Survival comorbidity

Mrs Retha Steenkamp
Senior Statistician
UK Renal Registry

UK Renal Registry
2011 Annual Audit Meeting

Importance of co-morbidities in survival

- Co-morbidities collected by the Renal Registry
- Missing co-morbidities
- Accuracy of co-morbidities
- Importance of co-morbidities

Co-morbidities collected by the Renal Registry

UK Renal Registry comorbidities

15 Comorbidities:

- Heart disease: angina, MI in past 3 months, MI >3 months ago, CABG/angioplasty, heart failure
- Non-cardiac vascular disease: cerebrovascular disease, claudication, ischaemic/neuropathic ulcers, amputation for PVD, non-coronary angioplasty/vascular graft
- Other: diabetes (not cause of ERF), liver disease, *'smoking'*, malignancy, COPD

Drawbacks of current comorbidity data

- Important comorbidities not collected: dementia and mobility
- Heart failure not collected by all centres
- Degree of severity not collected
- Smoking: current smoker, smoking within last year
- Malignancy

Missing co-morbidities

Co-morbidity completeness of incident patients, 2004-2009

	2004	2005	2006	2007	2008	2009	2004-2009
Number of renal centres	50	56	57	62	63	63	
Number of new patients	4,888	5,531	5,811	6,161	6,244	6,078	**34,713**
Number of patients with comorbidity data	2,549	2,634	2,717	3,010	2,920	2,697	**16,527**
Percentage	52.1	47.6	46.8	48.9	46.8	44.4	**47.6**
Median % for centres returning >0% comorbidity	63.9	51.1	58.1	62.6	66.7	66.7	**61.9**

Problems caused by missing co-morbidity data

- Not adjusting for comorbidity might lead to inadequate case-mix adjustment

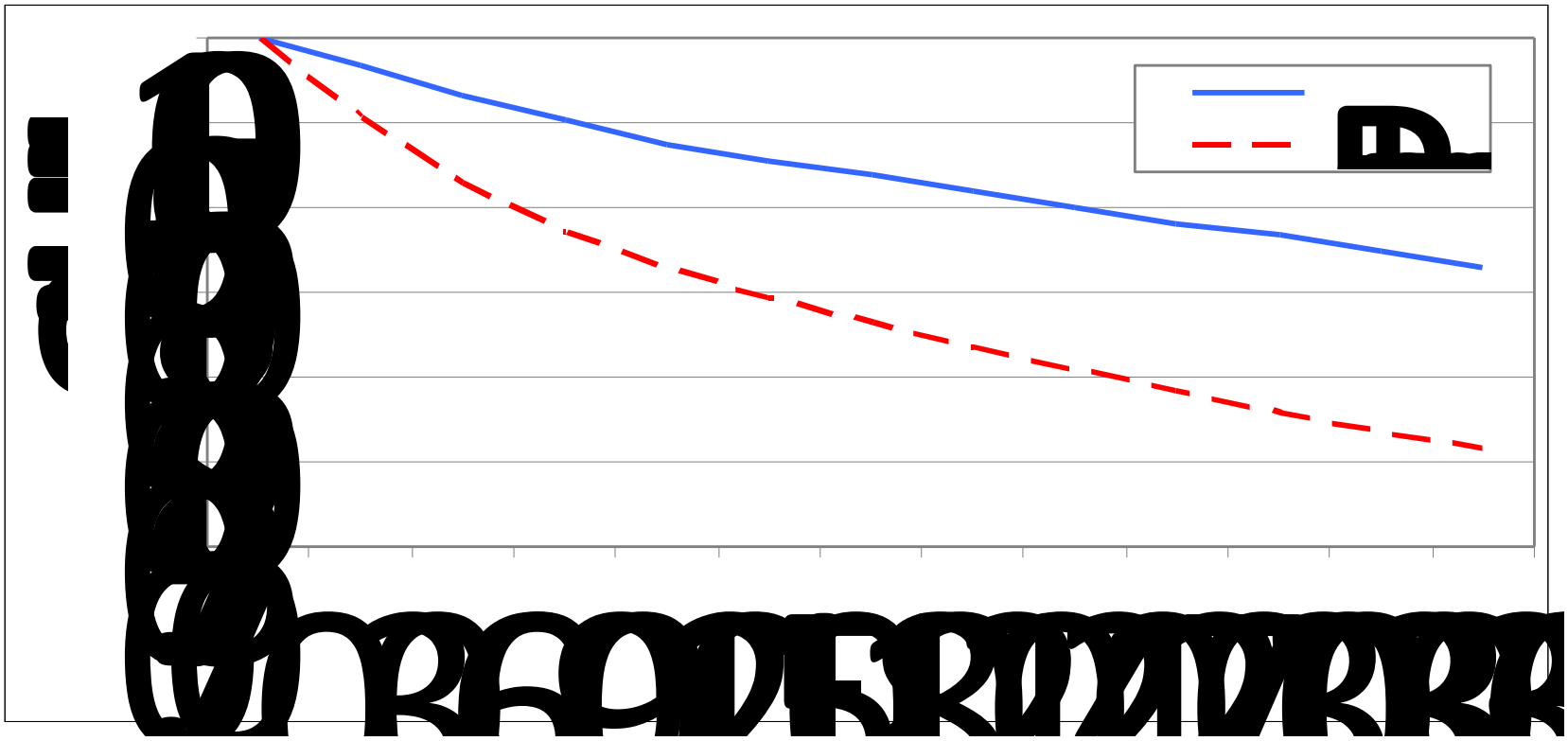
- Case-mix adjustment in statistical models are limited to complete cases
  - Loss of statistical power
  - Loss of information
  - Selection bias
  - Lack of generalisability

- Most standard statistical methods assumes complete data

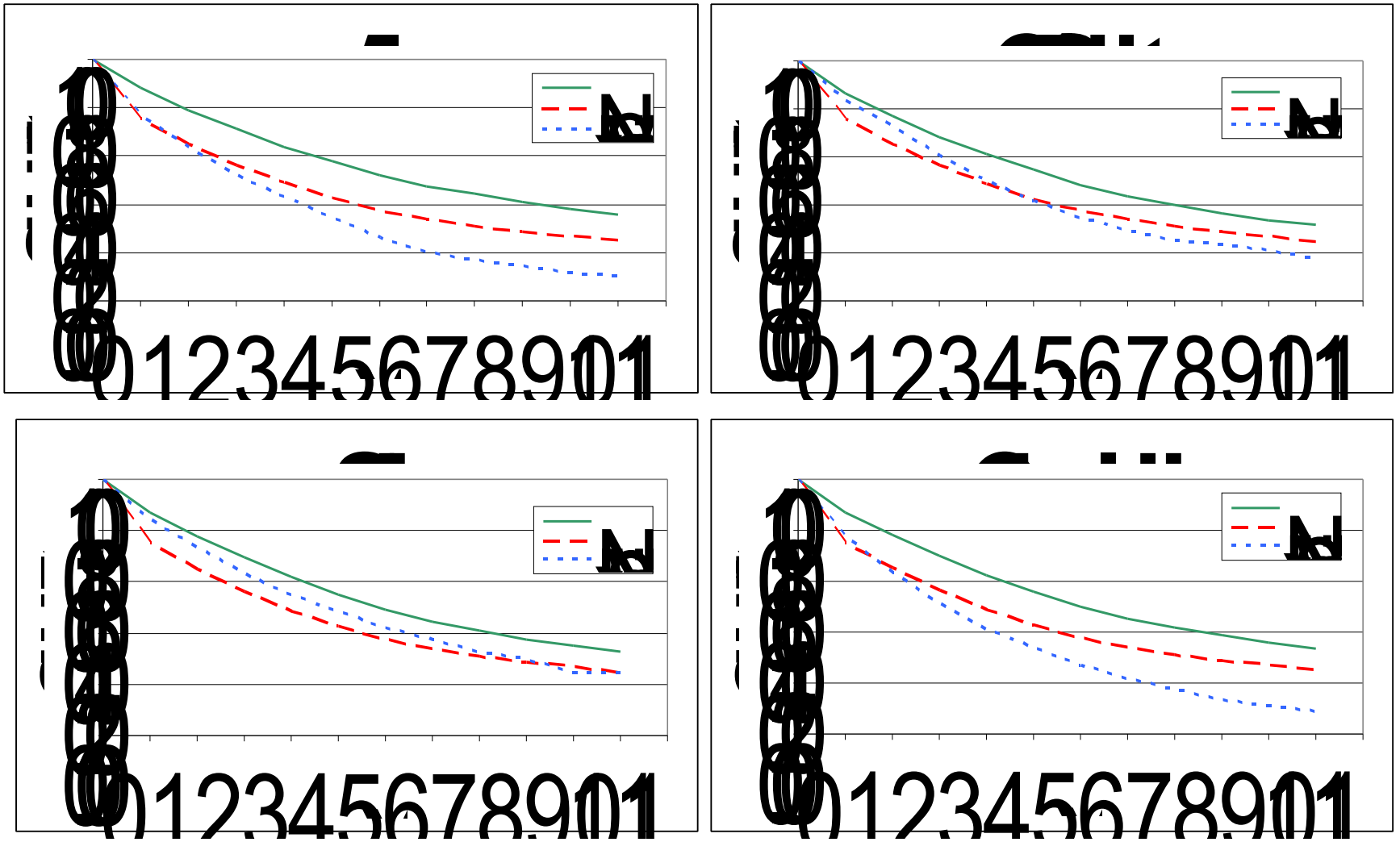
Patterns and effects of missing co-morbidity data - 1

- Patients with missing co-morbidity data do considerably worse
- Proportion of patients with co-morbid condition may be higher amongst those with missing co-morbidity data
- Multiple imputation found a higher prevalence of co-morbid conditions than seen in those with available data

Unadjusted 1 year survival of incident RRT patients, 1997-2007



Survival per comorbidity for incident RRT patients, 1997-2007



Patterns and effects of missing co-morbidity data – *2*

- Treating missing co-morbidity data as indication of an absent co-morbidity (i.e. a tick only if yes policy) would lead to an attenuation of the association between co-morbidity and survival

Accuracy of co-morbidities

Accuracy of co-morbidity data – 1

- 17 regularly collected co-morbidities (USRDS data) were validated against co-morbidities collected for the ICED

- Findings for sensitivity:
  - reasonably good (>0.80) for only 1 co-morbidity
  - moderate (0.77-0.67) for 4 co-morbidities
  - intermediate (0.52-0.40) for 7 co-morbidities
  - poor (<0.40) for 5 co-morbidities
  - Average across all 17 co-morbidities was 0.59%
  - Higher in PD and diabetic patients
  - Less accurate for each co-morbidity added

- The study has shown that co-morbidities were severely underreported

Longenecker , JASN 2000

Accuracy of co-morbidity data – 2

- Self-reporting of 8 co-morbidities compared to medical records and physician reports
- Self-reporting varied with specific co-morbid condition. Substantial agreement for diabetes (k=0.93) and coronary artery intervention (k=0.79), but poor agreement for COPD (k=0.20)
- Co-morbidities reported by the physician equal or lower to patient self-reporting
- The study has shown that co-morbidities were severely underreported

Merkin, Journal of Clinical Epidemiology, 2007

Accuracy of co-morbidity data – 3

- The UK Renal Registry performed a data validation exercise in the Welsh centres
- Registry data was validated for completeness and accuracy against information held in the unit's renal IT system and patient notes
- Twenty patients were randomly selected from each unit
- Only 2 renal centres were found to regularly capture co-morbidity data and completeness and accuracy was 87-100%

Accuracy of co-morbidity data – 4

- The ANZDATA registry investigated the accuracy of co-morbidities:
  - confirmed co-morbid conditions were accurately reported
  - result opinion based in the absence of a gold standard

  (Karamadoukis, NDT, 2009)

- Canadian Organ Replacement Register (CORR) assessed the quality of data collected by comparing with medical charts:
  - co-morbidities were under-reported
  - sensitivities ranged from 89% for hypertension to 47% for PVD
  - specificity was >0.93 for all co-morbidities except hypertension

  (Moist, CJASN, 2011)

Importance of co-morbidities

Importance of co-morbidities in patients on RRT -1

- The selection of modality and patient outcomes are affected by case-mix factors such as co-morbidity
- Well completed co-morbidity data will enable the selection of patients based on their co-morbidities for further study
- Individual patient co-morbidity and prognosis
- UK country and centre level comparisons and co-morbidities
- International co-morbidity comparisons

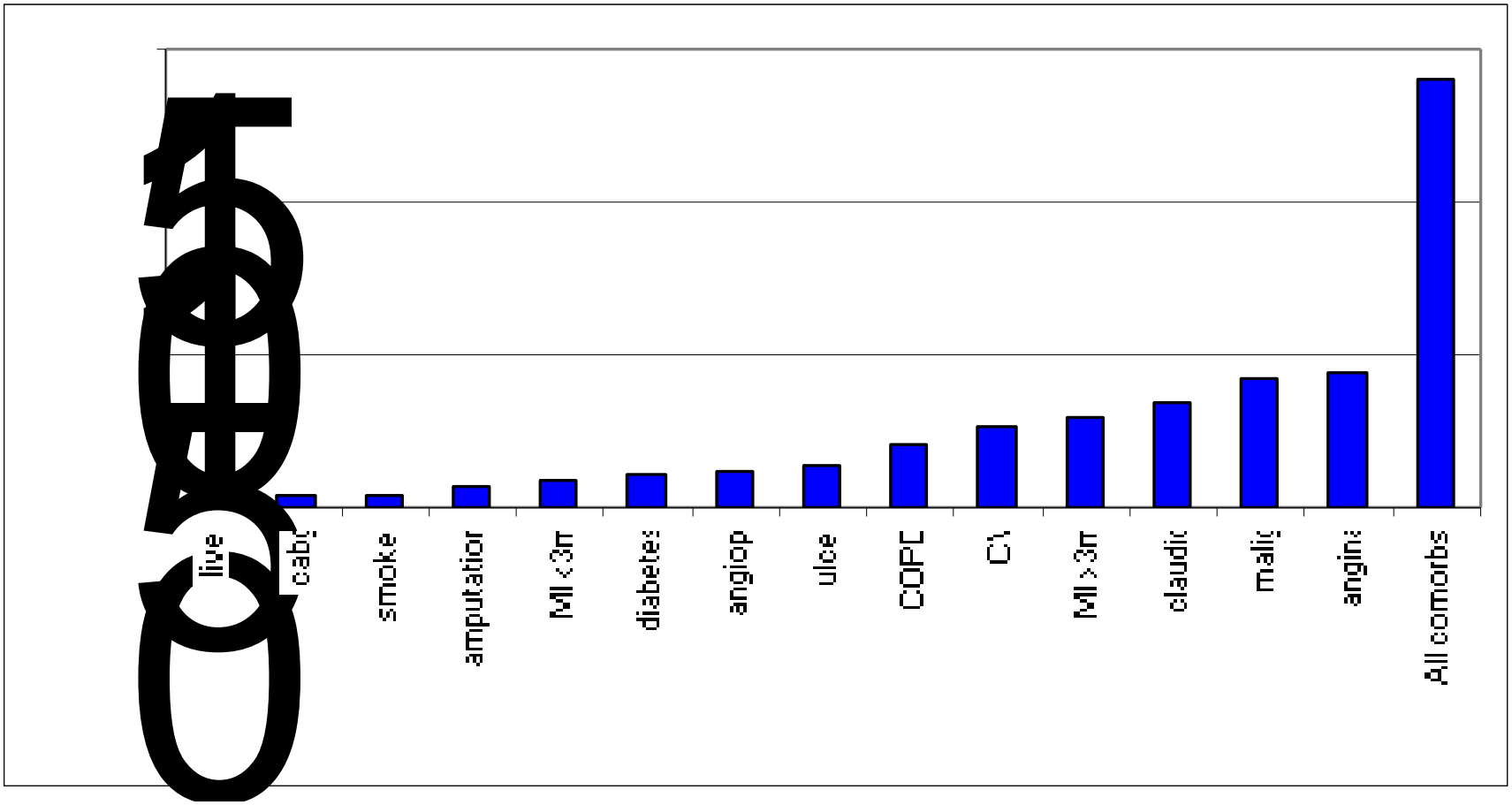
Variance explained by co-morbidity

- A study by van Manen *et al*. compared survival between 5 European countries

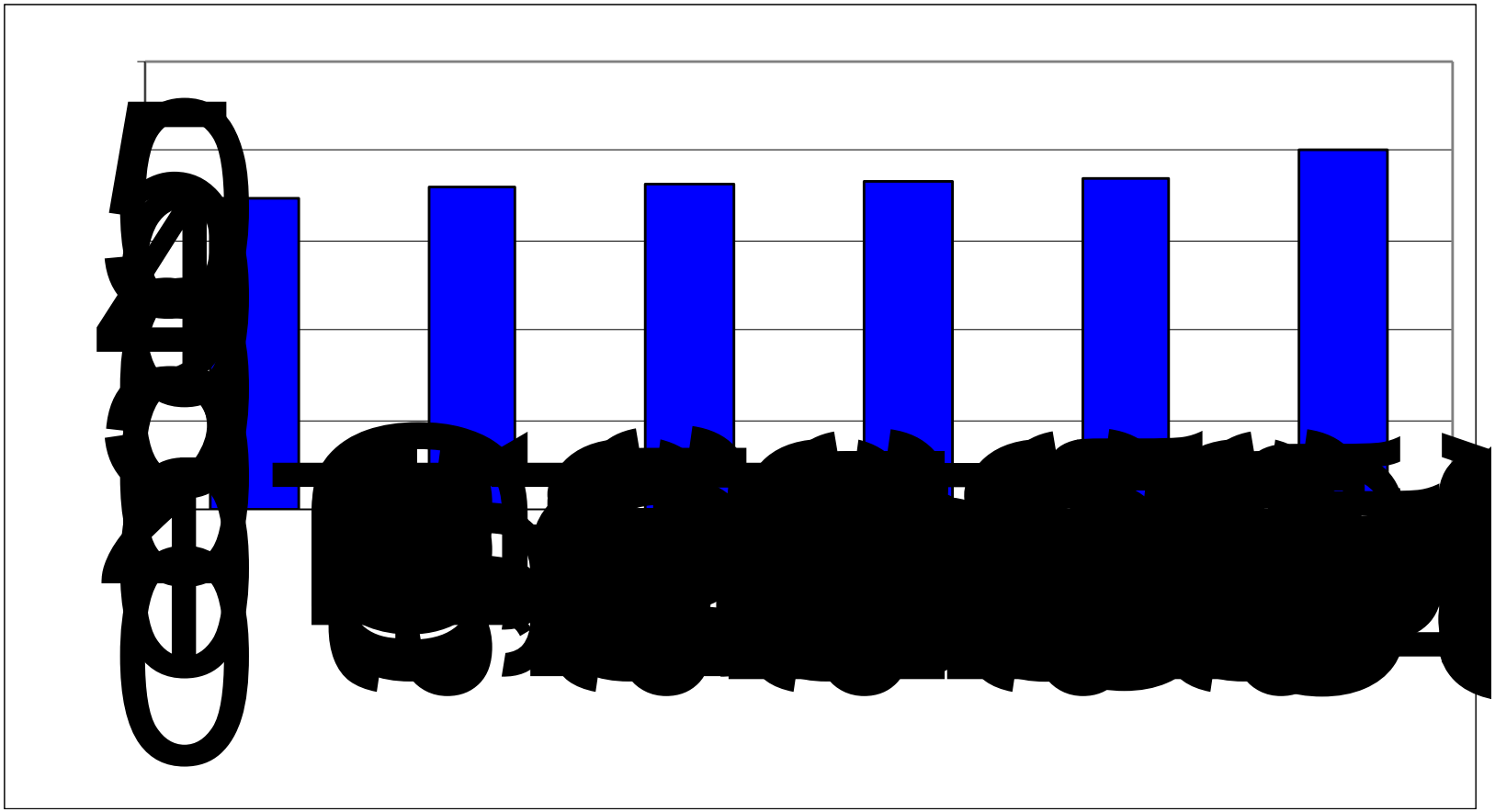
- After adjusting for age, gender, PRD, modality and country, adjusting for 5 co-morbidities (diabetes mellitus, ischaemic heart disease, PVD, cerebrovascular disease and malignancy) explained only 1.9% of additional variation in outcome on top of the 14.4%

van Manen, NDT, 2007

Variance explained by individual comorbidities, survival after 90 days



Additional variance explained, survival after 90 days



Prognostic co-morbidities

- Should co-morbidity collection be reduced to a core set with a strong association to outcome?

- A study by Miskulin *et al.* tried to determine which co-morbidities are most prognostic and whether co-morbidities continue to contribute to survival once laboratory and clinical factors have been accounted for

Prognostic co-morbidities - 2

Result:

- 17 out of a total of 45 co-morbidities are most prognostic and provide equivalent discrimination and explained variance compared to the 45 co-morbidities

- Variance explained increased from 13% to 17% upon adding co-morbidities to demographic and laboratory/clinical parameters

Miskulin, CJASN, 2009

Prognostic co-morbidities - 3

Hospitalised for CHF in past 12 mo	Amputation as result of PVD
Hypertension	Use of home oxygen
Depression within the past 12 mo	Dementia
Previous diagnosis of PVD	Substance abuse within past 12 mo
Diabetes treated with insulin	Gastrointestinal bleed in past 12 mo
MI ever	Stroke with deficit
COPD	Ascites within past 12 mo
Recurrent cellulitis/gangrene	HIV/AIDS
History of cancer	

CHF, Congestive heart failure
PVD, Peripheral vascular disease
MI, Myocardial infarction
COPD, Chronic obstructive pulmonary disease

Is the severity of co-morbidities important?

- A study by Miskulin *et al.* investigated if the change in co-morbidity predict survival in incident dialysis patients

- Results: the increase in the severity of existing co-morbid conditions and additional co-morbidities after start of RRT are important prognostic markers, independent of other case-mix factors

Miskulin, AJKD, 2003

Is the severity of co-morbidities important?

- Large multicentre study compared existing co-morbidity indices (Khan, Davies and Charlson) with a new index that included disease severity

- Charlson index discriminated best

- Adding severity grading for 4 co-morbid conditions did not improve discrimination

van Manen, AJKD, 2002

Prognostic co-morbidities based on UKRR data

Prognostic risk factor	1 year HR	3 year HR	5 year HR
Co-morbidities			
Liver disease	1.68	1.57	1.62
Ulceration	2.02	1.57	1.60
Malignancy	2.52	1.88	1.82
MI<3m	1.65	1.50	1.47
MI >=3m	1.54	1.52	1.49
Cerebro VD	1.59	1.40	1.30
Interactions			
Diab*age	0.96	0.96	0.97
Ulcer*age	1.05	1.04	1.04
Malig*age	0.97	0.98	0.97

Conclusion

- Outcome differences between patients with and without co-morbidity
- Co-morbid conditions are important predictors of outcome
- Important in explaining differences between centres and UK nations and important for individual prognosis
- Validation exercises have shown that co-morbidities are severely under-reported
- Co-morbidities do add to variance explained and add a modest amount of independent prognostic information that cannot be substituted by clinical/laboratory parameters

Acknowledgements

Many thanks to:

- UK renal centres and patients
- Data and systems staff (UKRR)
- Biostatisticians (UKRR)

Prognostic survival prediction tool

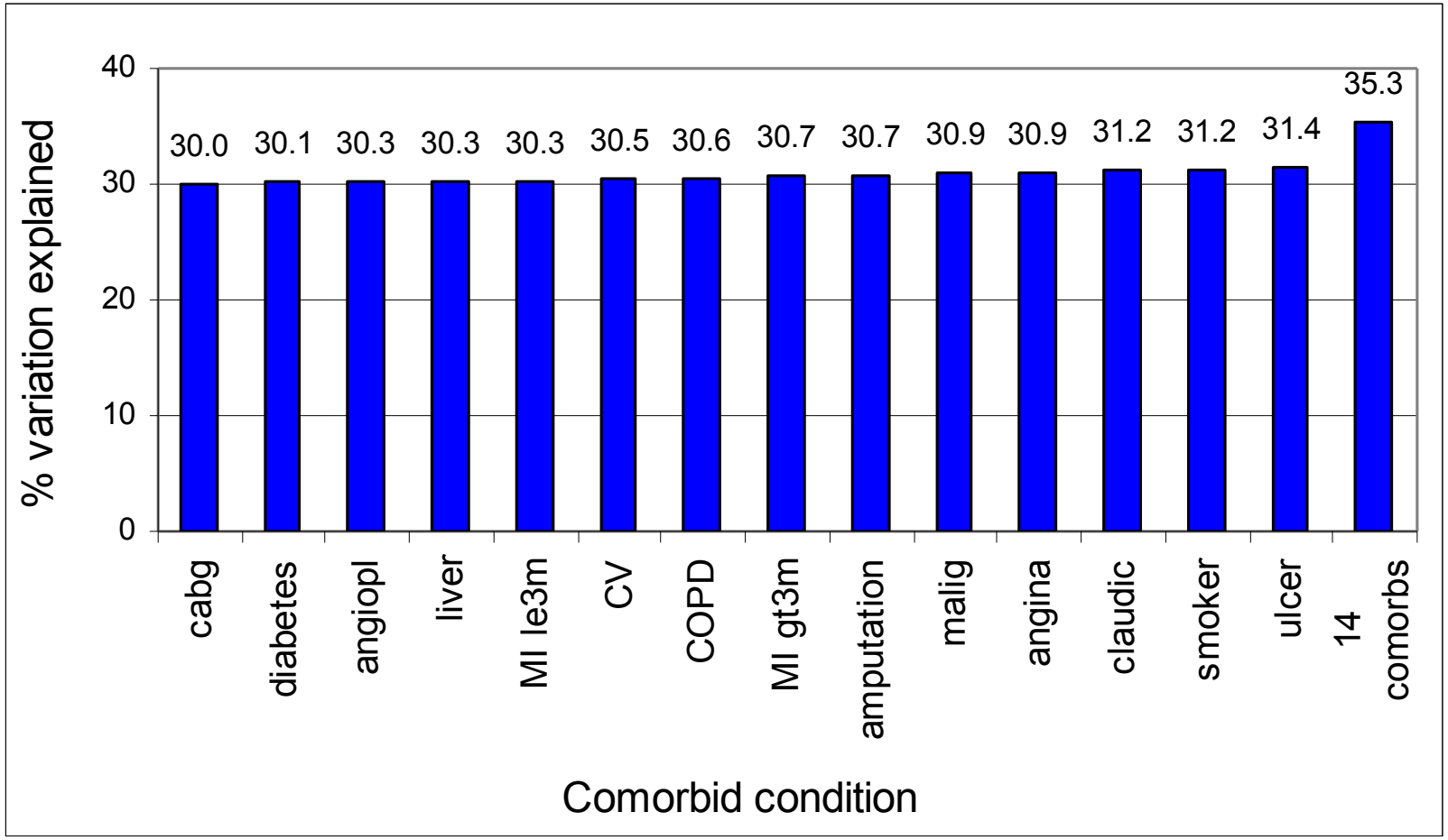
- Prognostic information is rarely discussed with patients because of clinical uncertainty about accuracy

- Promising methods for formulating prognosis applied to ESRD:
  - Survival estimates using a statistical model
  - The clinician's prediction of survival
  - Combination of the two methods

- Prognostic survival tool was developed and validated for HD population

LM Cohen, R Ruthazer, AH Moss, MJ Germain: Predicting six-month mortality for patients who are on maintenance hemodialysis. Clin J Am Soc Neprol 2010; 5:72-79

Variance explained by individual comorbidities after adjusting for age and gender, survival after 90 days



What is multiple imputation?

Developed by Rubin in a survey setting as a statistical technique for analysing data sets with missing observations

1. Imputation:

   Missing values are replaced by imputations

   The imputation procedure is repeated many times with each dataset having the same observed values and different sets of imputed values for missing observations

2. Analyse using standard statistical methods

3. Pooling parameter estimates

Missing data mechanism and multiple imputation

- *Missing Completely At Random (MCAR)*:

  The probability of a value being missing does not depend on observed or unobserved measurements

- *Missing at Random (MAR)*:

  Given the observed data, the missingness mechanism does not depend on the unobserved data.

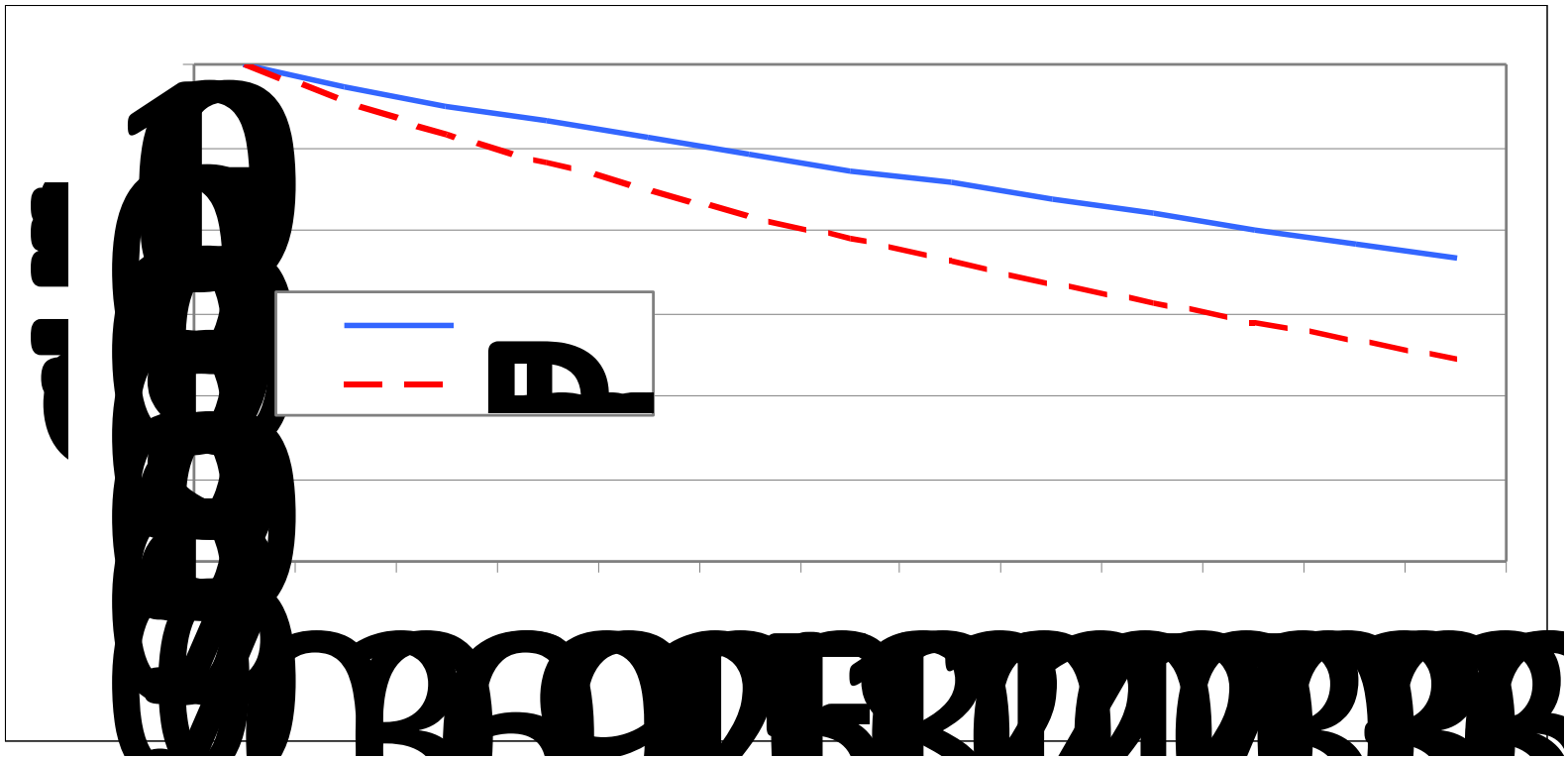
- *Missing not at Random (MNAR):*

  Even when accounting for all the available observed information, the reason for being missing still depends on the unseen observations themselves

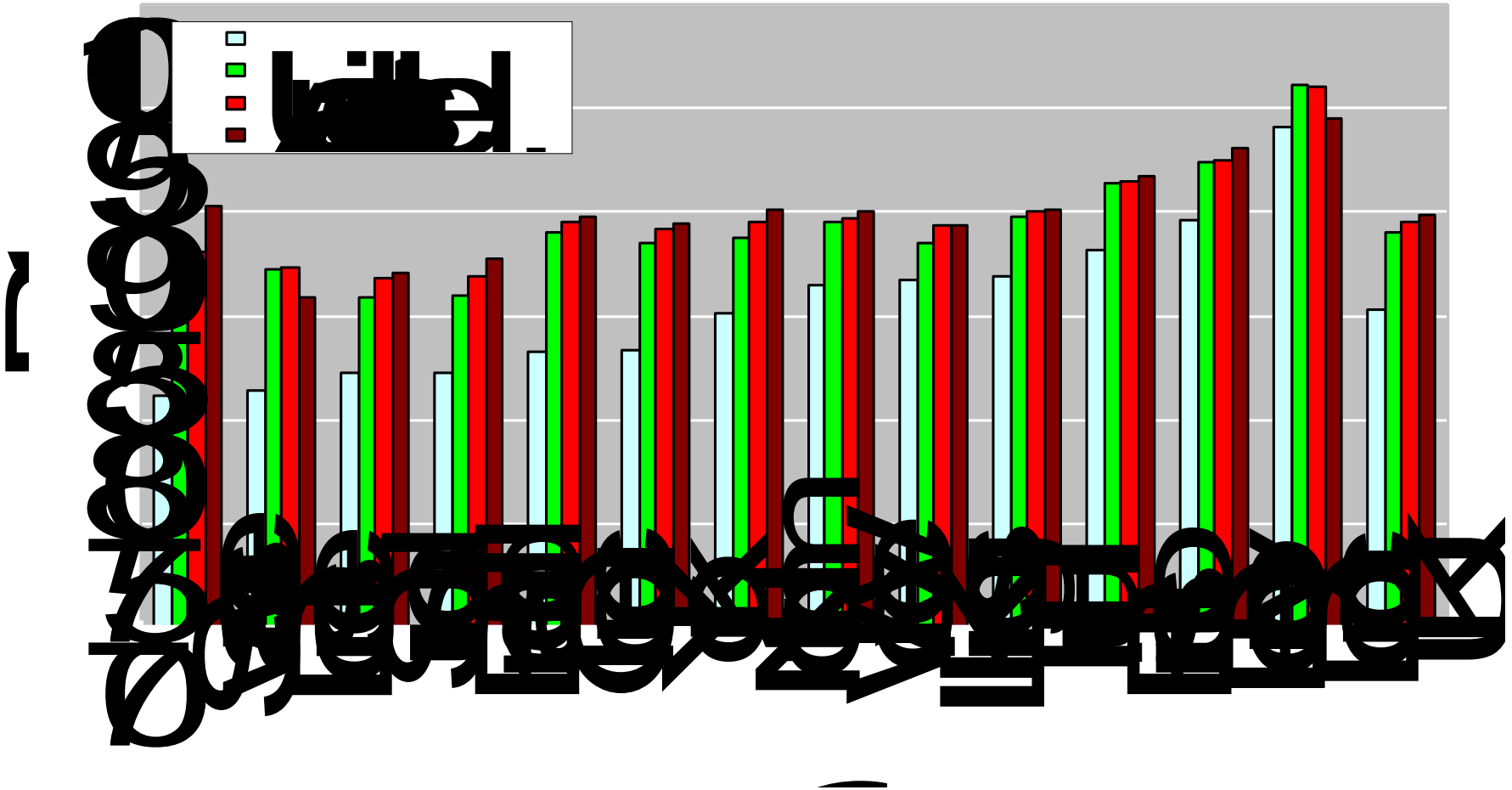
Cox model estimates

Prognostic risk factor	1 year HR	3 year HR	5 year HR	Prognostic risk factor	1 year HR	3 year HR	5 year HR
Demographic							
Age at start	1.06	1.06	1.06	Quintile 1	0.68	0.79	0.73
Ethnicity	-	0.62	0.73	Quintile 2	0.73	0.94	0.86
PRD				Quintile 3	0.71	0.81	0.78
• Glom	1.00	1.00	1.00	Quintile 4	1.44	1.14	1.00
•Diab	1.06	1.44	1.58	Quintile 5	1.00	1.00	1.00
•Hypert	1.48	1.62	1.51	Start of RRT	0.68	0.71	0.77
•Other	2.00	1.90	1.89	Treat start	0.54	0.70	0.79
•Polyc	0.86	0.75	0.98	Diabetes	2.17	1.85	1.67
•Pyelo	1.02	1.43	1.34				
•RVD	1.30	1.61	1.70				
•Uncert	1.33	1.43	1.45				

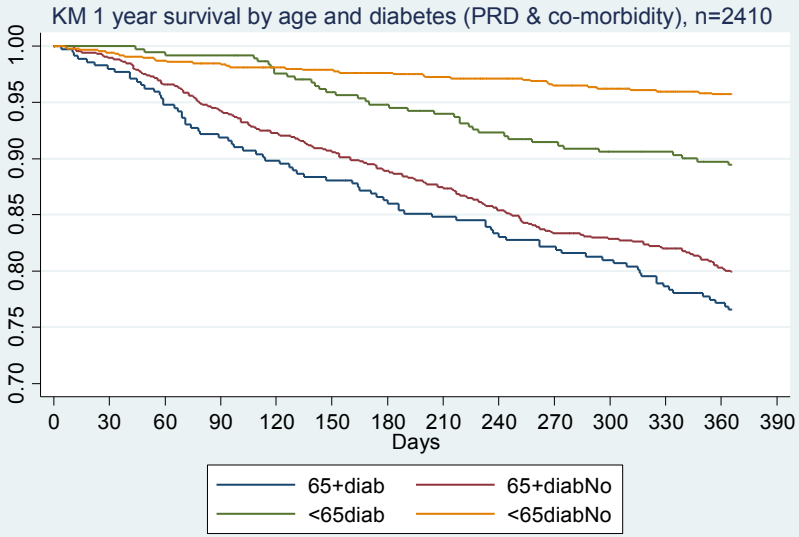
Unadjusted 1 year after 90 days survival of incident RRT patients, 1997-2007

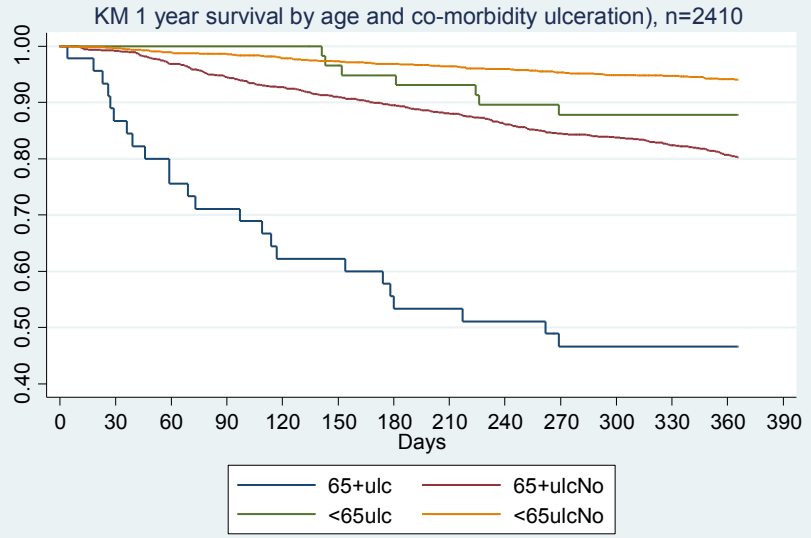


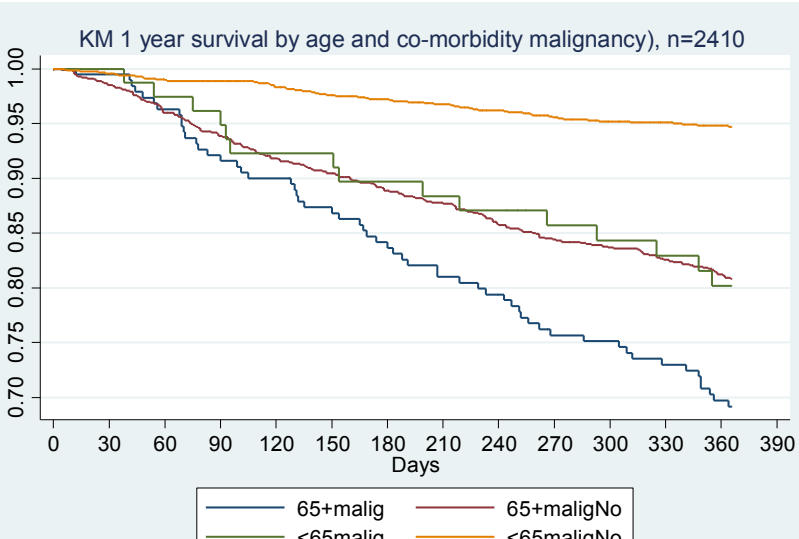
Survival 1 year after 90 days for incident RRT patients in 2003-2007, adjusted for age, diagnosis and comorbidity



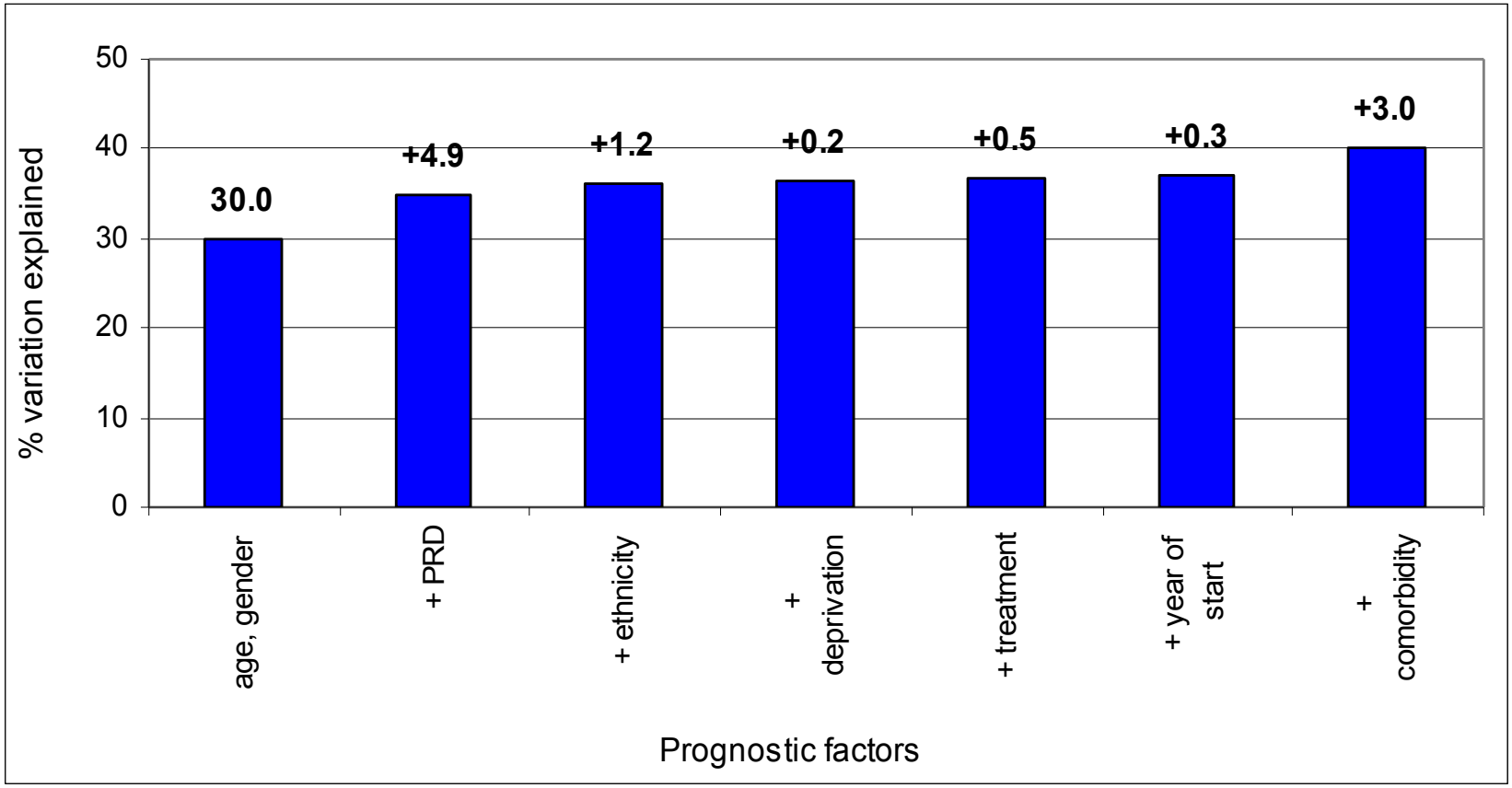
Interactions in the prognostic model







Additional variance explained by prognostic factors, survival after 90 days



Recording of comorbidities

- Comorbidities are captured at start of renal replacement therapy (RRT)
- Manual data entry into the renal IT system
- Process of data entry varies by renal centre:
  - Directly entered by senior medical staff (consultant)
  - Entered from updated form by data management staff

Percentage prevalence of co-morbidity in those with complete data and in those with missing data

Co-morbidity	Complete data %	Imputed %	Combined total %	Difference %
Angina	16.9	19.3	18.3	2.4
Angioplasty (non-coronary)	3.3	4.6	4.1	1.3
Claudication	8.8	10.8	9.9	2.0
COPD	6.7	8.0	7.5	1.3
Diabetes (not causing RF)	6.0	10.6	8.2	4.6
Ulceration	3.5	5.3	4.6	1.8
Liver disease	2.2	3.3	2.8	1.1
Malignancy	11.3	13.3	12.5	2.0
MI ≤ 3months	2.6	4.1	3.5	1.5
MI >3 months	10.8	12.6	11.9	1.8
PTCA/CABG	6.4	7.1	6.8	0.7
Amputation	2.1	3.1	2.7	1.1
Cerebro-vascular	10.5	12.1	11.4	1.6
Smoker	16.4	17.6	17.2	1.2

Figure 6.16: The effect on 1 year after 90 day survival after adjustment for age, PRD and comorbidity, 2004-2008 cohort