WHAT TRIAL DO WE NEED IN CONSERVATIVE TREATMENT OF AKI?

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Thank you very much. Good afternoon ladies and gentlemen, dear colleagues. The advantage of being involved in guideline writing is and it may be the most important advantage of guidelines is that at least when you’re supported by good evidence rating people, they can pinpoint the weaknesses in our knowledge because there’s a lot of eminence-based medicine. Not necessarily meaning that eminences are always wrong, for example, the two co-chairs, the next speakers are all eminences and automatically I believe every word they have
written and told us. But on the other hand, there may be some other questions on the eminence-based medicine. So what I'm going to try to do is give you a few examples of what I think, based on what the KDIGO guidelines have found, what may be in the near future some interesting trials, principally I have chosen quite simple examples, could be realized.

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For example, if you go to what is called in this title 'Conservative management' what I prefer to call 'Non-dialytic management' we found 12 recommendations of level 1. That doesn't mean that this was always very strong evidence but at least there was level 1, there was enough suggestion that probably this for the time being, because guidelines are always for the time being, was true.

On the other hand pointing to the lack of evidence in many aspects, we could formulate only on that aspect 37 research suggestions. I'm going to discuss with you some of them.

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You will find the target populations for prevention trials for AKI in four major domains. First of all, trials where the exposure and the time and the severity of the renal insult is known, a classic example is surgery. Most of the studies have been done in cardiopulmonary bypass or in even a little bit in abdominal surgery. Prevention of contrast-induced AKI in at risk patients, prevention of nephrotoxic AKI, then you know exactly when the renal insult has started and what the intensity was. So this is a good example of doing prevention trials.

On the other hand, much more difficult to are trials where the exposure in time and severity of the insult is unknown. Most urgently, of course, are sepsis because this is still in critically ill patients the most common cause of AKI and are tremendously associated with mortality. For example, a clinical example of sepsis does not necessarily mean the patient coming in in septic shock but for example, community acquired pneumonia is an example of sepsis or abdominal infections.

### Frequency of individual outcomes in post cardiac surgery according use or non-use of ACEi

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Preoperative ACE Inhibitors</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 3,983)</td>
<td>No (n = 4,906)</td>
</tr>
<tr>
<td>Major adverse events</td>
<td>1,518 (38.1%)</td>
<td>1,649 (33.6%)</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>144 (3.6%)</td>
<td>199 (4.06%)</td>
</tr>
<tr>
<td>Postoperative renal dysfunction</td>
<td>522 (13.1%)</td>
<td>495 (10.1%)</td>
</tr>
<tr>
<td>Postoperative stroke</td>
<td>123 (3.1%)</td>
<td>125 (2.6%)</td>
</tr>
<tr>
<td>Postoperative atrial fibrillation</td>
<td>1,062 (26.7%)</td>
<td>1,166 (23.8%)</td>
</tr>
<tr>
<td>Postoperative myocardial infarction</td>
<td>144 (3.6%)</td>
<td>146 (2.98%)</td>
</tr>
</tbody>
</table>

Bandeali et al. Am J Cardiol 2012;110:919–923
One first question is, a patient that is referred for cardiovascular surgery or for bypass and the anaesthesiologist calls you, whenever he calls you, and they ask you this patient is on an ACE inhibitor should I stop that or not? A very simple question. Well here is one paper out of many by Doctor Bandeali in the American Journal of Cardiology very recently who found that in fact, if patients were on pre-operative ACE inhibitors and it’s a substantial number of patients, that there was a significantly higher post-operative renal dysfunction in that patient, now be careful these patients were selected. There is a reason why a patient is on an ACE inhibitor. So this was more or less controlled for the underlying comorbidity but still despite that, they found that when a patient was on an ACE inhibitor and continued in the immediate post-operative phase that actually this was not a good thing and was associated with a higher risk.

**Slide 5**

**Incidence of CI-AKI before and after propensity score matching in ACE/ARB users and non-users**

![Incidence of CI-AKI before and after propensity score matching in ACE/ARB users and non-users](image)


Another paper in the American Journal of Kidney Disease looked at contrast-induced AKI before and after patients were taking an ACE inhibitor or an ARB or not taking it. They did the propensity score, so they tried to compensate for all other associated risk factors and again, these people found that even after propensity scoring matching that there was indeed a higher incidence of contrast AKI. So based on this and other papers there may be a reason that we say we should be careful with ACE inhibitors, particularly when the patient has to undergo cardiovascular surgery.

**Slide 6**
On the other hand, there are other studies and that’s again in another prestigious journal, read particularly by cardiovascular surgeons, again 2012 where they found that pre-operative ACE inhibition after and followed by coronary artery bypass surgery had absolutely no impact whatsoever. It didn’t improve the risk but it certainly was not associated with increased risk.

Another example, very classic, very common, what about statins? If a patient is referred for cardiovascular surgery and many of them are taking a statin, should we continue the statin? Should we stop the statin? For example, a population-based study, this is population-based in Canada published 2 months ago in the British Medical
Journal where they looked at thousands of Canadians over all the provinces of Canada, they found when they compared two groups of patients: ones taking a high dose of a statin and you see the dose is there, compared with patients who took a low dose of statin. I can assure you the reasons why many patients take a high dose of statins are not clear. Many of the patients taking a high dose should actually also be very well with a low dose statin. That was good because the control group was already taking a statin but then a lower dose and you see indeed the risk for AKI in patients who were taking high dose of statins after cardiovascular surgery was very high.

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Association of Statin Use with Risk and Outcome of AKI in Community-Acquired Pneumonia

Another study coming from our friend John Cullum, who is an expert in AKI and particularly, in community acquired pneumonia, he also found that patients who were coming in with community acquired pneumonia and who were on pre-hospital statin use or continued the statin just during their stay in the intensive care unit because they were all critically ill patients also had an increased odds ratio for AKI. So the lesson from these studies could be better be careful with a statin or it’s better we stop the statin whenever the patient is critically ill.

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But this study, American Journal of Medicine, again last year showed that pre-operative statin use and looking at post-operative AKI on the contrary, the statin patients did better. Here of course, the control group was not taking statins at all, so it is different from the study that I showed you before, but here there was a decreased risk. So what are you doing if you writing guidelines on this?

Another study showed on the contrary Quintavalle, a highly cited study in Circulation, they showed that if you give a single high dose of atorvastatin and this probably applies also to other statins but a high dose, one single dose in patients at risk for contrast-induced AKI is protective. The atorvastatin group had 4.5% of the group did CI-AKI, the control 17.8%.

So I think both in the field of ACE inhibitors and in the field of statins better studies should be done and this could be relatively simple to do, to find out because I think this is an important clinical question, what should you do with a statin? What you should do with an ACE inhibitor
in patients going to surgery or exposed to contrast?

Another topic, a little bit more complex for doing trials, is early goal directed therapy. We know from the study of Rivers in sepsis patients that if you treat the patient at certain targets and this was done in septic shock, for example, these are the targets: central venous pressure, they are critically ill patients between 8 and 12 and a mean arterial pressure of more than 65 mmHg, a urine output of 0.5. By the administration of 500 mL boluses of crystalloids and Rivers added between brackets colloids, I’ll come back to that and vasopressor agents as necessary.

EGD patients require a central venous catheter capable of measuring ScvO₂, and they have to achieve a ScvO₂ of ≥70%, pursued by red blood cell (RBC) transfusion for anemic patients (hematocrit, ≥30%) and dobutamine therapy for patients above that threshold.

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On the other hand, another set of targets in these critically ill septic shock patients said that you should have a central venous oxygen saturation of at least 70%. If you don’t achieve that and your patient is anaemic, you give them a blood transfusion and you keep trying to add dobutamine if it is needed. Don’t forget a very critically ill patient, septic shock.

It has been suggested that in patients undergoing surgery we probably could apply the same early goal directed therapy and KDIGO had the tremendous difficulty to recommend that and the recommendation if you go to KDIGO they will say ‘it is better to have targets than having no targets’. But carefully we drew from setting some numbers about it.
This is a meta-analysis of several patients that were operated on and why this goal directed therapy was achieved at or was at least followed. They found that indeed there was a much less incidence particularly in high risk patients and in patients that were following, that were treated by the anaesthesiologist and the surgeon with these targets in mind during the operation, a much lower incidence of AKI. You see the better results were obtained with a combination of fluids, inotropes and vasopressors.

What kind of fluid should we give? Well, there have been and this is one study and there are many others also very recently where they applied in septic shock these targets. You see they treated patients with starch, with a gelatine, with crystalloids and one of the targets was having a normalization of serum lactate, a normalization of mean arterial pressure, a better oxygen saturation, normalization of central venous pressure and you see immediately that there was no difference in outcome between the three types of fluid, whether it was...
a gelatine or whether it was starches or whether it was fluid. There was one major caveat.

The risk for AKI in the gelatine group compared to the isotonic saline group was 85% bigger and the risk using the starch was 155% bigger and for the time being and based on other studies that came out last year where they carefully compared saline with starches they showed in the intensive care patients that not only the outcome was the same but you see here that with the starches there...
was a rise in the serum creatinine. For the time being it is suggested, but still we need more trials for that, but it is suggested that starches do not give you an absolute benefit and that there is a risk for doing harm. Now physiologic serum is probably the worst name we have ever used for a fluid because first of all, it is not serum and secondly it is absolutely not physiologic.

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**Impact of fluid chloride concentration in prevention of AKI in ICU**

<table>
<thead>
<tr>
<th></th>
<th>0.9% Saline</th>
<th>Hartmann</th>
<th>4% Gelatin</th>
<th>Plasma-Lyte 148</th>
<th>Albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>150</td>
<td>129</td>
<td>154</td>
<td>140</td>
<td>140</td>
</tr>
<tr>
<td>Potassium</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Chloride</td>
<td>150</td>
<td>109</td>
<td>120</td>
<td>98</td>
<td>128</td>
</tr>
<tr>
<td>Calcium</td>
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<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Magnesium</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>Lactate</td>
<td>0</td>
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<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>Acetate</td>
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<td>0</td>
<td>0</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>23</td>
<td>0</td>
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<tr>
<td>Octaroate</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6.4</td>
</tr>
</tbody>
</table>

*All concentrations in mmolL

Yunos et al, *JAMA. 2012;308(15):1566-1572*

It has a sodium chloride concentration, you see the first pink bar there a sodium of 150 and a chloride of 150. If you compare that with plasma, this is completely different. So there was already the feeling that if you give a certain amount of isotonic saline that by giving this chloride rich solution this may have repercussions on acid-base metabolism. Indeed it has been shown in meta-analysis and by the Cochrane that if you give physiologic serum, then there is a hypercloremic acidosis that you provoke. So Rinaldo Bolomo’s group did a study which is certainly not randomized and not prospective but where keeping this in mind they compared an episode in their ICU where they gave chloride rich solutions in pink and then they switched to chloride, let’s say normal chloride solutions in green.

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To their surprise I think, they saw that indeed the incidence of AKI in traditional fluid infusion and chloride-restricted fluid was completely different. For example, when they looked at the RIFLE criteria, they saw that there was a higher incidence or a lower incidence of AKI in the intervention period where they used the low chloride or the more physiologic concentrations and when they combined the injury and the failure group, there was also a significantly lower incidence of AKI. So there is a tendency but again, we badly need good prospective studies where we compare randomized trials, the so-called balance solutions with a normal chloride concentration with the classical physiologic so-called isotonic sodium chloride.

Other topic the biomarkers. I'm not going to dwell on that because yesterday we had a very nice session on biomarkers. There was a little bit of animosity there and I tried to be calm because I know many experts on biomarkers are here in the audience but you remember
this slide, very famous slide from Michael Haase who collected an ICU population and where he compared the outcome for dialysis or the combined outcome dialysis and mortality based on a combination of serum creatinine that we still use for the definition of AKI and the presence or absence of a classical quite well and popular biomarker of disease NGAL. Remember NGAL is a protein that is what the gene upregulates whenever there is damage to the tubule, whether it is ischemic damage or nephrotoxic damage. Indeed, this is very promising that we could use this biomarker to distinguish whether there is only a purely hemodynamic what we called at the time pre-renal AKI where apparently there is no structural abnormality and whether we could use these biomarkers as differentials diagnosis. Here he distinguished four classes, four groups where indeed the NGAL was negative and the creatinine was negative, the first column and there was already some dialysate mortality, don’t forget this word ‘critically ill patients’. In the second column he found interestingly a group where the NGAL was positive but the creatinine didn’t rise. There I respectfully disagree a little bit with my good friend Claudio Ronco in the name of sub clinical AKI. First of all this is a contradiction in terminis because AKI is still defined by creatinine or urine output but without that that would mean that if we accept that term and maybe that the trials later on are going to confirm that, it would mean then that we define AKI as simply finding a high level of NGAL in the urine and not looking at the serum creatinine. I still have some trouble with that but OK we can discuss it. The third group is interesting because this is what we would call the old name of pre-renal AKI where the biomarker was negative but the creatinine was high. Then, of course, the classical fourth group where both were positive, the classical intrinsic AKI. What you see here is that in these three groups the mortality and the need for dialysis was increased compared to patients who had absolutely neither functional nor hemodynamic AKI.

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Study flow diagram in transient AKI

The most interesting part when I read all these papers about biomarkers that intrigued me was can we use them in the differential diagnosis, which is more than theoretical between the so-called pre-renal and intrinsic one. We know that when there is a pre-renal hemo constricting, hemo vasoconstriction in the kidney, probably because the patient is volume depleted, you should give some fluid. When it is...
intrinsic well, be aware that you easily overfill the patient. So I thought these biomarkers are going to teach us to make this distinction because it’s not always easy to make that clinically. This is an interesting study written by people who really are very strong in the biomarker field. They had 337 patients but that’s not important they had 129 patients who were diagnosed as AKI and then they made a distinction between what they called transient AKI, these were people with a creatinine coming down and normalised after 48 hours after giving them some fluids. Of course, they had a group of patients with established AKI. In the transient AKI, they looked at the fractional excretion of sodium and they found a group where it was more than 1%. You see this is a magic number, the fractional excretion of sodium distinguishing between let’s say purely functional and already a beginning of structural abnormality. They also found a group that was transient and with a fractional excretion of sodium below 1.

Now if there is one doubt, there is no doubt here that that is a group that I would have called in my young days a pure pre-renal AKI.

*Slide 20*

**Urinary NGAL in prerenal AKI**

[Graph showing NGAL levels in different AKI stages]

Doi et al, Kidney Intl, 82: 1114-1120, 2012

What they then looked at was at urinary NGAL and that was a little bit disappointing, where you would expect in the pure functional AKI the NGAL to be normal, they found, they first of all looked at the enormous variation within a certain group of the NGAL and secondly also in transient AKI with low fractional excretion of sodium they found a slightly but still significantly elevated NGAL. Now the explanation is either this is not true, NGAL is not worth it or the explanation the authors gave was ‘but wait a minute in pre-renal
AKI there are already some structural abnormalities. So the jury is still out.

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**Clinical models of prediction of AKI in elective cardiac surgery- effect of adding immediate postsurgery ΔScr**

<table>
<thead>
<tr>
<th>Model and Variables</th>
<th>Coefficients (OR [95% CI])</th>
<th>Global Model P</th>
<th>Model AUROC (OR [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline model</td>
<td>&lt;0.001</td>
<td>0.69 (0.62-0.77)</td>
<td></td>
</tr>
<tr>
<td>Pump time [min]</td>
<td>1.59 (1.13-2.24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>euroSCORE [1 point]</td>
<td>1.10 (1.00-4.70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline eGFR [ml/min/1.73 m²]</td>
<td>0.96 (0.49-2.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enriched model</td>
<td>&lt;0.001</td>
<td>0.78 (0.71-0.85)*</td>
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<tr>
<td>Pump time [min]</td>
<td>1.41 (0.96-2.06)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>euroSCORE [1 point]</td>
<td>1.09 (0.97-1.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline eGFR [ml/min/1.73 m²]</td>
<td>0.97 (0.96-0.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate postsurgery ΔScr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10% decrease Scr</td>
<td>0.37 (0.18-0.76)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%ΔScr = 10% of baseline</td>
<td>1.00 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10% increase Scr</td>
<td>6.38 (2.37-17.2)</td>
<td></td>
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</tr>
</tbody>
</table>

Abbriviations: AUROC, Area under the receiver operating characteristic curve; CI, confidence interval; ΔScr, change in serum creatinine; eGFR, estimated glomerular filtration rate; euroSCORE, European System for Cardiac Operative Risk Evaluation; OR, odds ratio


Just to end up this is a nice study that I found in the American Journal of Kidney Disease where they predicted AKI in elective cardiac surgery and they simply looked at the basic clinical model. The pump time, the time of the extracorporeal circulation, a clinical scoring, the baseline eGFR, you know and they came up with an area under the curve of 0.69 as prediction of AKI.

When then they looked at the creatinine immediately taking creatinine post-surgery meaning early, they had 3 groups, a group that they took as reference were the serum creatinine did not change from before operation, before surgery, where the serum creatinine went down and then in most of these cardiac surgery patients it should go down because of some dilution due to the extracorporeal circulation where there was absolutely no AKI and then a group where the serum creatinine was higher with 10% of the basal value. When they added these simple parameters to the clinical model, the area under the curve increased to 0.78. I bet you there will be a good biomarker needed to beat that in this purely clinical evaluation.

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My last slide is a comment on the power of most of these studies. For example, the incidence of severe AKI (doubling of sCr or RRT requirement postcardiac surgery) is aprr 5%.

Thus, with this incidence rate, a=0.05, power of 0.9, and 30% effectiveness of an intervention (i.e., 30% relative reduction in the development of severe AKI from 5% to 3.5%), 3799 patients per arm would be needed.

With inclusion of high-risk patients, the incidence of AKI post cardiac surgery is still generally low; for example, the risk of AKI requiring RRT after cardiac surgery in patients with a sCr of 2–4 mg/dl is 10%–20%.

In such population, with 20% incidence and 30% effectiveness, 822 patients per arm would be required to successfully show a reduction in the need for RRT.

Thus, it is notable that only 3 of 30 of the registered cardiac surgery trials in adults are enrolling 800 or more patients.

Sample size and power of a prevention study for AKI post-cardiac surgery

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Thus, it is notable that only 3 of 30 of the registered cardiac surgery trials in adults are enrolling 800 or more patients.