Serum creatinine elevation after renin-angiotensin system blockade and long term cardiorenal risks: cohort study

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Abstract

Objective To examine long term cardiorenal outcomes associated with increased concentrations of creatinine after the start of angiotensin converting enzyme inhibitor/angiotensin receptor blocker treatment.

Design Population based cohort study using electronic health records from the Clinical Practice Research Datalink and Hospital Episode Statistics.

Setting UK primary care, 1997-2014.

Participants Patients starting treatment with angiotensin converting enzyme inhibitors or angiotensin receptor blockers (n=122 363).

Main outcome measures Poisson regression was used to compare rates of end stage renal disease, myocardial infarction, heart failure, and death among patients with creatinine increases of 30% or more after starting treatment against those without such increases, and for each 10% increase in creatinine. Analyses were adjusted for age, sex, calendar period, socioeconomic status, lifestyle factors, chronic kidney disease, diabetes, cardiovascular comorbidities, and use of other antihypertensive drugs and non-steroidal anti-inflammatory drugs.

Results Among the 2078 (1.7%) patients with creatinine increases of 30% or more, a higher proportion were female, were elderly, had cardiorenal comorbidity, and used non-steroidal anti-inflammatory drugs, loop diuretics, or potassium sparing diuretics. Creatinine increases of 30% or more were associated with an increased adjusted incidence rate ratio for all outcomes, compared with increases of less than 30%: 3.43 (95% confidence interval 2.40 to 4.91) for end stage renal disease, 1.46 (1.16 to 1.84) for myocardial infarction, 1.37 (1.14 to 1.65) for heart failure, and 1.84 (1.65 to 2.05) for death. The detailed categorisation of increases in creatinine concentrations (<10%, 10-19%, 20-29%, 30-39%, and ≥40%) showed a graduated relation for all outcomes (all P values for trends <0.001). Notably, creatinine increases of less than 30% were also associated with increased incidence rate ratios for all outcomes, including death (1.15 (1.09 to 1.22) for increases of 10-19% and 1.35 (1.23 to 1.49) for increases of 20-29%, using <10% as reference). Results were consistent across calendar periods, across subgroups of patients, and among continuing users.

Conclusions Increases in creatinine after the start of angiotensin converting enzyme inhibitor/angiotensin receptor blocker treatment were associated with adverse cardiorenal outcomes in a graduated relation, even below the guideline recommended threshold of a 30% increase for stopping treatment.

Reviewer: 4 - Patient and Public Reviewer

Comments: BMJ.2016.035107 Serum creatinine elevation following renin-angiotension system blockade and long term cardio-renal risk

The topic is very relevant as ACE-I and ARBs are recommended treatments for a variety of illnesses and therefore would affect a significant number of patients.

Previous Research has shown that patients with an increase in creatinine of > 30, after initiation of treatment, are advised to stop taking the medication because of long term cardio-renal risk but there has previously not been any research into the consequences of lower increases of Creatinine after the initiation ACE-I /ARBs.

Some findings from this study of the long term repercussions were quite worrying, "In general risks were highest in the first year after ACE-I / ARB initiation but were sustained up to 10 years later for end stage renal disease, myocardial infarction and death. Importantly we demonstrated a dose-responsive relationship between the level of increase in creatinine value and risk of adverse outcomes indicating that increases between 30% cannot be viewed as clearly safe."

Likewise the conclusion, "Creatinine increases following ACE-I /ARB initiation were associated with adverse cardio-renal outcomes in a dose-responsive relation, even below the guidelines recommended threshold of 30% increase for stopping treatment"

This was a long Research trial (1997-2014) it was good that it was adapted as time went on to take into consideration changes in the Quality and Outcome Framework. It would be interesting to see if there has been an increase in usage of ACE-I and ARBs since the introduction of the QOF, part of the new GP contract and whether there is a correlation with an increase in patient cardio-renal problems. There are numerous indicators in QOF where ACE-I /ARB is recommended and obviously whilst there is health benefit for the patient there is also a financial incentive for GPs to comply.

For example from the Guidance of GMS Contract 2016/17 DM006.1 Rationale The progression of renal disease in patients with diabetes is slowed by treatment with ACE-I and trial evidence suggests that they are most effective when given the maximum dose quoted in the BNF. * (see research conclusion above regarding dose -responsive relation)

Although trial evidence is based largely on ACE-I, it is believed that similar benefits occur with ARBs in patients who are intolerable of ACE-I. It is recommended that patients with a diagnosis of microalbuminuria or proteinuria are commenced on an ACE-I or considered for treatment with ARBs. (Further information : SIGN clinical guidelines 116. Management of diabetes. 2010).

HF 003.1 Rationale There is strong clinical and cost-effectiveness evidence to support the use of ACE-I in all patients with HF with LVSD. ACE-I improve symptoms, reduce the hospitalisation rate and improve the survival rate. This is applicable in all age groups. ARBs are also effective in the treatment of patients with HF due to LVSD, but may only be used in patients intolerant of ACE-I.
It is possible to have a diagnosis of LVSD without HF, for example, asymptomatic people who might be identified coincidently but who are at high risk of developing subsequent HF.

In such cases, ACE-I's delay the onset of symptomatic HF, reduce cardiovascular events and improve long-term survival.
This indicator only applies to patients with HF and therefore excludes this other group of patients who are nevertheless to be considered for treatment with ACE-I. NICE clinical guideline CG108 and SIGN clinical guideline 95 recommend that ACE-I is used as first-line therapy in all patients with HF due to LVSD and that ARBs are used only in patients who are intolerant of ACE-I.
The above examples give no indication of possible cardio-renal problems and there is no mention of the importance of creatinine monitoring post initiation.

This paper concluded that, "only 1/10th of patients initiating ACE-I/ARB therapy receive the guideline recommended creatinine monitoring. Moreover the vast majority of patients fulfilling post initiation discontinuation criteria for creatinine and potassium increases, continued on treatment."

It would be better for patient care if guidelines could take into consideration all recommendations to ensure best outcome for the patient. Perhaps there is a need for creatinine monitoring to become part of future QOF to ensure compliance.

The bigger a Practice Disease register is the more valuable their QOF point is. (Adjusted Disease Prevalence Factor - ADPF) This is because obviously the more patients who have a certain disease there is more work for the GP. However Disease Registers are compiled by diagnostic Read code. Exception codes can be used which sometimes can mask diagnostic Read code error. Diagnostic Read codes are not always entered by the Clinician, some are entered by Admin staff from letters. CKD and HT Registers are notoriously inaccurate as data protocol often differs from Practice to Practice. NICE have published guidelines of new classification of CKD incorporating GFR and ACR. There has been reclassification of the 5 CKD groups and altered codes so unless Practices have kept on top of this there may be error. Until there are national data entry protocols with a national qualification for data entry and more thorough audit of Read and CTV-3 codes one cannot be assured that the data is completely accurate.

However there are many good Practices and there is a wealth of patient data in Primary Care. I think it was good that the Research team utilised this valuable resource. The Research team mentioned searching on Read Codes (CPRD) and ICD-10 codes (HES) but not CTV-3 codes which are also used in General Practice.

It is important that a patient's health is looked at holistically and not only from a singular disease perspective. Also financial benefit whilst important to reflect the hard work of GPs should not be seen to be at the possible expense of patient health.

This study was population based, although patients were not actively involved. Patients could have been consulted to give a patient perspective of various aspects of this study, from conception to monitoring.
• An expert patient from each of the disease areas could have been consulted and the results could then have been cascaded through these patients back to other patients in these relevant disease areas with feedback follow up.
• Random patients could have been asked to keep diaries of their quality of life or through questionnaires. This may have highlighted any medication changes, other drugs introduced or stopped. Follow up of patients may not have been the fault of the Clinician

but some patients may have cancelled their appointments or been away for a long period of time.

Queries The up to 12 months time-frame for pre-initiation seems quite a long time. Later it was amended for up to 24 months? Patients could have been quite well at that time and therefore the difference in increase of creatinine could appear more pronounced or vice versa. Also were search criteria adjusted for medication, hospital admissions to be inclusive in the longer time-frame.

"we did not have access to blood tests performed in Hospitals systems..."
Some Practices enter blood test results by code from Hospital letters into the patient's computer file. Also some Practices have automatic electronic transfer of laboratory data which GPs can allow to enter the Patient's computer file. Therefore hospital results can sometimes show in Patient's computer file.
The Research authors were detailed and open in their possible limitations, however their study was robust and relevant resulting in several pertinent findings.

"Although patients with prior myocardial infarction, hypertension or high baseline potassium level were at higher risk of sudden decline of kidney function after ACE-I/ARB initiation there was no evidence that these patient groups were monitored more frequently while initiating the drugs."

"Patients with sustained increases in creatinine after ACE-I / ARB initiation should be recognised as a very high risk group requiring ongoing monitoring. Review is needed of the risks and potential benefits of drug continuation for the specific prescribing indication for each patient"

From a patient perspective it was neatly summarised by the authors as follows:- "The majority of patients initiating treatment with ACE-I /ARB experience only minor changes in renal function. However substantial increases in creatinine levels after ACE-I/ ARB initiation may not be as rare as previously suggested, reinforcing the need for adherence to clinical guidelines for both pre and post-initiation monitoring.... More work is needed to determine the prognostic importance of the changes in renal function we have observed"

This study has highlighted the need for more careful monitoring of patients receiving ACE-I /ARB and the authors should be commended for their work. It is very important that a balance of risk and benefit is presented to patients to ensure that they receive the best treatment for them personally.

This important medical quandary needs to be addressed as soon as possible. It will be interesting to see the results of the STOP-ACE trial.

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Ref: Guidance of GMS Contract 2016/17

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