

# Acute Dialysis Quality Initiative

## 4<sup>th</sup> International Consensus Conference

### Workgroup 2

#### Secondary Prevention of Acute Renal Failure

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### Introduction

Secondary renal injury in the setting of acute renal failure (ARF) is “an additional renal injury developing in the setting of a primary renal injury”. The nature of prevention of secondary renal injury in the setting of ARF may depend on the process initiating primary renal injury. It is often impossible to separate primary from secondary renal injury when the process of primary acute renal injury is ongoing. The goal is to both prevent a second primary insult and alter the natural sequelae of the primary insult. In patients with isolated acute renal injury the focus would be on altering the natural sequelae of the original insult. In relation to secondary prevention, there are several fundamental questions that need to be addressed. They are discussed below.

**What are the Potential targets (physiologic or pharmacological) to alter the natural sequelae of the initial primary insult or prevent an additional injury?**

The major physiological targets for possible secondary prevention include blood pressure, cardiac output, intravascular volume, and renal blood flow.

***Is there a threshold and/or optimal mean arterial pressure (renal perfusion pressure) for secondary prevention?***

Although there are insufficient data to make firm recommendations as to what is optimal mean arterial pressure (MAP) for the injured kidney, level III evidence suggests that maintaining a systolic arterial pressure < 80 mmHg (equivalent to MAP at least < 65 mm Hg) is independently associated with an increased risk of developing ARF (odds ratio: 15) (1). The MAP required to maintain adequate renal perfusion pressure may vary according to the patient’s underlying co-morbid conditions or prior

preconditioning. There are small case series and cross-over randomized controlled studies (Level II) showing that ornipressin or terlipressin (with or without concomitant albumin or starch or gelatin infusion) can increase mean arterial pressure and short term renal function in patients with renal injury and dysfunction due to hepatorenal syndrome (2-9).

There is a small short-term randomized cross-over study (Level II) suggesting that there is no increase in short-term creatinine clearance by increasing MAP above 65 mm Hg with norepinephrine therapy in patients with acute renal injury in the setting of septic shock (10). There is a small randomized controlled trial (RCT) comparing to norepinephrine to alpha dose dopamine in patients with septic shock which shows that mean arterial pressure was better restored with norepinephrine and that such restoration was associated with a significant increase in urine output (Level II) (11). A further study by the same group (12) compared 14 septic shock patients randomized to a MAP > 65 mmHg with a group of 14 patients randomized to a MAP>85 mmHg using norepinephrine. No differences in renal outcomes were found.

### ***Is there a threshold and/or optimal cardiac output for secondary prevention?***

A low cardiac output induces renal ischemia and loss of GFR. This is typically seen in cardiogenic shock. A low cardiac output or decreased cardiac function is also a risk factor for acute renal failure (ARF) after cardiac surgery (13). Restoration of cardiac output to adequate levels is an important form of secondary prevention. However, what constitutes an adequate cardiac output must be determined individually. Similarly, except of the example of end-stage cardiac failure, in acute illness it is difficult to separate out reductions in cardiac output from reductions in MAP. There is no evidence that increasing cardiac output from adequate to supranormal has beneficial renal effects in patients with recent or ongoing renal injury (Level I).

### ***Is there a threshold and/or optimal fluid therapy for secondary prevention?***

Hydration with saline has been shown to protect humans from radiocontrast nephropathy (14, 15) and is likely to be protective both as a primary and secondary preventive intervention (Level I). There is uncontrolled evidence that aggressive fluid resuscitation can protect patients from progressive renal failure from crush injury (16) (Level III). A single center RCT showed the beneficial effect (blunted rise in serum creatinine and urea) of volume expansion with albumin in patients with liver failure, primary peritonitis and a variable but generally mild degree of renal dysfunction (17) (Level II).

### ***Are there treatment strategies that alter renal blood flow (or regional renal perfusion) independently of mean arterial pressure (eg, dopamine, diuretics, ANP, fenoldopam)?***

There is a biologic rationale that renal blood flow may be affected by pharmacological intervention. Various agents have been proposed over the last 4 decades as having a beneficial effect on renal function by means of selectively increasing renal blood flow. However, a multicenter RCT provided Level I evidence that “low dose” dopamine” in patients with acute renal injury does not increase urine output or

alter the natural sequelae of the insult (18). More recently a small single centre RCT showed some benefit in the primary prevention of ARF in cardiac surgery patients requiring significant inotropic or vasoactive support when rhANP (atrial natriuretic peptide) was used. These findings might extrapolate to secondary prevention (Level II) (19). However, other randomized controlled trials of either urodilatin (renal natriuretic peptide) or anaritide (a synthetic form of ANP) have failed to show any protective effect on the kidney in the setting of major abdominal surgery (20) or acute tubular necrosis (21) or oliguric acute renal failure (22) (Level I). There is no evidence of a specific benefit of diuretics (loop diuretics or mannitol) on renal blood flow or in terms of renal protection from secondary injury. Fenoldopam (a selective DA-1 receptor agonist) has been studied for the primary prevention of contrast nephropathy and has been found to be ineffective in two randomized trials (Level I) (23, 24). There are no published RCTs of this agent in the treatment of patients with acute renal failure.

Consensus Statement: There is insufficient evidence to recommend specific physiologic targets (mean arterial pressure, cardiac output, filling pressures) that will ensure adequate renal perfusion pressure in all or most patients. Extreme hypotension (<80 mmHg systolic BP) should be avoided. Therapy should be individualized based on the pathophysiology involved in the individual case, the baseline physiologic condition of the patient in question and the clinical course and response (urine output, serum creatinine, lactate, peripheral perfusion) to hemodynamic management. Drugs which selectively alter renal blood flow have not been shown to alter the natural sequelae of ARF.

Recommendations for Clinical Practice: Preservation of renal perfusion by support of cardiac output, mean arterial pressure and intravascular volume is recommended to facilitate renal recovery (Grade E). When vasopressor agents are required to reverse system vasodilatation (e.g. septic shock), norepinephrine is the drug of choice (Grade C). Drugs should not be used to induce renal vasodilatation (Grade A).

Recommendations for Future Research: Further clinical research in the possible role of renal vasodilators (fenoldopam or rh ANP) using clinical endpoints (e.g. survival) appears desirable. A suitably powered randomized controlled study comparing two levels of MAP control appears justified.

## Could modulation of renal metabolism reduce secondary renal injury?

An important possible approach to secondary renal protection might be by modulating renal metabolism. Thus a major question is whether renal metabolism might be a viable target for modulation of secondary renal injury.

### *Are there treatment strategies that alter renal metabolism and show evidence of renal protection?*

Hypothermia might be expected to reduce renal metabolism and thereby protect the kidney from further injury. This hypothesis was indirectly tested in two randomized controlled trials of hypothermia after cardiac arrest. These trials provide Level I evidence that hypothermia following cardiac arrest (core temperature 33°C x 12 hours or core temperature 33-34 °C x 24 hours) does not alter the course of acute

renal injury (25, 26). Thyroxine might affect renal metabolism and enhance renal recovery. Animal experiments suggest a possible beneficial effect. However, a single center randomized controlled trial (Level II) was stopped at interim analysis because the administration of thyroxine in the setting of ARF was associated with a significant increase in mortality (27). Insulin-like growth factor 1 (ILGF-1) might affect renal metabolism and renal recovery and has been shown to accelerate renal recovery in animal studies. However, an RCT in patients with ARF (Level II) failed to show any benefits of ILGF-1(28). Similarly, in an RCT in recipients of cadaveric allografts (Level I), ILGF-1 failed to provide any benefit (29). Although loop diuretics reduce renal oxygen conception, there is no evidence that they provide renal protection from primary or secondary injury.

Consensus Statement: Though theoretically attractive, available strategies for reducing renal metabolism have not shown any benefit in treatment of ARF.

Recommendations for Clinical Practice: No currently available strategy to reduce renal metabolism can be recommended to treat ARF.

## Can modulation of the stress response improve renal function?

The stress response and the inflammatory system are involved in the response to renal injury. Their modulation might affect renal function and renal recovery. A major question is whether modulation of these responses might benefit the injured kidney

### *Is up-regulation of the acute stress response an effective approach to secondary prevention?*

The induction of stress response (heat shock) proteins (HSPs) is a highly conserved response that protects many cell types from diverse physiological and environmental stressors. In experimental ischemic renal injury HSPs have been shown to attenuate renal injury (30). Thus, animal studies indicate that there is biologic plausibility that up regulation of the stress response might be effective in acute renal injury. However, there are no data investigating the use of any agent able to independently up-regulate the heat shock response in patients with acute renal injury.

### *Are endothelial protection strategies (eg, anti-complement, anti-adhesion molecule strategies, activated protein C,) beneficial to renal function?*

Endothelial injury is likely to be an important mechanisms of primary and secondary renal injury. Several pathways appear to participate in such endothelial injury. Complement has been shown to be activated via the alternate pathway in human tubular necrosis (31), complement depletion inhibits renal injury secondary to ischemia (32) and ischemia injury is attenuated in animals deficient in C3, C5, C6 and Factor B (33). However, no human studies have shown a beneficial effect of complement manipulation on renal function. Adhesion molecules have also been shown to participate in the pathogenesis of ischemic ARF (34, 35) and

blockade of E-selectin and/or P-selectin and/or ICAM-1 all protect from ischemia-reperfusion injury in mice (36, 37, 38). However, no studies have yet been conducted in humans. Activated Protein C may protect the endothelium from inflammatory injury (39) and thereby attenuate endothelial injury in severe sepsis or in ischemia-reperfusion injury. A large multicenter RCT (Level I) has shown that recombinant human Activated Protein C (rhAPC) decreases all cause mortality in patients with severe sepsis including those with acute renal failure (40). However, no specific RCT has yet addressed its efficacy in patients with ARF.

Consensus Statement: Modulation of the stress response is a theoretically attractive and relatively understudied area for treatment of ARF.

Recommendations for Clinical Practice: No currently available strategy to reduce the stress response can be recommended specifically to treat ARF.

Recommendations for Future Research: Pilot clinical investigations should be undertaken to study the possible beneficial effects of modulators of the stress response in patient with ARF. A large randomized double-blind controlled trial of rhAPC in patients with ARF appears justified.

## What other strategies have emerged from experimental models that might prove useful for secondary prevention of ARF?

Another important area of renal protection relates to animal experimentation and the emergence of new techniques or biological approaches to attenuating renal injury or accelerating renal recovery. These new approaches might lead to important therapeutic advances in humans in the near future. Thus, it is important to define what approaches have been studied so far and which ones might offer greatest promise.

Furthermore as more attention is focused on the possible beneficial effects of so called “pre-conditioning” on organ protection, this field needs to be considered in answering the question of which approaches offer initial experimental evidence for a beneficial effect.

### *What interventions have shown evidence of a possible beneficial effect for secondary prevention in experimental models and what are suitable targets for future interventions?*

Several interventions have been shown to have a possible beneficial effect on kidney function in the setting of secondary prevention (41-47) and there are several targets for potential manipulation as identified in experimental studies. They are summarized in Figure 1. They involve manipulation of several biological pathways including endothelin, adhesion molecules, adenosine receptors and so on. The data are insufficient to identify interventions which are more likely to be beneficial in humans. The relationship between animal models of ARF and the human syndrome remains tenuous.

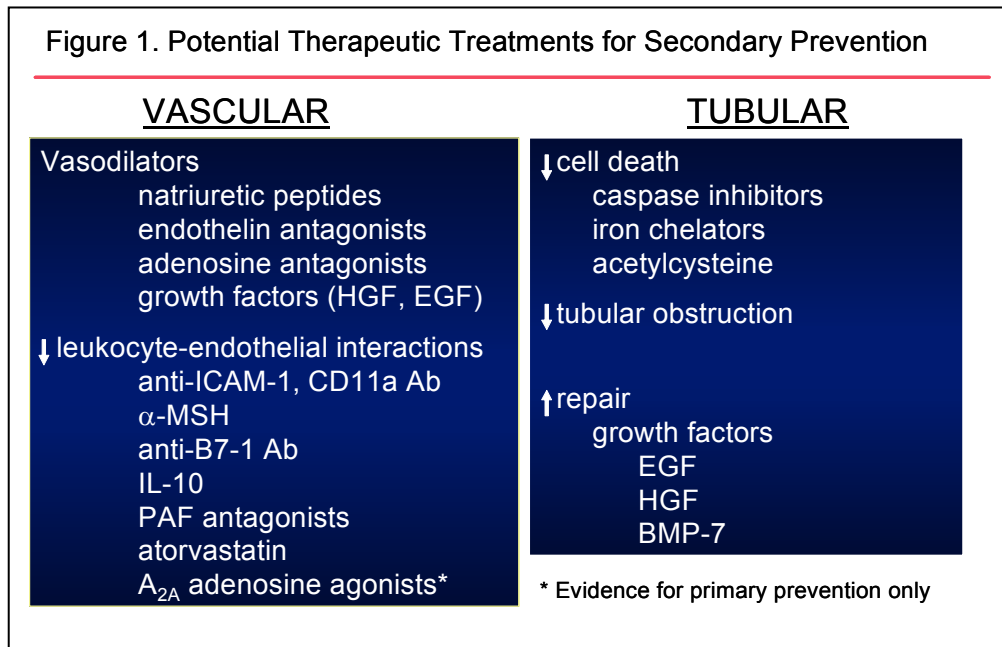
*What is the significance and possible future therapeutic role of ischemic pre-conditioning?*

Ischemic preconditioning has been shown to be a powerful mechanism of renal protection in experimental ARF (48-50). The protective effect of preconditioning is greater than most reported protective effects with pharmacological intervention in animals. Its direct applicability to humans, however, remains clinically very difficult except perhaps for the setting of renal transplantation and no human data exist to understand its efficacy in human disease. However, understanding the mechanisms which subtend its development and harnessing such mechanisms for therapeutic intervention might represent a major therapeutic development in the near future.

Consensus Statement: Advances in our understanding of the mechanisms involved in producing and sustaining the beneficial effects associated with ischemic pre-conditioning provide tremendous therapeutic promise. Ischemic preconditioning for the kidney is an important field for investigation and therapeutic development.

Recommendations for Clinical Practice: None.

Recommendations for Future Research: Further investigations should be undertaken in this field to study the magnitude of benefit derived from ischemic pre-conditioning in the setting of both septic and ischemic models of acute renal failure. The molecular mechanisms responsible for such benefits should be elucidated.



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