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Citation for final published version:

Allen, Lowri A, Pyart, Rhodri D, Holmes, Jennifer, Donovan, Kieron L, Anderson, Richard A and Phillips, Aled O 2019. Cardiovascular and renal outcomes following percutaneous coronary intervention in a population with renal disease: a case-control study. QJM: An International Journal of Medicine 112 (9) , pp. 669-674. 10.1093/qjmed/hcz130 file

Publishers page: <http://dx.doi.org/10.1093/qjmed/hcz130>
<<http://dx.doi.org/10.1093/qjmed/hcz130>>

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1 Cardiovascular and renal outcomes following percutaneous coronary intervention in a population
2 with renal disease: a case-control study

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20

21 Word count:

22 Abstract: 250

23 Main body: 2379 (excluding abstract, references, acknowledgements and figures)

24

25

26

1 **Abstract:**

2 **Background:** Patients with renal disease are less likely to undergo percutaneous coronary
3 intervention (PCI) due to concerns about poor outcomes.

4

5 **Aim:** We describe outcomes following PCI in individuals with chronic kidney disease (CKD), as
6 compared with matched controls with comparable CKD who did not undergo PCI. We also identified
7 factors predictive of poor outcomes following PCI amongst patients with CKD.

8

9 **Design:** Retrospective observational case-control study.

10

11 **Methods:** Cases were individuals with CKD (stages 1-5) undergoing PCI between 2008-2014.
12 Controls were age, gender and creatinine matched individuals not requiring PCI. We compared
13 mortality between groups using Kaplan Meier curves and Cox regression modelling. We assessed
14 changes in serum creatinine using Wilcoxon Rank testing. We explored the relationship between
15 biochemical and haematological measures (baseline creatinine, calcium, phosphate, calcium-
16 phosphate product, parathyroid hormone, white cell count, haemoglobin, platelet count, c-reactive
17 protein, total cholesterol) and post-PCI mortality, using logistic regression.

18

19 **Results:** We identified 144 cases and 144 controls. Mortality was significantly lower amongst cases
20 compared with controls (hazard ratio 0.46 (95% confidence intervals 0.31,0.69)). PCI did not result
21 in a significant change in renal function ($p=0.52$). Amongst cases, serum creatinine and calcium-
22 phosphate product were predictors of mortality following PCI.

23

24 **Conclusion:** Cases undergoing PCI had lower mortality, and PCI was not associated with accelerated
25 CKD progression. On this data, PCI should not be deferred as a treatment option in patients with

- 1 CKD. Serum creatinine and calcium-phosphate product predict mortality following PCI in this cohort,
- 2 and may be useful in risk-stratifying patients with CKD being considered for PCI.
- 3

1 **Background:**

2 Cardiovascular disease is one of the leading causes of mortality in patients with chronic kidney
3 disease (CKD)¹⁻⁴. Cardiovascular mortality is 10-20 times more common in patients with CKD Stage 5
4 who are on dialysis, compared with the background population². Furthermore, there is evidence to
5 suggest that cardiovascular disease typically occurs at an earlier age, and follows a more accelerated
6 course in patients with CKD, as compared with the background population^{5,6}. Unlike in the
7 background population, cardiovascular disease is not typically the result of progressive
8 atherosclerosis, but instead is due to dysregulation of calcium and phosphate homeostasis, and the
9 development of medial vascular calcification⁷⁻⁹.

10

11 There is no consensus regarding how best to manage cardiovascular disease in patients with CKD.
12 Most trials of treatments for cardiovascular disease exclude patients with renal disease, and as such
13 the evidence base underpinning the management of these patients' cardiovascular disease is
14 sparse^{10,11}. In practice, patients with CKD are less likely to receive medications such as Aspirin, ACE
15 inhibitors and Beta blockers, due to concerns about side effects/toxicity and adverse effects on renal
16 function^{10,12}. In addition, patients with CKD are less likely to be offered angiography and or
17 percutaneous coronary intervention (PCI)¹². This is in part a reflection of the fact that renal
18 impairment predicts poorer outcomes including mortality and procedural complications such as
19 bleeding and in-stent stenosis following PCI¹²⁻¹⁵. Furthermore, many clinicians are concerned that
20 the contrast load associated with angiography can lead to an accelerated loss of renal function and
21 an earlier need for renal replacement therapy^{16,18}.

22

23 Whilst many studies have explored outcomes following PCI for patients with CKD compared with
24 patients with normal renal function, few have compared outcomes for patients with CKD undergoing
25 PCI and those with comparable CKD not requiring PCI^{13,14,19,20}. As such, it is unclear whether the poor

1 outcomes previously described amongst patients with renal disease undergoing PCI are a result of
2 the PCI, or simply a marker of the high degree of morbidity and mortality associated with CKD itself.
3
4 This study aimed to describe mortality, cardiovascular and renal outcomes following PCI in patients
5 with CKD, as compared with age, sex and creatinine matched controls who had not undergone PCI.
6 We also explored the relationship between baseline biochemistry and haematology results and
7 mortality following PCI. In particular, we explored whether serum measurements of calcium,
8 phosphate and/or calcium-phosphate product are useful predictors of mortality amongst this
9 cohort, as dysregulation of calcium and phosphate metabolism is thought to be the main reason for
10 the medial vascular calcification that drives excess cardiovascular morbidity and mortality in patients
11 with renal disease.

1 **Methods:**

2 *Study population:*

3 We conducted a retrospective case-control study. Cases were individuals who had undergone
4 percutaneous coronary intervention between 1st January 2008 and 31st December 2014, and who
5 were known to the nephrology team at the time of intervention. Cases were identified by cross-
6 checking all individuals who underwent PCI in a tertiary cardiology centre (University Hospital of
7 Wales) during the study period, with a database of patients receiving care under a nephrology
8 service (Vital Data). Controls were individuals receiving care from nephrology services who had not
9 undergone percutaneous coronary intervention. Controls were age, gender and creatinine matched.
10 For individuals who underwent PCI, the indication for PCI, number of vessels treated, and location of
11 lesions treated were documented. Data regarding left ventricular function was not available in this
12 retrospective study. To minimise the risk of contrast induced nephropathy, the lowest volume of
13 low osmolar contrast agent was used for all individuals who underwent PCI, in line with current
14 guidelines²¹. We compared outcomes for cases and controls.

15

16 *Outcomes:*

17 Cases were followed up from the time of PCI to the end of the data collection period (1st July 2016)
18 or until the time of death. Controls were followed up from the date of the blood test upon which
19 age and creatinine-based matching was based until the end of the data collection period (1st July
20 2016) or until the time of death.

21

22 The primary outcome was mortality at the end of follow up. We also collected data regarding
23 changes in serum creatinine following PCI, to ascertain whether PCI was associated with acceleration
24 in the progression of CKD in the long term. We identified cases of contrast induced nephropathy
25 using the recognised definition of a relative (>25%) or absolute (≥ 44 $\mu\text{mol/l}$) increase in serum

1 creatinine from the baseline value within the first 48-72hours following percutaneous coronary
2 intervention²².

3

4 We also collected data on cardiovascular outcomes amongst cases. Specifically, we documented
5 whether they had experienced recurrent angina; an acute coronary syndrome; symptomatic heart
6 failure, or if they required further angiography/PCI prior to the end of the follow up period.

7

1 *Secondary analysis:*

2 We collected data regarding baseline creatinine, calcium, phosphate, calcium-phosphate product,
3 parathyroid hormone, white cell count, haemoglobin, platelet count, c-reactive protein, and total
4 cholesterol for all cases. Baseline measures were defined as the mean value of all results during the
5 3 months preceding PCI. We explored the relationship between these variables and mortality.

6

7 *Statistical methods:*

8 Survival time was compared between cases and controls using Kaplan Meier survival curves. Cox
9 regression modelling was subsequently used to obtain an adjusted hazard ratios (aHR) with 95%
10 confidence intervals. Data were right censored at the end date of the follow up period for patients
11 who remained alive.

12

13 For cases, we used a Wilcoxon rank test to compare serum creatinine at baseline with serum
14 creatinine at the end of the follow up period (due to the non-parametric distribution of the data).

15 The proportion of cases experiencing adverse cardiovascular outcomes were described.

16

17 Logistic regression modelling was used to explore the relationship between the baseline
18 haematology and biochemistry results of cases and mortality following PCI. Estimates of effects
19 between cases and controls are reported as crude odds ratios (ORs) and adjusted ORs (aORs)
20 alongside 95% confidence intervals. Adjusted odd ratios were derived after adjusting for age, gender
21 and baseline creatinine as appropriate.

22

23 Ethics and Information Governance: Patient data and outcomes were retrieved from internal
24 databases. This work represents an audit of outcomes in our department, and as such ethical
25 approval was not required.

26

1 Data analyses were carried out using IBM SPSS Statistics version 22 and Stata version 14.

1 **Results:**

2 We identified 144 patients who underwent PCI between 1st January 2008 and 31st December 2014,
3 who were known to the nephrology team at the time of intervention. 144 age, gender and creatinine
4 matched controls were identified. The mean follow-up period was 42.2 months for cases (range 1-
5 100 months) and 36.0 months for controls (range 0-87 months.)

6

7 Baseline characteristics are described in table 1. Characteristics were similar for cases and controls,
8 indicating appropriate matching of cases to controls. Indications for percutaneous coronary
9 intervention amongst cases are described in table 2a. The commonest indication for PCI was acute
10 coronary syndrome, followed by angina. A small proportion of cases underwent elective angiography
11 and percutaneous coronary intervention in the absence of any symptoms or signs of coronary
12 ischaemia, as part of the routine work up for renal transplantation and subsequent demonstration of
13 ischaemia.

14

15 The cases included 106 patients treated for single vessel coronary artery disease, 35 patients with 2
16 vessel disease and 1 with 3 vessel disease (table 2b). Lesions treated were located in the right
17 coronary artery lesions in 60 cases, the left circumflex in 17 cases and the left anterior descending
18 artery in 51 cases, and the left main stem vessels in 4 cases (table 2c). The remainder of treated
19 lesions related to side branch disease involving either large diagonal vessel or obtuse marginals.

20

21 PCI was associated with lower mortality compared to the non-PCI matched control group. Mortality
22 was high in both groups (28% at the end of follow up in cases, and 55% at the end of follow up
23 amongst controls). Time to mortality was lower amongst the control group, and this was statistically
24 significant (hazard ratio 0.46 (0.31, 0.69)) (figure 1.)

25

1 PCI did not lead to long-term deterioration in renal function. There was no statistically significant
2 change in creatinine amongst cases following percutaneous coronary intervention (mean creatinine
3 prior to intervention = 198 micromol/L, mean creatinine at the end of follow up =196 micromol/L,
4 p=0.52.)

5

6 Data regarding contrast induced nephropathy was available for 88 (61%) of cases, of whom 9
7 (10.2%) met the criteria for a diagnosis of contrast induced nephropathy.

8

9 Cardiac outcomes for cases are described in table 2b. Most patients had a favourable outcome.

10 82% remained free of symptomatic cardiovascular disease at the end of the follow up period. The
11 commonest adverse cardiovascular outcome was a recurrence of angina, affecting 19% of patients.

12

13 Univariate analysis revealed increased age, calcium, phosphate, and calcium-phosphate product to
14 be associated with a statistically significant increased risk of mortality amongst cases. Increased
15 haemoglobin was associated with a lower risk of mortality (table 3).

16

17 After adjusting for age and gender, an increased creatinine continued to be associated with
18 increased mortality after PCI (p=0.003.) After adjusting for age, gender and creatinine, serum
19 phosphate and haemoglobin were no longer significantly associated with mortality. However,
20 calcium-phosphate product was still significantly associated with an increased mortality (p=0.04)
21 (table 3).

22

1 Discussion

2 Our results confirm that mortality is high amongst patients with CKD, as would be expected from the
3 results of previously published studies^{23,24}. Whilst studies have previously demonstrated high
4 mortality amongst patients with CKD undergoing PCI as compared with individuals with normal renal
5 function undergoing PCI, it is unclear whether the excess mortality is a result of PCI, or whether it
6 reflects the high levels of mortality associated with renal disease itself. In order to elucidate this, it
7 is necessary to compare outcomes between individuals with renal disease undergoing PCI, and
8 individuals with comparable CKD not requiring PCI. Our study used a case-control approach to
9 compare outcomes between individuals with renal disease undergoing PCI and creatinine-matched
10 controls who did not undergo PCI.

11

12 The first key finding from our study is that patients with renal disease who underwent PCI had lower
13 mortality than creatinine-matched controls. This data would suggest that PCI may protect against
14 short term mortality in a cohort of patients with renal disease. This is in-keeping with the findings
15 of a previously published systematic review which concluded that early angiography and/or PCI
16 conferred a survival benefit, at least in those with early-moderate CKD²⁵. We therefore suggest that
17 the excess of mortality following PCI previously documented amongst patients with renal disease is
18 likely to reflect the poor prognosis associated with having renal disease in itself, rather than being
19 directly related to the PCI procedure.

20

21 In addition to the perceived high rates of mortality amongst CKD patients undergoing PCI, many
22 clinicians have expressed concern that PCI may lead to an accelerated loss of renal function amongst
23 patients with CKD as a result of the contrast burden associated with the procedure^{16,18}. The concern
24 that PCI may hasten time to end stage renal failure and the need for renal replacement therapy has
25 contributed to the reluctance to offer PCI to many patients with renal disease¹². 10.2% of cases
26 developed contrast induced nephropathy, which is comparable with the incidence of contrast

1 induced nephropathy in previously published studies^{26,27}. Importantly we did not observe an
2 accelerated rate of decline in renal function in the long-term following PCI amongst our cases.
3 Whilst one of the limitations of this study is the relatively short follow up period (mean 42.24
4 months, range 1-100 months), deteriorating renal function as a direct result of PCI is usually due to
5 an acute effect of contrast and associated acute kidney injury, and would have been apparent during
6 this period of follow up^{16,18}.

7

8 Since our data suggests that PCI confers a survival advantage in this group, and is not associated with
9 an accelerated decline in renal function amongst patients with CKD, we suggest that having CKD in
10 itself should not be considered a contraindication to PCI. Furthermore, since patients with renal
11 disease have high mortality rates independently of the need for coronary revascularisation, much of
12 the focus of care for patients with progressive renal disease is on trying to maximise quality of life
13 and minimise distressing symptoms^{23,24}. Amongst our cohort, 81% did not experience recurrent
14 angina during the follow up period, thereby suggesting PCI had a positive impact on their symptom
15 profile, at least in the short term. We therefore believe that PCI is a treatment that has the potential
16 to dramatically improve quality of life in patients with renal disease, without accelerating the
17 progression of their underlying renal disease.

18

19 We recognise that our case mix includes patients with a broad spectrum of renal disease. We
20 therefore sought to identify factors associated with an increased risk of mortality amongst our cases.
21 As expected, we found that increased creatinine was associated with a higher mortality post
22 procedure, independently of age and gender. Similarly, a high serum phosphate and low serum
23 haemoglobin, both of which are markers of severe renal disease, were significantly associated with
24 higher mortality. After correcting for creatinine, neither remained significantly associated with
25 mortality, illustrating the fact that they act as surrogate markers of the severity of renal disease in

1 this setting. These findings support our observation that the severity of renal disease is one of the
2 main predictors of mortality amongst this cohort.

3
4 The only biochemical marker that remained significantly associated with mortality, after adjusting
5 for age, gender and creatinine, was the calcium-phosphate product. It is well recognised that in
6 patients with CKD, the excess cardiovascular mortality is not due to the traditional model of
7 atherosclerotic disease, but is instead a result of vascular calcification that occurs secondary to
8 disruption of calcium and phosphate homeostasis⁷⁻⁹. Studies have previously demonstrated that
9 calcium-phosphate product may be a useful tool in estimating the risk of mortality and
10 cardiovascular disease in patients with CKD²⁸⁻³⁰. Our data suggest that calcium-phosphate product
11 may also be useful in predicting mortality following PCI in this group. In addition, since calcium-
12 phosphate product may be affected by several modifiable factors such as diet, the use of phosphate
13 binders and effective vitamin D replacement, it is possible that efforts to lower calcium-phosphate
14 product could lead to more favourable outcomes in this group. Further studies are required to
15 explore this³⁰.

16
17 Although this study to our knowledge is the first to compare the outcome of PCI in CKD patients
18 compared to an age matched control group, a limitation of this study is that the majority of cases
19 underwent PCI to treat single vessel disease with the highest proportion of treated vessels being
20 RCA. , We acknowledge therefore that we should be cautious in generalising the findings to
21 individuals undergoing PCI for multi vessel disease who by definition have more severe coronary
22 artery disease. ~~and are likely to have higher levels of exposure to contrast during the procedure.~~
23 However, our findings remain relevant to clinical practice, as data from the British Cardiovascular
24 Intervention Society Adult Interventional Procedure Audit 2016 demonstrate that nationally, the
25 vast majority of PCI procedures are undertaken to treat single vessel disease (77.2% of all PCI)³¹.
26 ~~Whilst in our study the commonest location of lesions treated was the right coronary artery,~~

1 nationally the commonest location for lesions treated by PCI is the left anterior descending artery²¹.

2 Further studies are however required to establish whether there is an association between the

3 location of lesions treated and outcomes in patients with chronic kidney disease.

4

5 **Summary**

6 We have demonstrated that PCI was associated with a reduction in mortality, and did not lead to an

7 acceleration in the progression of CKD in a cohort of patients with CKD compared with creatinine

8 matched controls who did not undergo percutaneous coronary intervention. We therefore suggest

9 that CKD in itself should not be considered a contraindication to PCI. The decision to undertake PCI

10 should be considered on an individual patient basis, and should take into account the severity of

11 their CKD. Calcium-phosphate product may be a useful tool in identifying patients with renal disease

12 who are at high risk of mortality following PCI.

- 1 **Acknowledgments:** Nil.
- 2 **Funding:** Nil.
- 3 **Conflict of interest:** None of the authors have any conflicts of interest or disclosures.
- 4 **Author contributions:** LAA was involved in collating the data for cases and was responsible for
- 5 undertaking statistical analysis and writing the manuscript. RDP was responsible for identifying
- 6 matched controls, collating the data for controls, and also provided statistics advice and support. JH
- 7 was responsible for identifying cases and extracting biochemistry and haematology data from
- 8 internal databases. KLD, RAA and AOP supervised the project, provided critical feedback and helped
- 9 shape the research, analysis and manuscript. All authors discussed the results and contributed to
- 10 the final manuscript.

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12 [web.pdf](http://www.bcis.org.uk/wp-content/uploads/2018/03/BCIS-Audit-2016-data-ALL-excluding-TAVI-08-03-2018-for-web.pdf). Accessed April 2019.
- 13

	Cases	Controls
Age (years)	69 (62.0, 77.0)	69 (61.7, 77.4)
Creatinine (micromol/L)	142 (103, 206)	142 (102, 209)
Gender	103 (72%)	103 (72%)
Diabetes	41 (28.4%)	45 (31.3%)

- 1 **Table 1:** Baseline characteristics of cases and controls. Values are median, interquartile range (as
- 2 data was positively skewed). Gender is described as the number and % of males in each group. The
- 3 number and % of individuals with co-existing diabetes are also described.

1

	Proportion of cases
Acute coronary syndrome	86 (60%)
Angina	42 (29%)
Investigation of heart failure	3 (2%)
Pre renal transplant	6 (4%)
Ventricular Tachycardia of unknown origin	2 (1%)
Unknown	5 (4%)

2 **Table 2a:** Indication for percutaneous coronary intervention.

	Proportion of cases
Single vessel coronary artery disease treated	106 (74%)
Two vessel disease treated	35 (24%)
Triple vessel disease treated	1 (1%)

3 **Table 2b:** Number of vessels treated.

	Proportion of lesions
Right coronary artery	60 (34%)
Left circumflex artery	17 (10%)
Left anterior descending artery	51 (29%)
Left main stem vessels	4 (2%)
Side branch disease (large diagonal vessel or obtuse marginals)	45 (25%)

4 **Table 2c:** Location of lesions treated

5

6

7

8

	Proportion of cases
Death	40 (27.8%)
Recurrent angina	27 (18.8%)
Recurrent ACS	14 (9.7%)
Heart failure	18 (12.5%)
Repeat angiogram needed	26 (18.1%)
Further PCI	23 (16%)

1 **Table 3:** Cardiovascular outcomes following percutaneous coronary intervention.

1

	Odds Ratio ± 95% CI	p value	Adjusted Odds Ratio ± 95% CI	p value
Age	1.60 (1.16, 2.23)	0.01		
Gender	0.94 (0.41, 2.11)	0.87		
Creatinine	1.00 (1.00, 1.01)	0.01	1.00 (1.00, 1.01)*	0.003
Calcium	0.25 (0.01, 4.92)	0.81	0.78 (0.03, 20.69)**	0.877
Phosphate	5.57 (1.56, 19.89)	0.008	6.43 (0.97, 42.64)**	0.054
Calcium Phosphate product	2.32 (1.24, 4.35)	0.008	2.34 (1.03, 5.34)**	0.042
PTH	1.04 (0.99, 1.09)	0.15	1.04 (0.99, 1.10)**	0.146
Hb	0.97 (0.94, 0.99)	0.005	0.98 (0.95, 1.01)**	0.220
WCC	1.05 (0.90, 1.24)	0.53	1.08 (0.91, 1.28)**	0.399
Platelets	1.00 (0.96, 1.00)	0.89	1.00 (1.00, 1.01)**	0.485
CRP	1.00 (0.99, 1.02)	0.62	1.00 (0.99, 1.02)**	0.784
Total Cholesterol	1.17 (0.81, 1.70)	0.40	1.27 (0.84, 1.92)**	0.267

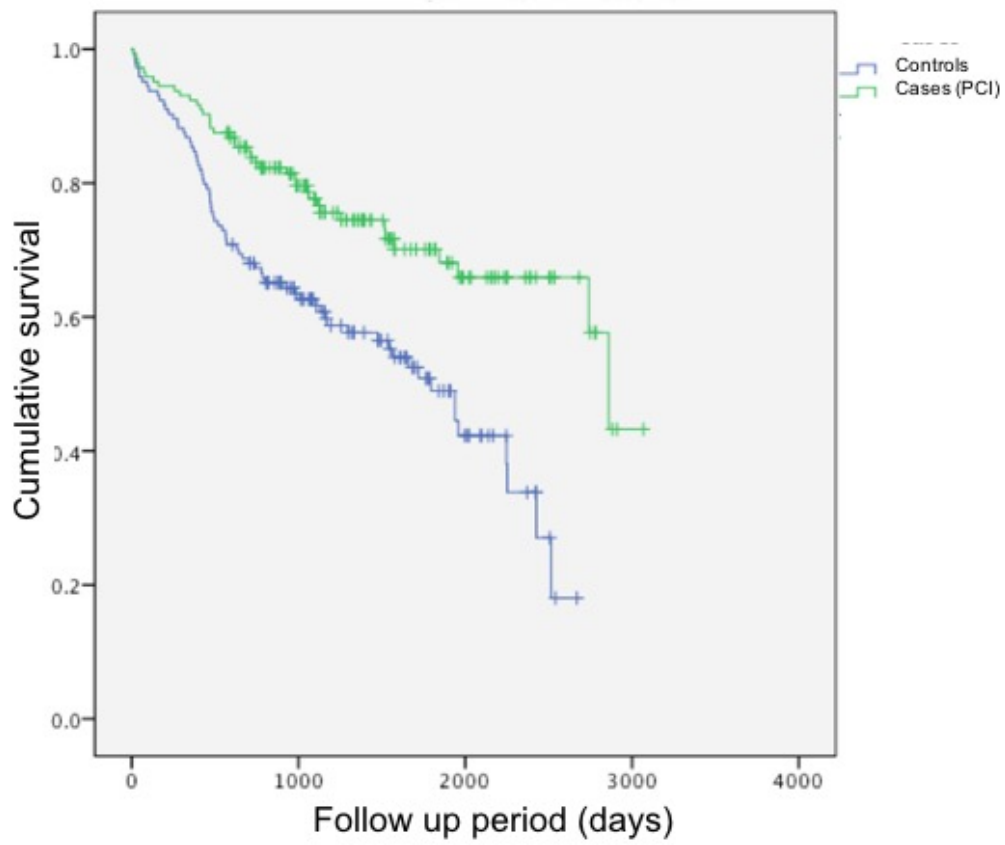
2 **Table 3:** Relationship between baseline biochemistry and haematology results and mortality.

3 Results are crude and adjusted odds ratios with 95% confidence intervals and p values derived from

4 logistic regression models.

5 *Adjusted for age and gender

6 ** Adjusted for age, gender, creatinine



1

2 **Figure 1:** Kaplan Meier Curves demonstrating time to mortality (in days) amongst cases and

3 controls.