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EDITORIAL

Risk of knowing too much: the tricky case of estimated glomerular filtration rate and treatment decisions in heart failure

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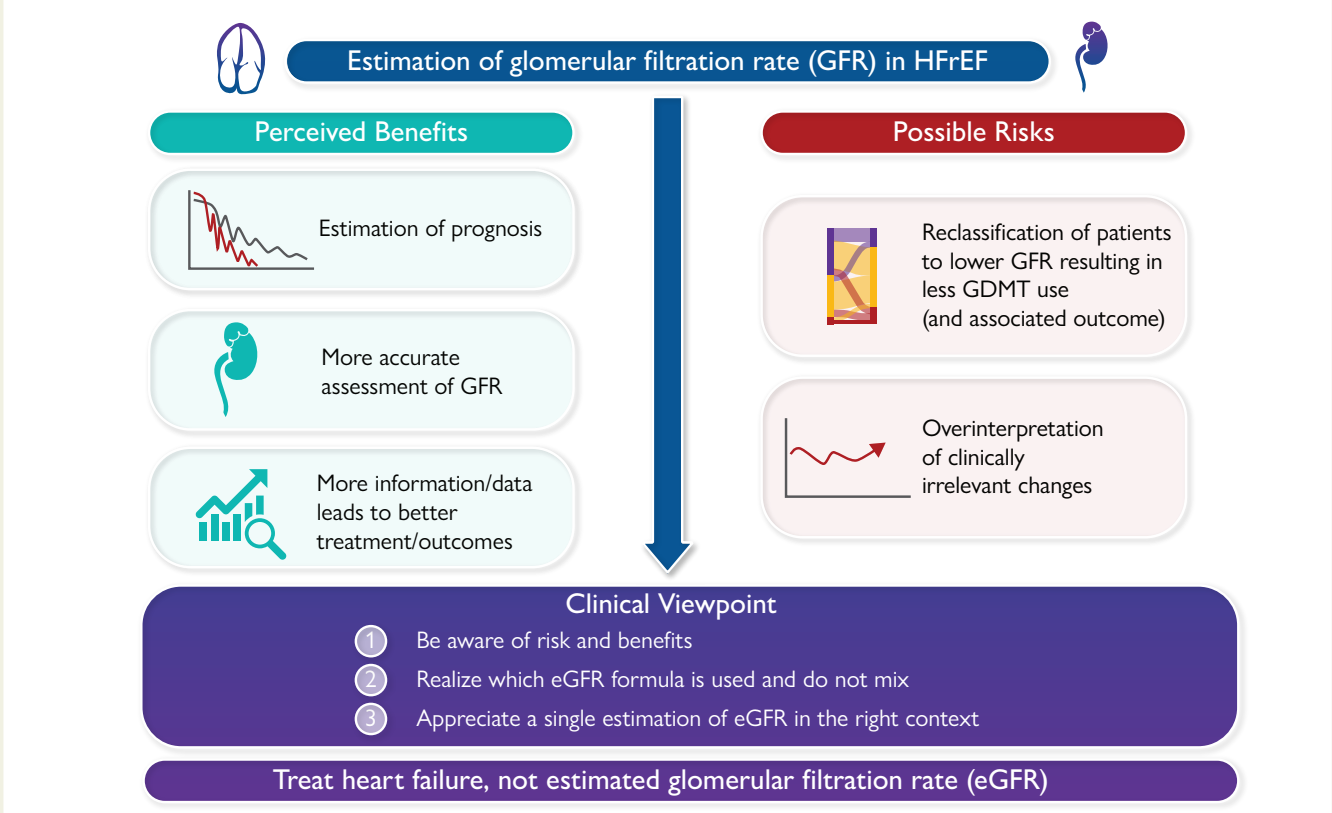
This editorial refers to 'Importance of cystatin C in estimating glomerular filtration rate: the PARADIGM-HF trial', by P. Tolomeo *et al.*, https://doi.org/10.1093/eurheartj/ehad210.

Graphical Abstract



Central illustration.

For each diagnostic test, a clinician should consider the incremental information and potential effect on treatment decisions that the additional information will provide. This information should be weighed against possible unwanted effects or risks of the procedure or diagnostic test.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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For (relatively) invasive assessment such as biopsies, angiography, or tests that require radiation, radioactive substances, or contrast, it is clear that there is a certain inherent risk to these procedures that needs to be taken into account in relation to the expected benefit in gathering this often vital information. Both risks and benefits are clear.

In the case of simple lab tests that are done—by default—in millions and millions of patients worldwide, it may be more difficult to see the balance between risk and benefit. For patients with heart failure with reduced ejection fraction (HFrEF), this is no exception.

In patients with HFrEF, because of changes in renal haemodynamics and intrarenal physiology, renal function as indicated by glomerular filtration rate (GFR) is often strongly impaired.[1] When present, reduced GFR is one of the most important predictors of poor clinical outcome in these patients.[2] GFR can be measured by clearance techniques using tracers such as inulin or iothalamate, but in practice this is only used for scientific purposes.[3] Typically, GFR is estimated by using one of many validated formulas (such as the CKD-EPI formula), which use variables easy obtainable in all patients, such as gender and serum creatinine.[4] This gives a reasonably accurate estimate of GFR, even in patients with HFrEF, although these estimates do tend to perform less well at the extremes of GFR.[5] Because this CKD-EPI formula relies mostly on serum creatinine as the clearance marker, and serum creatinine levels can be influenced by factors other than glomerular filtration, the CKD-EPI formula has been further developed to also include cystatin C.[4] This CKD-EPI formula which uses both creatinine and cystatin C was shown to be more accurate in large cohorts of patients.

Since there is a strong relationship between lower eGFR and outcome in patients with HFrEF and treatment decisions are often influenced by eGFR, in this issue of the *European Heart Journal*, Tolomeo and colleagues evaluated the difference between eGFR as estimated by CKD-EPI based on creatinine alone and CKD-EPI based on creatinine and cystatin C.[6] In a retrospective analysis of a subgroup of patients included in the PARADIGM-HF study, they found that on a population level, both estimates of GFR were similar. However, by using the creatinine–cystatin C CKD-EPI formula, eGFR was estimated to be >10 mL/min/1.73 m^2 lower in almost 20% of patients. The opposite was true for just over 10% of patients. If GFR was estimated to be lower by using the creatinine–cystatin C CKD-EPI formula, prognosis was worse. The authors also showed that with more severe heart failure phenotypes, the difference between creatinine only and creatinine–cystatin C estimates of GFR was larger.

It is incredible to notice that two formulas that essentially estimate the same parameter (GFR) show overall similar levels of GFR on a population level, but for individual patients the estimation of GFR may be entirely different, and with it the associated outcome. There are some important points to consider.

Why do we want to know GFR in patients with HFrEF? Do we know the risks and benefits of using this specific diagnostic tool?

As a prognostic tool, eGFR is almost unrivalled in patients with heart failure. The lower the eGFR, the higher the risk of cardiovascular events. However, there are many other prognostic markers in patients with HFrEF, and knowing the prognosis of an individual patient does not necessarily change or improve treatment. Another reason for wanting to know the eGFR in patients with HFrEF may be because of dosing of renally cleared drugs, such as certain direct non-vitamin K antagonists, or renally cleared non-heart failure therapies.[7] Using eGFR may also be helpful in determining the loop diuretic dose since lower GFR necessitates higher dosages to achieve adequate diuretic effects.[8] Finally, and probably most importantly, eGFR is often used to determine whether guideline-directed medical therapy (GDMT) may be either initiated or uptitrated.[9] Typically, all four class I recommended GDMT drug classes have been shown to improve clinical outcome to an eGFR as low as 30 mL/min/1.73 m^2.[2,10] For SGLT2 inhibitors (and beta-blockers) this evidence is available up to 20 mL/min/1.73 m^2. Below that, evidence is scarce, and clinicians (and guidelines) rely on expert opinion and consensus, but also a degree of common sense. It is unrealistic to think of eGFR as an all or nothing entity. If a drug works in patients with an eGFR of 35 mL/min/1.73 m^2, it is unlikely not to work if the eGFR is 25 mL/min/1.73 m^2.

This is where the work from Tolomeo and colleagues comes in and makes things now even more complicated. Their findings suggest that if this higher eGFR was estimated by the creatinine-only-based CKD-EPI formula, a lower eGFR could have been estimated if cystatin C would also have been taken into account.[6] Now realize that the patient did not change. The kidneys still function the same. The patient was also actually randomized in the trial and received study medication. However, if the threshold of 30 mL/min/1.73 m^2 is taken as a hard boundary for starting or continuing GDMT, in this case sacubitril/valsartan, this particular patient would never be exposed to this (or other) life-saving drug if the creatinine and cystatin C CKD-EPI formula had been used.

We have to stop fooling ourselves. Yes, there may be a critically low eGFR threshold where the benefit of these drugs may be insufficient to overcome the risks. However, it certainly is not at 30 mL/min/1.73 m^2, and it is definitely not the same in every patient with HFrEF. The choice to start, continue, and up-titrate GDMT which impact GFR (renin–angiotensin–aldosterone system inhibitors, neprilysin inhibitors, and SGLT2 inhibitors) should be tailored to the individual situation, but the starting point should be to start or continue these life-saving drugs, even if eGFR is (very) low.

It is important to realize that the current results from PARADIGM-HF do not give any information on the accuracy of either formula in estimating true GFR in the population studied. Both formulas were compared with each other, not with the gold standard of clearance techniques. It is even possible that the creatinine–cystatin C formula is a better risk predictor, but may be a less accurate GFR estimate in patients with HFrEF. That further complicates translation into clinical practice.

So what should learn from these findings?

First, every clinician should be aware of the risk and benefits of estimating GFR (*Graphical Abstract*). Although it may seem trivial to determine eGFR at regular intervals, it may also make treatment decisions more difficult. It is a fact that patients with lower eGFR are less likely to be started or up-titrated on GDMT, and these life-saving drugs are often wrongly discontinued when eGFR drops. Second, if eGFR is determined, it is important to realize which formula is used and what are the pros and cons of this estimation. Do not use different formulas in the same patients as these are not interchangeable. Finally, appreciate a single eGFR measurement in the context of the entire patient. Acknowledge limitations of the estimation, and consider eGFR as a

continuous variable, not as an on/off phenomenon. Definitely be more careful with GDMT when eGFR gets lower and lower, but eGFR alone, by itself, is a poor guidance. Treat heart failure, not eGFR.

Conflict of interest

K.D. reports speaker fees from Boehringer Ingelheim, AstraZeneca, and Abbott.

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