Predict Pursuit: A Personalized Approach for Recommending Early Percutaneous Coronary Intervention (PCI) to Diabetic Patients

Jinsung Yoon and Mihaela van der Schaar,
Department of Electrical Engineering, University of California, Los Angeles

Summary:
Our proposed personalization method, *Predict Pursuit*, can discover the heterogeneity of patients groups for the specific intervention with statistical significance (*homogeneous patient subgroups can be defined as* which will react similarly to a specific intervention). In the experiments, *Predict Pursuit* discovered the patient subgroups that early PCI provides statistically significant improvement for older patients ($\geq$ 65 age) in both 30-day mortality**,** composite mortality**,** and severe LVD outcomes. On the other hand, there is no statistically significant improvement for young patients (< 65 age) by early PCI. We note that *Predict Pursuit* is general methodology, and can also be applied in more general settings, where the decision is among a variety of interventions, not a single one.

Introduction / Problem Definition:

The homogenous sub-groups of patients may be different for different types of clinical interventions. For instance, if a patient sub-group has similar clinical outcomes for a specific intervention (intervention 1), we can say that this patient sub-group is homogeneous with respect to that intervention (intervention 1). However, this patient sub-group may not be homogeneous with respect to another intervention (intervention 2) – for that intervention we may discover other homogeneous sub-groups of patients. Thus, from now on, when we talk about homogeneous sub-groups or patients that are similar, we need to specify on *what intervention they are considered to be similar*. It may be that Patient A and Patient B are similar on Intervention 1 but not on Intervention 2. Just that two patients are similar regarding features (old/young, man/female) – does not mean that they will respond similarly to a given intervention. *What are the characteristics that define the homogeneous subgroups that respond similarly to an intervention cannot be known in advance, it needs to be discovered from data*! Thus, personalization for a specific intervention is discovered by the available data. The more and better data, the better can our personalization approach perform.

The similarity of patients on a clinical outcome of a specific intervention is defined as the variance of the clinical outcomes of that specific intervention among the considered patients. For instance, if all the diabetic patients are "similar" on their outcomes for the early PCI intervention, there is no need to subdivide the patients into subgroups, and we can recommend early PCI intervention to all the diabetic patients. (In this case there is no need for personalization.) This is because in this scenario we can verify using the propensity score matching analysis that early PCI intervention provides statistically significant improvement in mortality, severe left ventricular dysfunction (LVD), and composite mortality. However, if the diabetic patients are heterogeneous (dissimilar) on the early PCI intervention (i.e. their clinical outcomes differ), personalization (i.e. dividing the patients into homogeneous subgroups) will be useful and different recommendations should be given to different subgroups. Thus, even though on "average" diabetic patients may achieve statistically significant improvement if they receive early PCI intervention, this does not mean that every patient will benefit from the intervention. In

this case, personalization, achieved by dividing patients into homogeneous subgroups can result in improved recommendations.

Predict Pursuit which we developed for personalization on clinical interventions *discovers* the patient subgroups that have statistically different outcomes for a specific clinical intervention regarding clinical outcomes (mortality and composite mortality and severe LVD outcomes). In other words, *Predict Pursuit* can discover heterogeneous patient subgroups (the patients within a subgroup are homogeneous) on a clinical treatment/intervention.

Methodology:

Predict Pursuit discovers patients' subgroups which can benefit from early PCI intervention. The discovered patient subgroups are verified to have statistically different outcomes when receiving early PCI using propensity score matching analysis. The details of *Predict Pursuit* are outlined next; it iteratively performs the following two steps:

1. The objective of *Predict Pursuit* is to maximize the statistical difference between two subgroups of patients on the clinical outcomes to a specific intervention (in our case early PCI). We find such patient subgroups in the following manner. We split the patients into two subgroups (according to their features) and perform propensity score matching for each subgroup. Next, we determine for each subgroup whether performing early PCI intervention leads to outcome improvements that are statistically significant or not – we compute p-values for this. Finally, among all the possible subgroups (subdivisions of the group), we select the ones for which the difference between their p-values is highest (maximized).

2. The maximization in step 1 above needs to be performed under two types of constraints: (i) constraints on the statistical difference between two sub-patient groups regarding outcomes and (ii) constraints on the resulting confidence of the propensity score matching analysis. The first constraint ensures that the discovered subgroups achieve statistically different (significant versus not-significant) improvement by early PCI intervention regarding clinical outcomes. The second constraint ensures that there is no statistical difference among the covariate distributions of two patient subgroups and that the number of patients in each subgroup should be larger than a threshold[1]. In other words, there is no statistical difference among the covariate distribution between two subgroups (i.e. we ensure that the patients in the subgroups come from the same distribution) and there are sufficient patients to perform a systematic propensity score matching analysis.

Fig. 1 portrays the block diagram of *Predict Pursuit*, which sequentially discovers patient subgroups until there is no further personalization feasible (based on the optimization performed in the method described above). The final leaves of the tree discovered by our personalization method represent will be patient subgroups to which early PCI intervention will be either recommended or not. (Our data is too limited, but if we would have more data, we could do further personalization, beyond age.) A hypothetical example to understand the key ideas portrayed in Fig. 1 above is given next: a first split is among two subgroups old and young patients (the old patients are recommended not to receive intervention 1), a second split is only among the young patients into males and females (the female patients are recommended to receive intervention 1) and the young males are further split into obese and not (and only to the

[1] In this paper, the threshold is set to be 100 patients.

young male non-obese patients intervention 1 is recommended and to the young male obese patients intervention 2 is not recommended)).

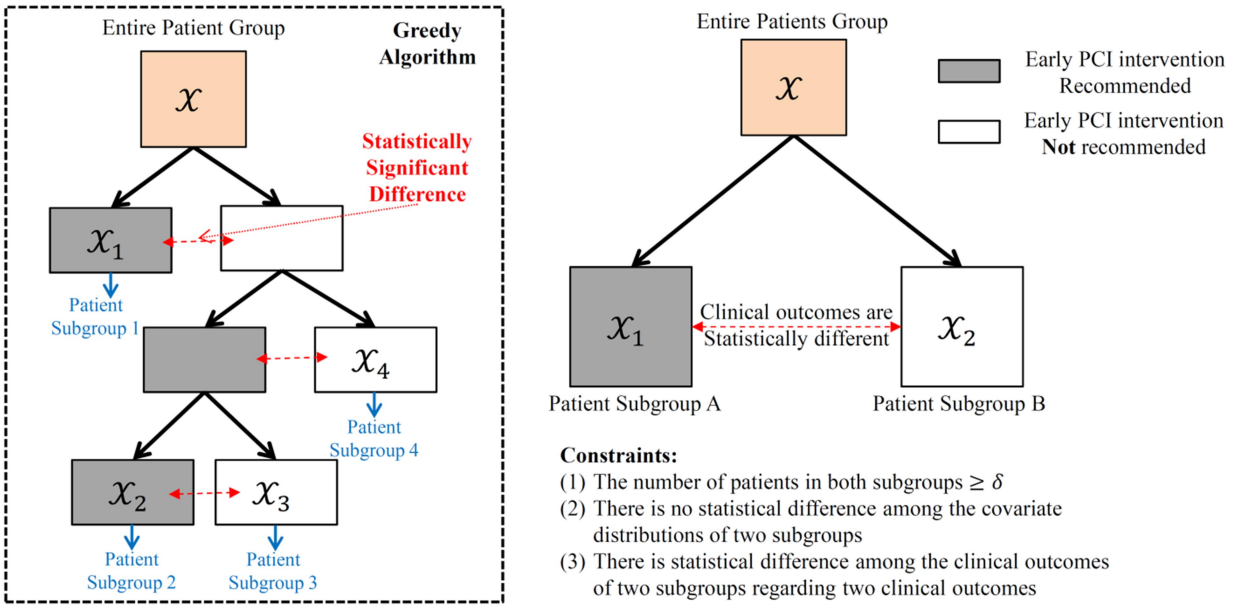

Fig 1. Block diagram of *Predict Pursuit* (left: our algorithm, right: one step of the algorithm)

Experiments:

In the experiment which we performed based on the diabetic patient's data set, we discovered two patient subgroups. The differentiating factor was age: patients with an age of at least 65 (older) and patients with age lower than age 65 (younger). Table 2 shows the propensity score matching results for different age thresholds. Using propensity score matching analysis, early intervention provides statistically significant improvement for older patients in both 30-day mortality, composite mortality, and severe LVD outcomes. On the other hand, younger patients do not achieve statistically significant improvement by early PCI intervention regarding both clinical outcomes. These results mean that even if the "average" patient achieves statistically significant improvements for early PCI intervention, there is heterogeneity among the diabetic patients and the clinical outcomes of younger and older patients when receiving early PCI intervention is statistically different. Therefore, based on the above, we can conclude that early PCI intervention should only be recommended to older patients.

Table 1 shows that personalization using different features rather than age cannot provide statistically significant difference regarding both clinical outcomes (30-day mortality and composite outcomes). Only age-dependent personalization can create subgroups (of younger versus older patients) that are statistically significant (significance level 0.05) for early PCI intervention in both clinical outcomes. We generated this table to highlight that the personalization discovered by *Predict Pursuit* is indeed the only statistically significant one for both clinical outcomes for the provided dataset. However, we would like to note that further personalization may be possible if we would get more data. This is what is discovered for the limited dataset.

Table 1. Clinical outcome analysis between two patient subgroups

Features	Clinical Outcomes	Patient Group 1 (Value = 0)			Patient Group 2 (Value = 1)		
		RMT	PCI	P-value	RMT	PCI	P-value
Age	30-day Mortality	16 (8.8%)	6 (3.3%)	0.0279	2 (1.2%)	6 (3.5%)	0.1533
	Composite Outcomes	35 (19.2%)	16 (8.8%)	0.0040	15 (8.8%)	11 (6.5%)	0.4158
GRACE/ TIMI	30-day Mortality	15 (15.8%)	5 (5.3%)	0.0180	7 (3.6%)	6 (3.0%)	0.7800
	Composite Outcomes	26 (27.4%)	16 (16.8%)	0.0812	22 (11.2%)	10 (5.1%)	0.0269
Gender	30-day Mortality	13 (5.9%)	5 (2.3%)	0.0543	9 (7.0%)	7 (5.4%)	0.6073
	Composite Outcomes	37 (16.9%)	16 (7.3%)	0.0020	13 (10.1%)	13 (10.1%)	1
Heart Rate	30-day Mortality	16 (6.5%)	11 (4.5%)	0.3233	4 (3.8%)	1 (1.0%)	0.1761
	Composite Outcomes	38 (15.4%)	18 (7.3%)	0.0045	12 (11.4%)	9 (8.6%)	0.4925
Hyper cholesterol	30-day Mortality	12 (6.9%)	8 (4.6%)	0.3583	6 (3.3%)	4 (2.2%)	0.5227
	Composite Outcomes	29 (16.8%)	14 (8.1%)	0.0144	17 (9.3%)	13 (7.1%)	0.4473
Current Smoker	30-day Mortality	18 (6.2%)	9 (3.1%)	0.0763	3 (4.6%)	2 (3.1%)	0.6514
	Composite Outcomes	41 (14.2%)	22 (7.6)	0.0112	11 (16.9%)	4 (6.2%)	0.0553
History of CAD	30-day Mortality	13 (6.0%)	6 (2.8%)	0.1010	3 (2.3%)	6 (4.5%)	0.3107
	Composite Outcomes	37 (17.0%)	20 (9.2%)	0.0157	9 (6.8%)	9 (6.8%)	1
Prior MI	30-day Mortality	15 (6.1%)	8 (3.3%)	0.1354	5 (5.3%)	4 (4.2%)	0.7344
	Composite Outcomes	33 (13.5%)	17 (7.0%)	0.0169	12 (12.6%)	11 (11.6%)	0.8251
Positive Cardiac Biomarkers	30-day Mortality	4 (5.8%)	1 (1.4%)	0.1742	17 (6.6%)	9 (3.5%)	0.1078
	Composite Outcomes	12 (17.4%)	8 (11.6%)	0.3370	40 (15.5%)	17 (6.6%)	0.0012

The current clinical guideline recommends early PCI intervention to diabetic patients whose GRACE scores are equal to or larger than 140 or TIMI scores that are equal or greater than 7 – such patients are considered high-risk patients. The underline assumption of this clinical guideline is that high-risk patients as identified by GRACE or TIMI scores will achieve clinical improvement if they receive early PCI intervention. However, the first run of propensity score analysis shows that high-risk patients as identified by GRACE and TIMI do not achieve statistically significant improvements from early PCI intervention regarding composite mortality

and severe LVD outcome. On the other hand, low-risk patients achieve statistically significant improvements if they receive early PCI intervention. Therefore, by the propensity score matching analysis, we can reject the underlining hypothesis for high-risk patients.

Table 2. Clinical outcome analysis between two subgroups divided using different age thresholds

Features	Clinical Outcomes	Patient Group 1 (Value = 0)			Patient Group 2 (Value = 1)		
		RMT	PCI	P-value	RMT	PCI	P-value
Age (50≥)	30-day Mortality	24 (7.0%)	11 (3.2%)	0.0241	0 (0%)	0 (0%)	Nan
	Composite Outcomes	55 (15.9%)	26 (7.5%)	0.0006	1 (9.1%)	0 (0%)	0.3293
Age (55≥)	30-day Mortality	21 (6.6%)	11 (3.5%)	0.0698	0 (0%)	0 (0%)	Nan
	Composite Outcomes	51 (16.1%)	27 (8.5%)	0.0037	1 (2.6%)	0 (0%)	0.3293
Age (60≥)	30-day Mortality	18 (6.9%)	9 (3.5%)	0.0755	1 (1.1%)	4 (4.5%)	0.1755
	Composite Outcomes	38 (14.6%)	25 (9.6%)	0.0809	9 (10.1%)	4 (4.5%)	0.1515
Age (65≥)	30-day Mortality	**16 (8.8%)**	**6 (3.3%)**	**0.0279**	**2 (1.2%)**	**6 (3.5%)**	**0.1533**
	Composite Outcomes	**35 (19.2%)**	**16 (8.8%)**	**0.0040**	**15 (8.8%)**	**11 (6.5%)**	**0.4158**
Age (70≥)	30-day Mortality	16 (12.7%)	5 (4.0%)	0.0121	4 (1.9%)	7 (3.2%)	0.3607
	Composite Outcomes	27 (21.4%)	14 (11.1%)	0.0265	19 (8,8%)	13 (6.0%)	0.2714
Age (75≥)	30-day Mortality	9 (14.8%)	4 (6.6%)	0.1447	10 (3.5%)	8 (2.8%)	0.6327
	Composite Outcomes	15 (24.6%)	10 (16.4%)	0.2658	33 (11.5%)	18 (6.3%)	0.0278

Appendix:

Appendix Table 1. The criteria of dividing patients into patient group 1 and 2

Feature	Patient Group 1	Patient Group 2
Age	Age >= 65	Age >= 65
GRACE/TIMI	GRACE >= 140 **and** TIMI >= 7	GRACE < 140 **or** TIMI < 7
Gender	Male	Female
Heart Rate	Heart Rate >= 80	Heart Rate < 80
Hyper cholesterol	No history of Hypercholesterolemia	History of Hypercholesterolemia
Current Smoker	No smoker	Current Smoker
History of CAD	No family history of CAD	Family history of CAD
Prior MI	No prior Myocardial Infarction	Prior Myocardial Infarction
Positive Cardiac Biomarker	No positive cardiac biomarkers	Positive cardiac biomarkers

Appendix Table 2. Clinical outcome analysis between two subgroups divided using different heart rate thresholds

Features	Clinical Outcomes	Patient Group 1 (≥)			Patient Group 2 (<)		
		RMT	PCI	P-value	RMT	PCI	P-value
Heart Rate (65)	30-day Mortality	22 (6.5%)	11 (3.3%)	0.0497	2 (8.0%)	1 (4.0%)	0.5609
	Composite Outcomes	51 (15.1%)	27 (8.0%)	0.0038	4 (16.0%)	1 (4.0%)	0.1638
Heart Rate (70)	30-day Mortality	21 (6.5%)	12 (3.7%)	0.1081	3 (7.3%)	1 (2.4%)	0.3111
	Composite Outcomes	49 (15.2%)	27 (8.4%)	0.0072	7 (17.1%)	2 (4.9%)	0.0791
Heart Rate (75)	30-day Mortality	16 (5.4%)	11 (3.7%)	0.3256	2 (3.3%)	1 (1.7%)	0.5626
	Composite Outcomes	42 (14.0%)	26 (8.7%)	0.0394	8 (13.3%)	2 (3.3%)	0.0480
Heart Rate (80)	30-day Mortality	16 (6.5%)	11 (4.5%)	0.3233	4 (3.8%)	1 (1.0%)	0.1761
	Composite Outcomes	38 (15.4%)	18 (7.3%)	0.0045	12 (11.4%)	9 (8.6%)	0.4925
Heart Rate (85)	30-day Mortality	4 (4.8%)	4 (4.8%)	1.00	18 (7.3%)	9 (3.6%)	0.0751
	Composite Outcomes	15 (18.1%)	10 (12.0%)	0.2807	33 (13.4%)	18 (7.3%)	0.0266
Heart Rate (90)	30-day Mortality	5 (6.7%)	3 (4.0%)	0.4707	20 (7.4%)	10 (3.7%)	0.0605
	Composite Outcomes	16 (21.3%)	9 (12.0%)	0.1268	38 (14.0%)	21 (7.7%)	0.0190
Heart Rate (95)	30-day Mortality	1 (2.2%)	3 (6.5%)	0.3118	22 (7.3%)	9 (3.0%)	0.0165
	Composite Outcomes	11 (23.9%)	8 (17.4%)	0.4453	41 (13.6%)	19 (6.3%)	0.0027
Heart Rate (100)	30-day Mortality	1 (2.5%)	2 (5.0%)	0.5620	21 (6.9%)	9 (3.0%)	0.0246
	Composite Outcomes	8 (20.0%)	7 (17.5%)	0.7779	40 (13.1%)	20 (6.6%)	0.0065
Heart Rate (110)	30-day Mortality	0 (0%)	0 (0%)	Nan	24 (7.1%)	12 (3.5%)	0.0399
	Composite Outcomes	3 (30.0%)	2 (20.0%)	0.6278	52 (15.3%)	25 (7.4%)	0.0011