consumption could reduce pollution from the metabolites of the medicines we consume that pass into our rivers and oceans. How many of our patients would love to stop their medicines, if they only knew that it was safe to do so?

Legend to Figure

Proposal for selection of patients for enrolment in clinical trials and for precision-medicine in clinical practice.

T2DM - type-2 diabetes mellitus; CAD = coronary artery disease; CKD = chronic kidney disease; AF* = atrial fibrillation – different threshold values for NT-proBNP will apply – possibly three-fold the values shown in the diagram; ♀ = women; ♂ = men; M/M = morbidity and mortality. Annual risk based on references 2 and 3.

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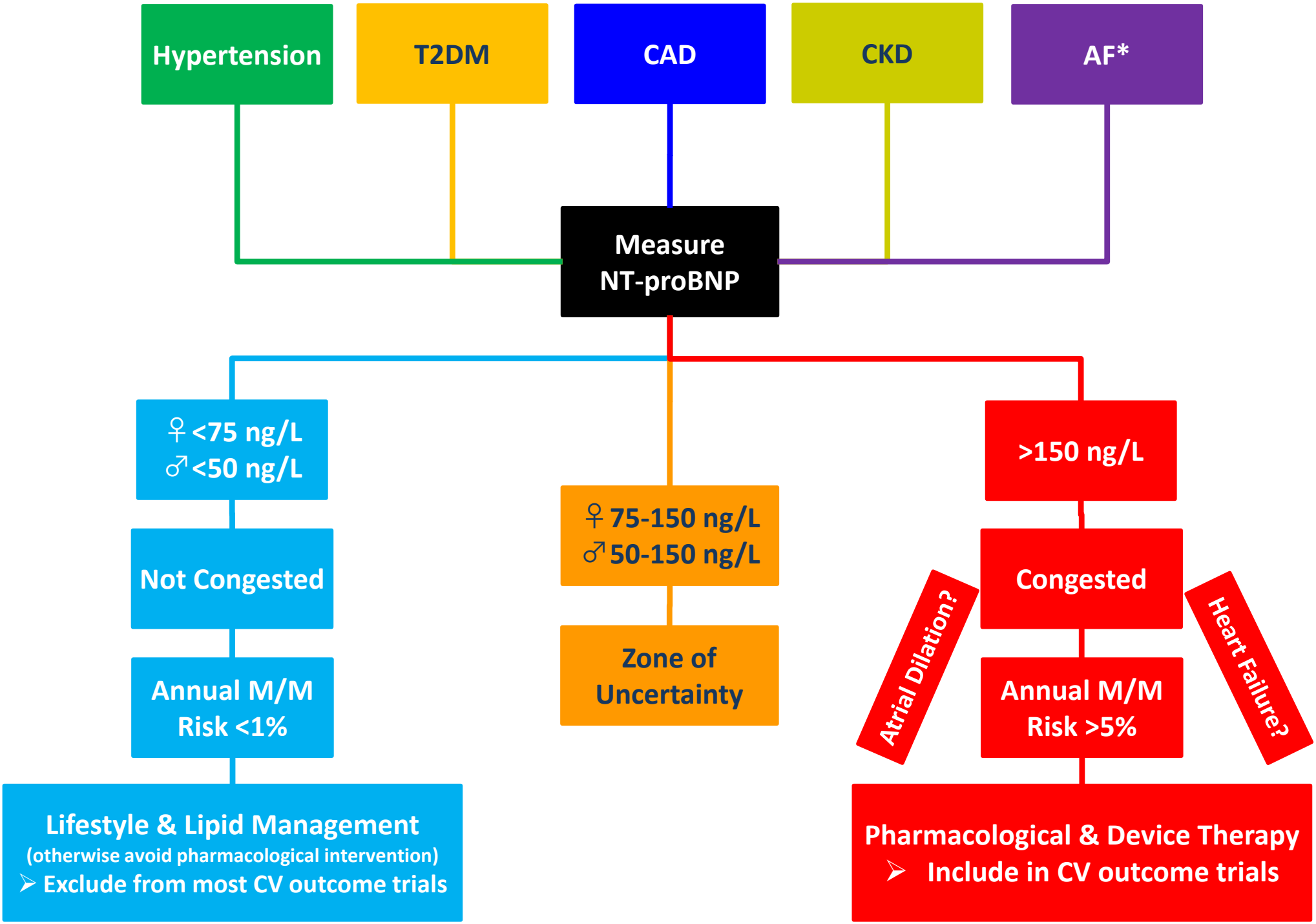
Hypertension
T2DM
CAD
CKD
AF*
Measure NT-proBNP
♀ <75 ng/L
♂ <50 ng/L
Not Congested
Annual M/M Risk <1%
Lifestyle & Lipid Management
(otherwise avoid pharmacological intervention)
➢ Exclude from most CV outcome trials
♀ 75-150 ng/L
♂ 50-150 ng/L
Zone of Uncertainty
>150 ng/L
Congested
Atrial Dilation?
Heart Failure?
Annual M/M Risk >5%
Pharmacological & Device Therapy
➢ Include in CV outcome trials