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FM ACP RESEARCH GRAND ROUND

Leveraging AI for personalized treatment in primary care… beginning with statin therapy

Andrew Fang

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AI in Health Grand Challenge

"How can AI help primary care teams stop or slow disease progression and complication development in 3H – Hyperglycemia (diabetes), Hypertension (high blood pressure) and Hyperlipidemia (high cholesterol) patients by 20% in 5 years?"

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Lipids in Health and Disease

RESEARCH Open Access

LDL-cholesterol change and goal attainment following statin intensity titration among Asians in primary care: a retrospective cohort study

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Abstract

Background: Clinical trials have demonstrated that either initiating or up-titrating a statin dose substantially reduce Low-Density Lipoprotein-Cholesterol (LDL-C) levels. However, statin adherence in actual practice tends to be suboptimal, leading to diminished effectiveness. This study aims to use real-world data to determine the effect on LDL-C levels and LDL-C goal attainment rates, when selected statins are titrated in Asian patients.

Methods: A retrospective cohort study over a 5-year period, from April 2014 to March 2019 was conducted on a cohort of multi-ethnic adult Asian patients with clinical diagnosis of Dyslipidaemia in a primary care clinic in Singapore. The statins were classified into low-intensity (LI), moderate-intensity (MI) and high-intensity (HI) groups according to the 2018 American College of Cardiology and American Heart Association (ACC/AHA) Blood Cholesterol Guidelines. Patients were grouped into "No statin", "Non-titrators" and "Titrators" cohorts based on prescribing patterns. For the "Titrators" cohort, the mean percentage change in LDL-C and absolute change in LDL-C goal attainment rates were computed for each permutation of statin intensity titration.

Results: Among the cohort of 11,499 patients, with a total of 266,762 visits, there were 1962 pairs of LDL-C values associated with a statin titration. Initiation of LI, MI and HI statin resulted in a lowering of LDL-C by 21.6% (95%CI = 18.9–24.3%), 28.9% (95%CI = 25.0–32.7%) and 25.2% (95%CI = 12.8–37.7%) respectively. These were comparatively lower than results from clinical trials (30 to 63%). The change of LDL-C levels due to up-titration, down-titration, and discontinuation were − 12.4% to − 28.9%, + 13.2% to + 24.6%, and + 18.1% to + 32.1% respectively. The improvement in LDL-C goal attainment ranged from 26.5% to 47.1% when statin intensity was up-titrated.

Conclusion: In this study based on real-world data of Asian patients in primary care, it was shown that although statin titration substantially affected LDL-C levels and LDL-C goal attainment rates, the magnitude was lower than results reported from clinical trials. These results should be taken into consideration and provide further insight to clinicians when making statin adjustment recommendations in order to achieve LDL-C targets in clinical practice, particularly for Asian populations.

Keywords: LDL-cholesterol, Statin, Percentage change, Asian, Real-world data, Goal attainment, Primary care

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Background

- In clinical trials, statin initiation has been shown to reduce LDL-C levels by 30-63%, while doubling of dose further decreased by 6%.[1-3]

SHP Clinical Guidebook - Dyslipidemia

Relative Lipid lowering (Adapted from FDA advisory on statins, 2011)

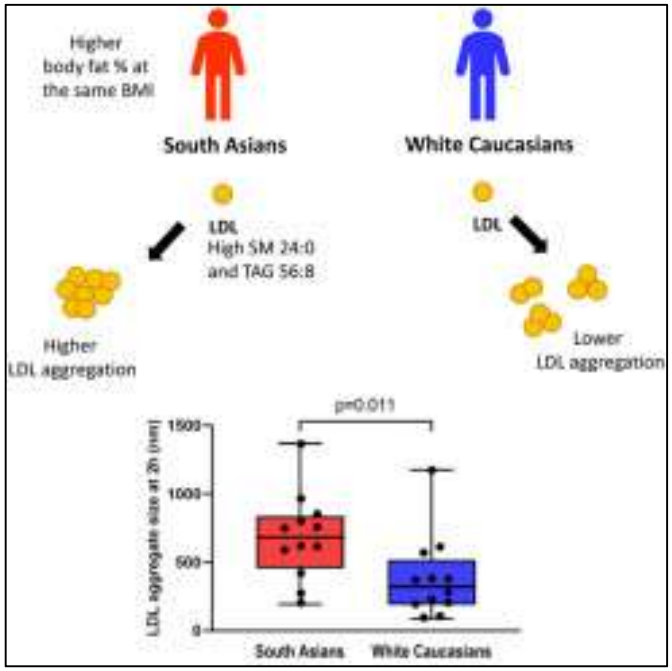
Lovastatin	Pravastatin	Simvastatin	Ezetimibe/ Simvastatin	Atovastatin	Rosuvastatin	% LDL lowering
20 mg	20 mg	10 mg				30%
40 mg	40 mg	20 mg		10 mg		38%
		40 mg	10 / 10 mg	20 mg	5 mg	41%
			10 / 20 mg	40 mg	10 mg	47%
			10 / 40 mg	80 mg	20 mg	55%
					40 mg	63%

Note: Every doubling of statins only lower the LDL by a further 6%

1 – Larsen et al. Drug treatment of dyslipoproteinemia. Med Clin North Am. 1994;78(1):225–45.
2 – Jones et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR trial). Am J Cardiol. 2003;92(2):152–60.
3 – Grundy et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the Management of Blood Cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. J Am Coll Cardiol. 2019;73(24):3168–209.

Background

- Data from trials mostly on Caucasian populations
  - Different vascular risk profiles from Asians. LDL more likely to aggregate in South Asians resulting in higher CVD risk.[4]
- Studies have shown that LDL-C lowering effect differ in actual practice
  - Due to suboptimal medication adherence in the real world



4 – Ruuth et al. LDL aggregation susceptibility is higher in healthy South Asian compared with white Caucasian men. J of Clinical Lipidology. 2019 Nov - Dec;13(6):910-919.e2.

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Study aim

- To determine, following statin dose titration
  - **Magnitude of LDL-C change** (primary aim)
  - **Effect on LDL-C goal attainment** (secondary aim)

- In context:
  - Asians
  - Primary care
  - Using real-world data

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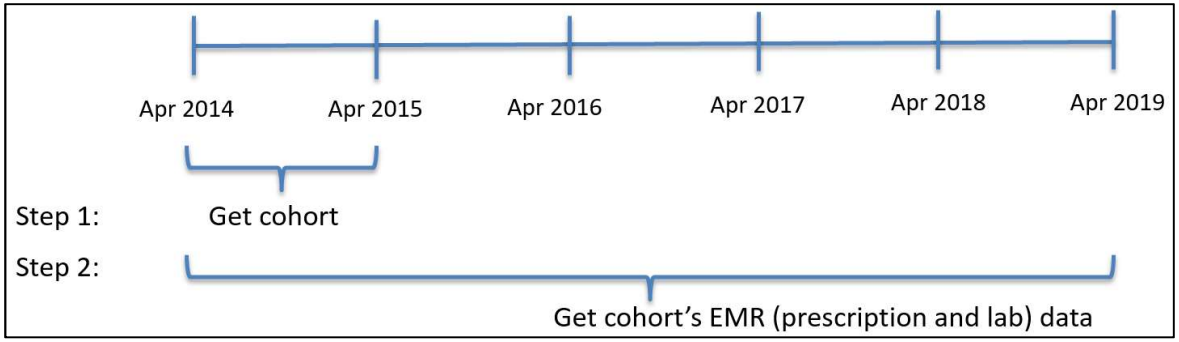
Method - Study design and population

- Study design: Retrospective cohort study

- Study population
  - Inclusion criteria:
    - Patients on follow-up with a single polyclinic for Hyperlipidemia from Apr 1, 2014 to Mar 31, 2015
  - Exclusion criteria:
    - Age <21 years
    - Patients who had taken other lipid lowering medications apart from statins (e.g. fibrates, ezetimibe)



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Method - Data processing

1. Grouped statin intensity levels based on statin type and dosage according to 2018 AHA/ACC guidelines

Table 1 Statin intensity level groupings based on types and doses of statins

Type of statin (x = dose in mg)	Low-intensity (LI)	Moderate-intensity (MI)	High-intensity (HI)
Pravastatin	$0 < x \leq 40$	$x > 40$	NA
Lovastatin	$0 < x \leq 40$	$x > 40$	NA
Simvastatin	$0 < x \leq 20$	$20 < x \leq 80$	$x > 80$
Atorvastatin	$0 < x \leq 10$	$10 < x < 40$	$x \geq 40$
Rosuvastatin	$0 < x \leq 5$	$5 < x < 20$	$x \geq 20$

LI Low-intensity statin, *MI* Moderate-intensity statin, *HI* High-intensity statin, *x* Statin dose in milligrams.

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Method - Data processing

2. Identification of pre-titration LDL-C and post-titration LDL-C values

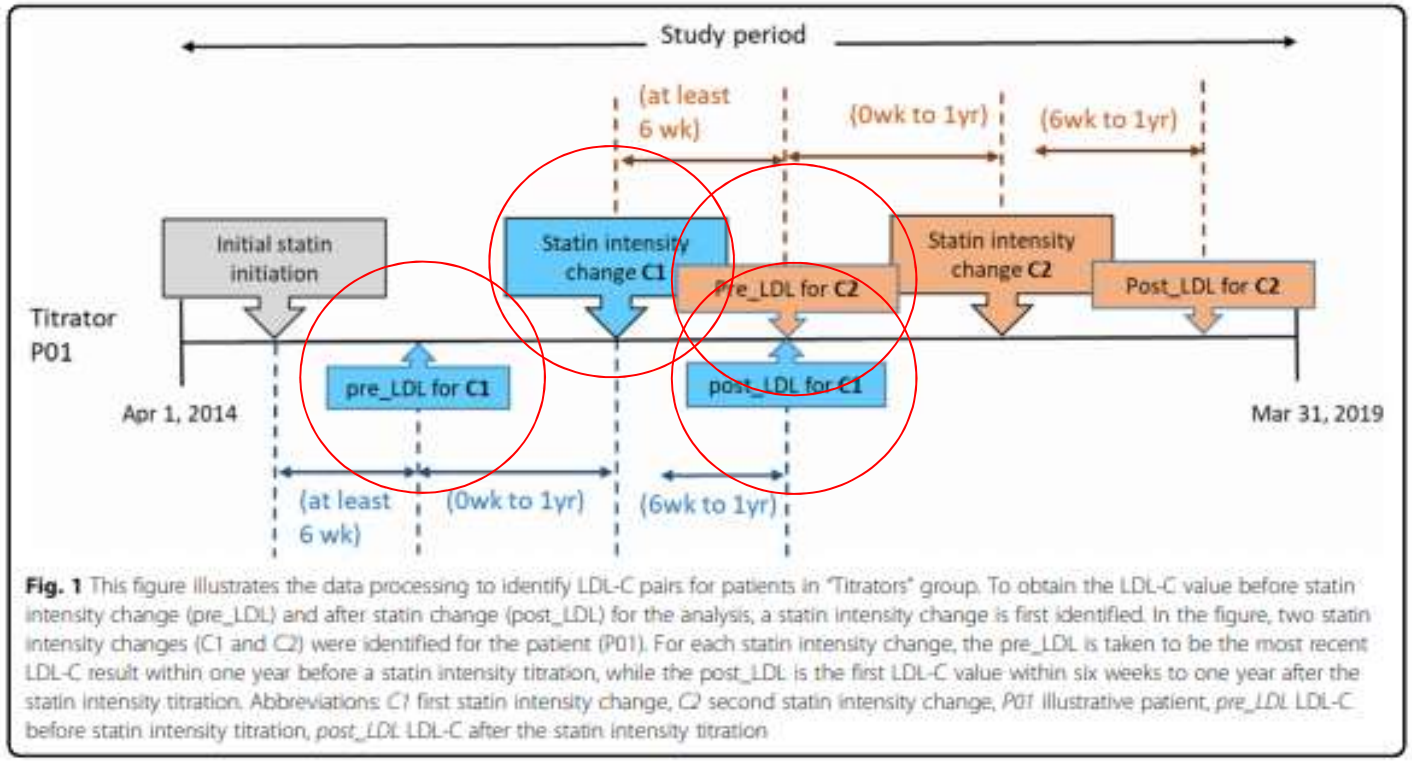

Fig. 1 This figure illustrates the data processing to identify LDL-C pairs for patients in "Titrators" group. To obtain the LDL-C value before statin intensity change (pre_LDL) and after statin change (post_LDL) for the analysis, a statin intensity change is first identified. In the figure, two statin intensity changes (C1 and C2) were identified for the patient (P01). For each statin intensity change, the pre_LDL is taken to be the most recent LDL-C result within one year before a statin intensity titration, while the post_LDL is the first LDL-C value within six weeks to one year after the statin intensity titration. Abbreviations: *C1* first statin intensity change, *C2* second statin intensity change, *P01* illustrative patient, *pre_LDL* LDL-C before statin intensity titration, *post_LDL* LDL-C after the statin intensity titration

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Method - Data processing

3. Compute CVD risk group using modified Framingham Risk Calculator, to obtain LDL-C goal (to investigate effect of statin titration of LDL-C goal attainment)

Table 2 LDL-C target levels in four risk categories

CVD Risk group based on modified Framingham Risk Calculator	LDL-C goal (mmol/L)
Very high	< 2.1
High	< 2.6
Intermediate	< 3.4
Low	< 4.1

LDL-C target levels based on Ministry of Health Singapore clinical guidelines on lipid disorders. Abbreviations: *CVD* Cardiovascular disease, *LDL-C* Low-density lipoprotein cholesterol.

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Results

- Total of 11,499 patients, with 266,762 visits
- Divided into 3 sub-cohorts

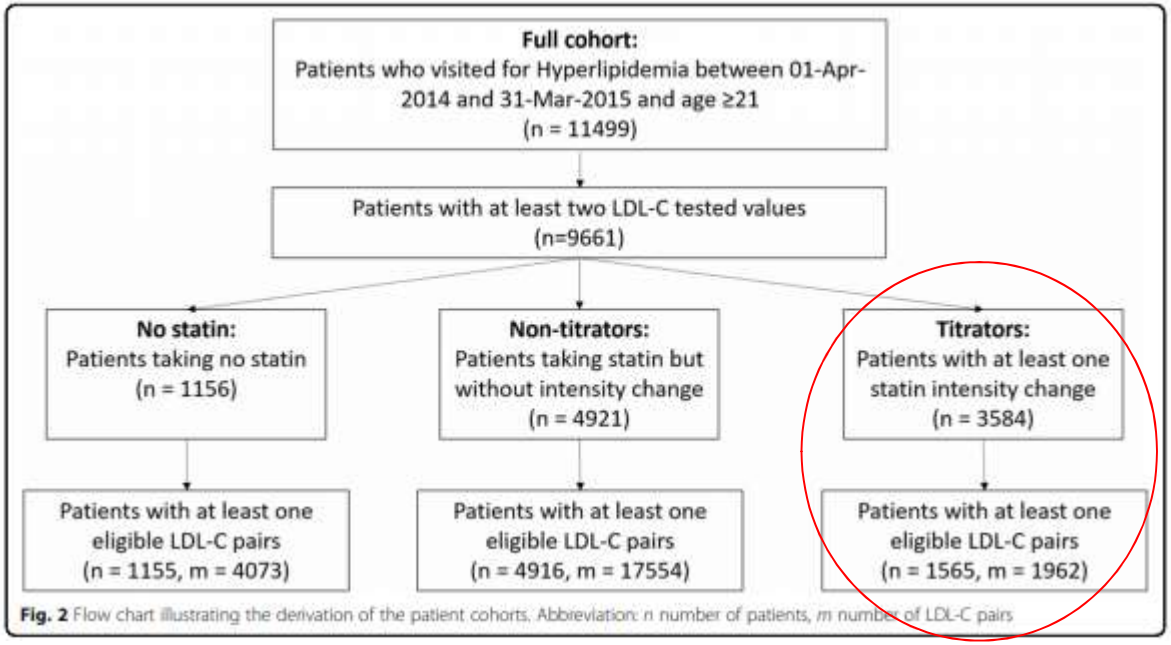

Fig. 2 Flow chart illustrating the derivation of the patient cohorts. Abbreviation: *n* number of patients, *m* number of LDL-C pairs

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Results – Baseline characteristics

Table 3 Baseline characteristics of patients in study cohort

Characteristics	No statin (*n* = 1156)	Non-titrators (*n* = 4916)	Titrators (*n* = 1565)	Full cohort (*n* = 11,499)
Total Patients, n (%)	1155 (100)	4916 (100)	1565 (100)	11,499 (100)
Age (year), mean (SD)	65.3 (11.0)	69.0 (10.3)	64.8 (10.0)	67.8 (11.3)
Sex, males, n (%)	461 (39.9)	2008 (40.8)	712 (45.5)	4967 (43.2)
Race, n (%)				
Chinese	1042 (90.2)	4185 (85.1)	1279 (81.7)	9606 (83.5)
Malay	22 (1.9)	282 (5.7)	109 (7.0)	726 (6.3)
Indian	55 (4.8)	236 (4.8)	105 (6.7)	655 (5.7)
Others	36 (3.1)	213 (4.3)	72 (4.6)	512 (4.5)
Diagnosis, n (%)				
Dyslipidaemia	1155 (100.0)	4916 (100.0)	1565 (100.0)	11,499 (100.0)
Diabetes	159 (13.8)	1915 (39.0)	594 (38.0)	4153 (36.1)
Hypertension	793 (68.7)	4166 (84.7)	1120 (71.6)	9101 (79.1)
Years with Dyslipidaemia at base visit, n (%)				
0	196 (17.0)	226 (4.6)	177 (11.3)	1074 (9.3)
1	76 (6.6)	298 (6.1)	125 (8.0)	797 (6.9)
2	81 (7.0)	600 (12.2)	184 (11.8)	1350 (11.7)
3	103 (8.9)	316 (6.4)	121 (7.7)	825 (7.2)
4	183 (15.8)	417 (8.5)	159 (10.2)	1133 (9.9)
>=5	516 (44.7)	3059 (62.2)	799 (51.0)	6320 (55.0)
Statin intensity at base visit, n (%)				
No	1155 (100.0)	0.0 (0.0)	333 (21.3)	2327 (20.2)
Low	0.0 (0.0)	3998 (81.3)	850 (54.3)	7076 (61.5)
Intermediate	0.0 (0.0)	812 (16.5)	349 (22.3)	1867 (16.2)
High	0.0 (0.0)	106 (2.2)	33 (2.1)	229 (2.0)
Patients in each risk group, n (%)				
Low	515 (44.6)	1111 (22.6)	453 (28.9)	2970 (25.8)
Intermediate	196 (17.0)	504 (10.3)	150 (9.6)	1162 (10.1)
High	331 (28.7)	1827 (37.2)	484 (30.9)	3942 (34.3)
Very high	113 (9.8)	1474 (30.0)	478 (30.5)	3425 (29.8)
Number of LDL tests per year, mean (SD)	0.8 (0.3)	0.8 (0.2)	1.0 (0.3)	0.7 (0.3)
Number of statinprescriptions per year, mean (SD)	0.0 (0.0)	2.6 (0.9)	2.4 (1.2)	2.3 (1.2)

Abbreviations: *LDL* Low-density lipoprotein, *SD* Standard deviation

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Results – LDL-C lowering effect

Table 4 Percentage change of LDL-C with titrations in statin intensity

From	To	LDL-C change (%)	95% CI	m
No statin				
No Statin	No Statin	−1.1	(− 1.6, − 0.6)	4073
Non Titrator				
Low-intensity	Low-intensity	0.4	(0.0, 0.8)	14,169
Moderate-intensity	Moderate-intensity	0.3	(−0.6, 1.2)	2961
High-Intensity	High-Intensity	0.9	(−2.6, 4.3)	424
Titrators (Up)				
No Statin	Low-intensity	−21.6	(−24.3, −18.9)	311
No Statin	Moderate-intensity	−28.9	(−32.7, − 25.0)	189
No Statin	High-Intensity	−25.2	(−37.7, −12.8)	33
Low-intensity	Moderate-intensity	−16.2	(−18.1, − 14.3)	637
Low-intensity	High-Intensity	−24.6	(−31.5, −17.8)	49
Moderate-intensity	High-Intensity	−12.4	(−15.7, −9.1)	281
Titrators (Down)				
Low-intensity	No Statin	18.1	(10.0, 26.1)	64
Moderate-intensity	No Statin	32.1	(4.5, 59.7)	22
Moderate-intensity	Low-intensity	13.2	(7.6, 18.9)	261
High-Intensity	No Statin	89.5	(− 125.2, 304.3)	3
High-Intensity	Low-intensity	24.6	(−20.2, 69.3)	10
High-Intensity	Moderate-intensity	18.4	(8.5, 28.2)	102

Abbreviations: *LDL-C* Low-density lipoprotein cholesterol, *m* number of LDL-C pairs

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Results – LDL-C goal attainment

Table 5 Change in LDL-C goal attainment with titration in statin intensity

From	To	Change in goal attainment (%)	Goal attainment before titration (%)	Goal attainment after titration (%)	m
No statin					
No Statin	No Statin	3.3	63.0	66.3	4073
Total for No statin		3.3	63.0	66.3	4073
Non Titrator					
Low-intensity	Low-intensity	2.2	77.9	80.1	14,169
Moderate-intensity	Moderate-intensity	3.7	65.1	68.8	2961
High-Intensity	High-Intensity	5.4	48.1	53.5	424
Total for Non-titrator		2.5	75.0	77.5	17,554
Titrators (Up)					
No Statin	Low-intensity	40.5	34.4	74.9	311
No Statin	Moderate-intensity	47.1	26.5	73.5	189
No Statin	High-Intensity	39.4	42.4	81.8	33
Low-intensity	Moderate-intensity	33.1	30.5	63.6	637
Low-intensity	High-Intensity	26.5	61.2	87.8	49
Moderate-intensity	High-Intensity	27.4	20.6	48.0	281
Total for Titrators (Up)		35.3	30.2	65.5	1500
Titrators (Down)					
Low-intensity	No Statin	−23.4	65.6	42.2	64
Moderate-intensity	No Statin	−13.6	59.1	45.5	22
Moderate-intensity	Low-intensity	−4.2	73.6	69.3	261
High-Intensity	No Statin	−66.7	100.0	33.3	3
High-Intensity	Low-intensity	−20.0	50.0	30.0	10
High-Intensity	Moderate-intensity	−10.8	61.8	51.0	102
Total for Titrators (Down)		−9.5	68.8	59.3	462

Abbreviations: *m* number of LDL-C pairs

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Discussion

Principal finding #1

- **LDL-C lowering effect when initiating LI, MI and HI (21.6-28.9%) statin was less compared to results from clinical trials (30-63%)**
- One possible reason is the suboptimal adherence among patients in actual practice.
  - 45.3% of primary care patients reported poor adherence to medications[5]
- Other possible reasons include lifestyle factors (diet, smoking) which could also affect LDL-C lowering.[6]

5 – Kang et al. Prevalence and factors associated with adherence to anti-hypertensives among adults with hypertension in a developed Asian community: A cross-sectional study. Proceedings of Singapore Healthcare. 2020.
6 – Tan NC et al. Asian patients with dyslipidemia in an urban population: Effect of ethnicity on their LDL-cholesterol treatment goals. J Clinical Lipidology. 2016.

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Discussion

Principal finding #2

- **LDL-C reduction is lower when HI statin (25.2%) is initiated compared to the commencement of MI (28.9%) statin therapy.** LI statin initiation resulted in 21.6% reduction.
- Patients who are started on HI statins are postulated to have lower adherence to their prescription, given the fear of adverse effects with a higher doses
  - Studies reported lower adherence (about 2%) of high-intensity statins compared to those on low- to moderate-intensity[7,8]
- Based on this finding, prescribers may wish to consider selectively initiating statin-naïve patients on LI or MI statins

7 – Grover et al. Correlation of compliance to statin therapy with lipid profile and serum HMGCoA reductase levels in dyslipidemic patients. Indian Heart J. 2017 Jan 1;69(1):6–10.
8 – Virani et al. Is high-intensity statin therapy associated with lower statin adherence compared with low- to moderate-intensity statin therapy? Implications of the 2013 American College of Cardiology/American Heart Association cholesterol management guidelines. Clin Cardiol. 2014;37(11):653–9.

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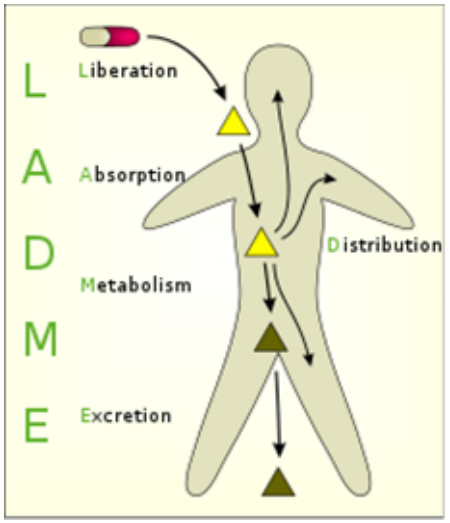
Discussion

Principal finding #3

- **Up-titration resulted in 16.2% (LI→MI) to 12.4% (MI→HI) reduction in LDL-C. This is more than the 6% in clinical trials.**
- Could be explained by genetic variations between Caucasians and Asians resulting in differences in pharmacokinetic and pharmacodynamics effects[9]
  - A large scale trial in Japan demonstrated that a 5-mg dose of simvastatin to be as effective as the 20-mg dose used in Western countries[10]



9 – Kim K, Johnson JA, Derendorf H. Differences in drug pharmacokinetics between east Asians and Caucasians and the role of genetic polymorphisms. J Clin Pharmacol. 2004;44(10):1083–105.
10 – Matsuzawa Y, Kita T, Mabuchi H, Matsuzaki M, Nakaya N, Oikawa S, et al. Sustained reduction of serum cholesterol in low-dose 6-year simvastatin treatment with minimum side effects in 51,321 Japanese hypercholesterolemic patients. Circ J Off J Jpn Circ Soc. 2003;67(4):287–94.

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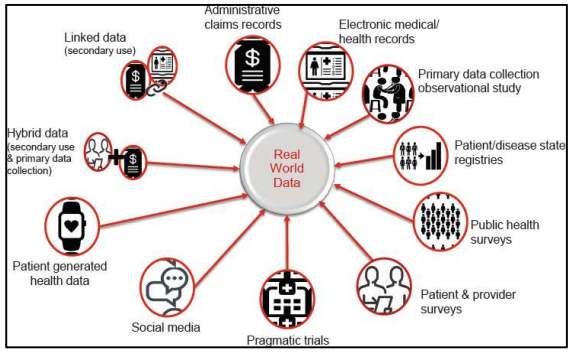
Discussion

Study strength

- Use of real-world data to generate real-world evidence:
  - Can complement results from clinical trials in setting more realistic expectations for LDL-C lowering and goal attainment
  - Provides the opportunity to gain insights to the impact of down-titrating and discontinuing statins (such changes would be challenging to elucidate from clinical trials due to ethical reasons)



Study limitation

- Only data from a single site was used (limited number of instances)
- Statins were grouped into intensity levels (less granular)

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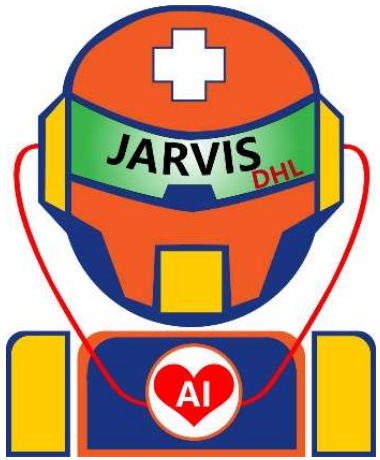
Discussion

"How can AI help primary care teams stop or slow disease progression and complication development in 3H – Hyperglycemia (diabetes), Hypertension (high blood pressure) and Hyperlipidemia (high cholesterol) patients by 20% in 5 years?"

Looking ahead

- Findings will be incorporated into a **JARVIS$_{DHL}$ Primary Care Decision Support Tool** to help to facilitate and positively influence decision-making
  - Comparison with peers
  - Risk prognostication
  - Personalized narratives (negative and positive)
  - Treatment effectiveness for shared decision-making



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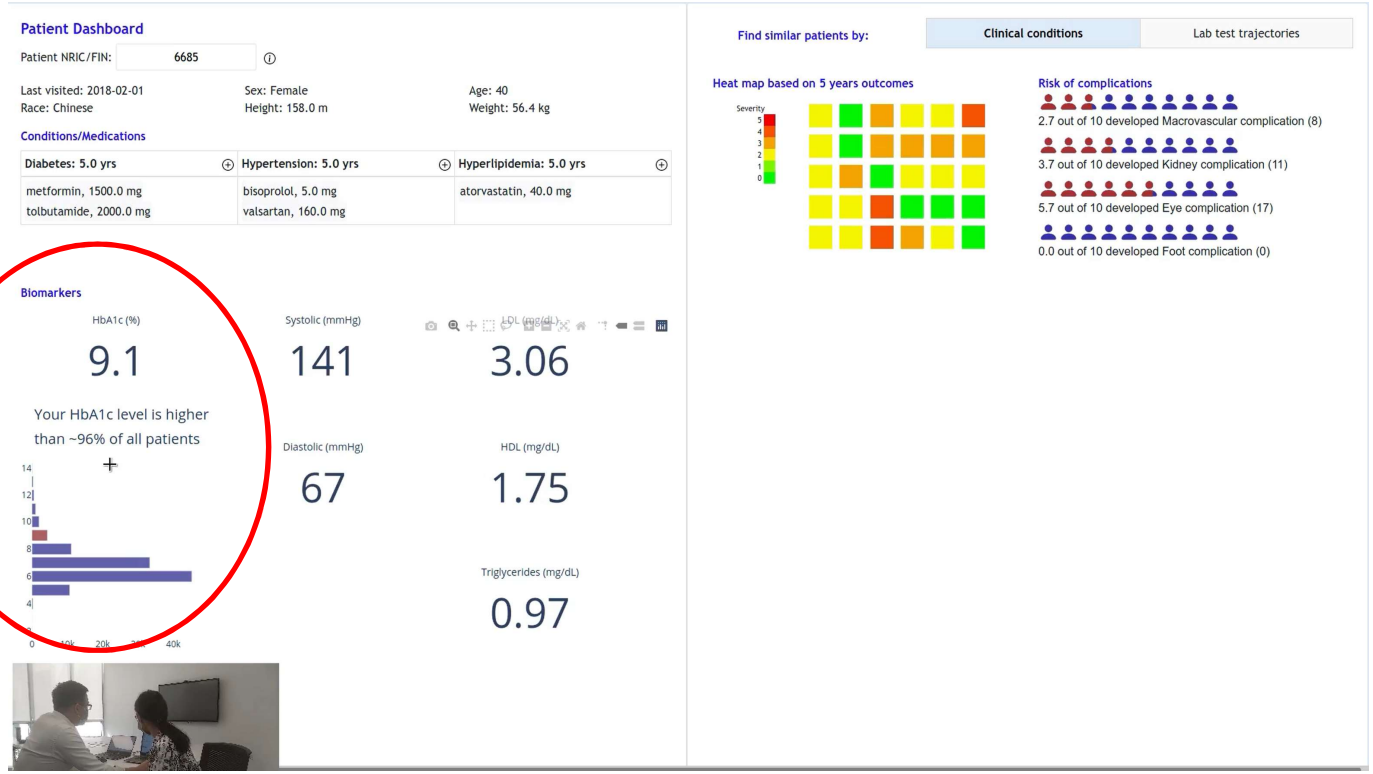
JARVIS$_{DHL}$ Primary Care Decision Support Tool

Comparison with peers



Aid patients with illness perception

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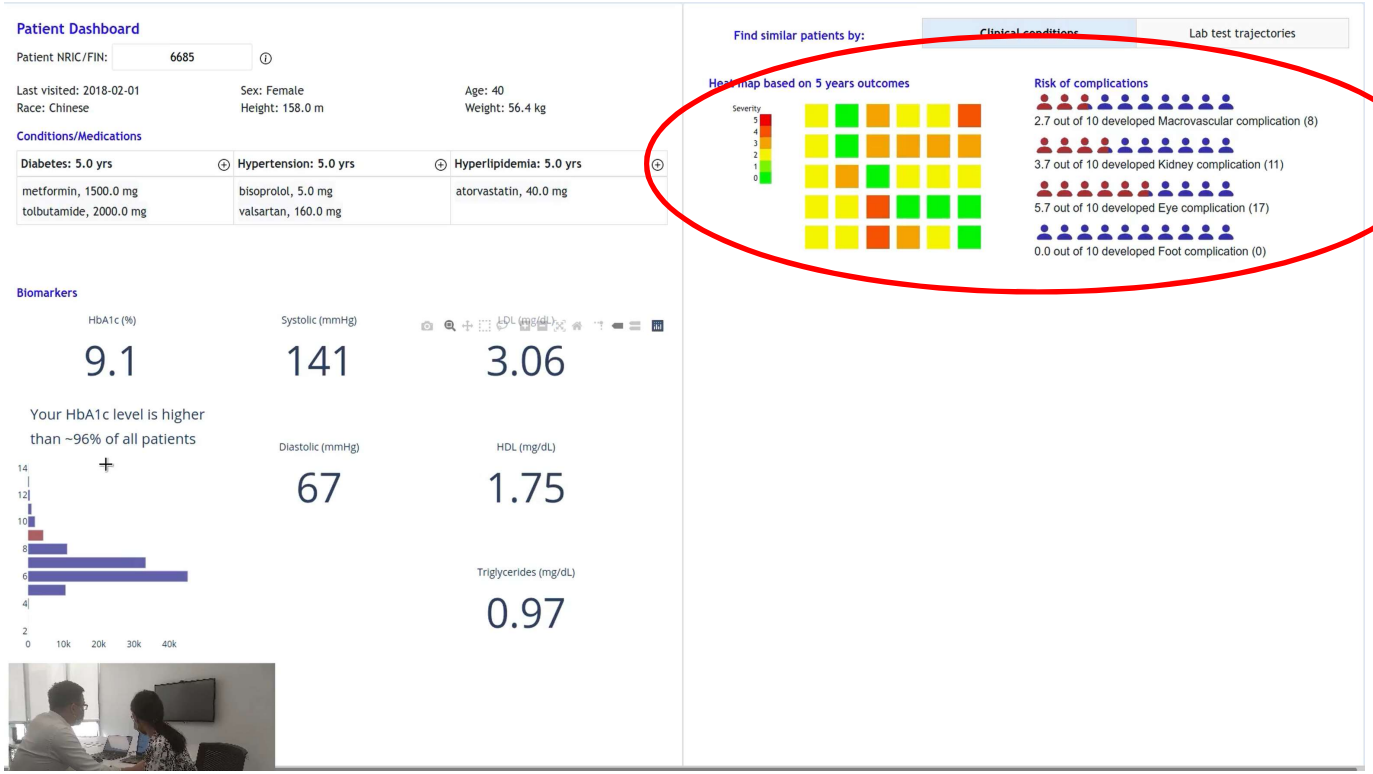
JARVIS$_{DHL}$ Primary Care Decision Support Tool

Risk prognostication (based on patient similarity analytics)



Provide explainable and relatable AI outputs

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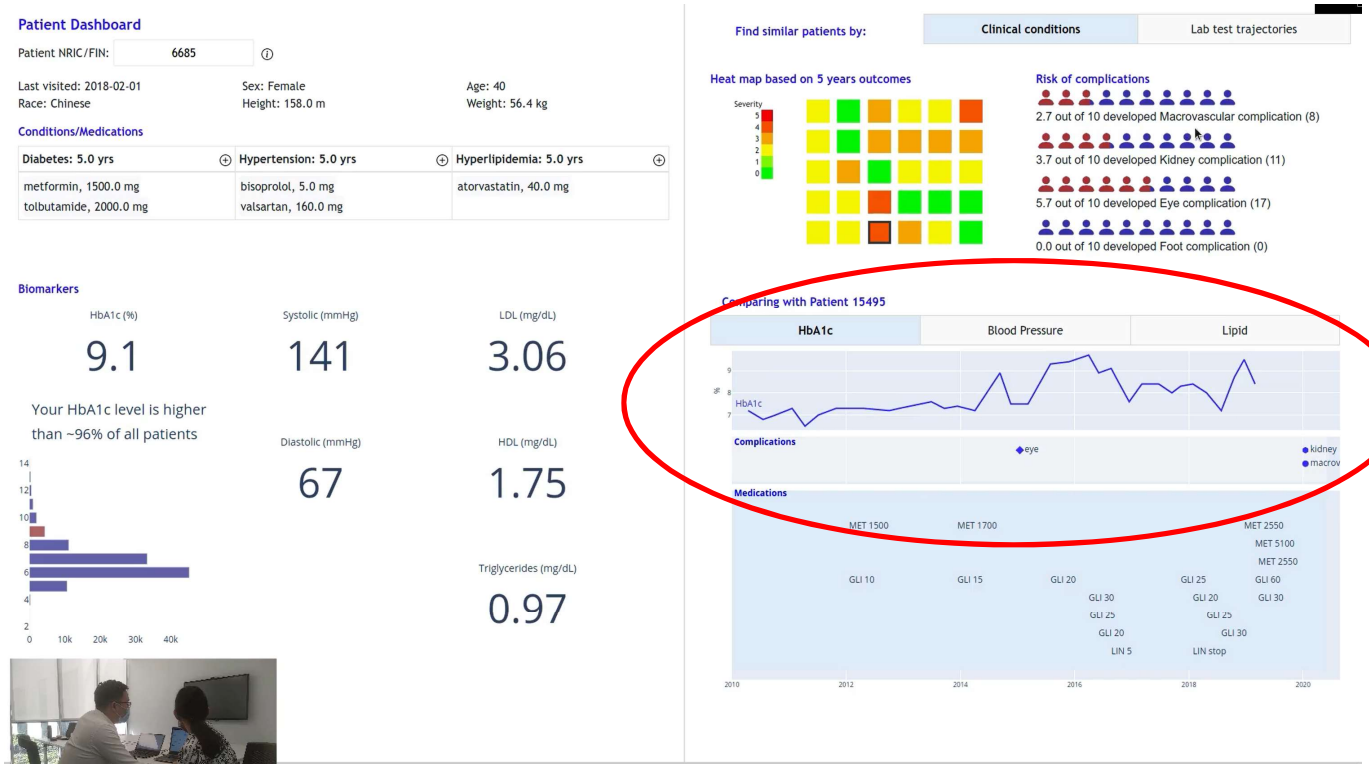
JARVIS$_{DHL}$ Primary Care Decision Support Tool

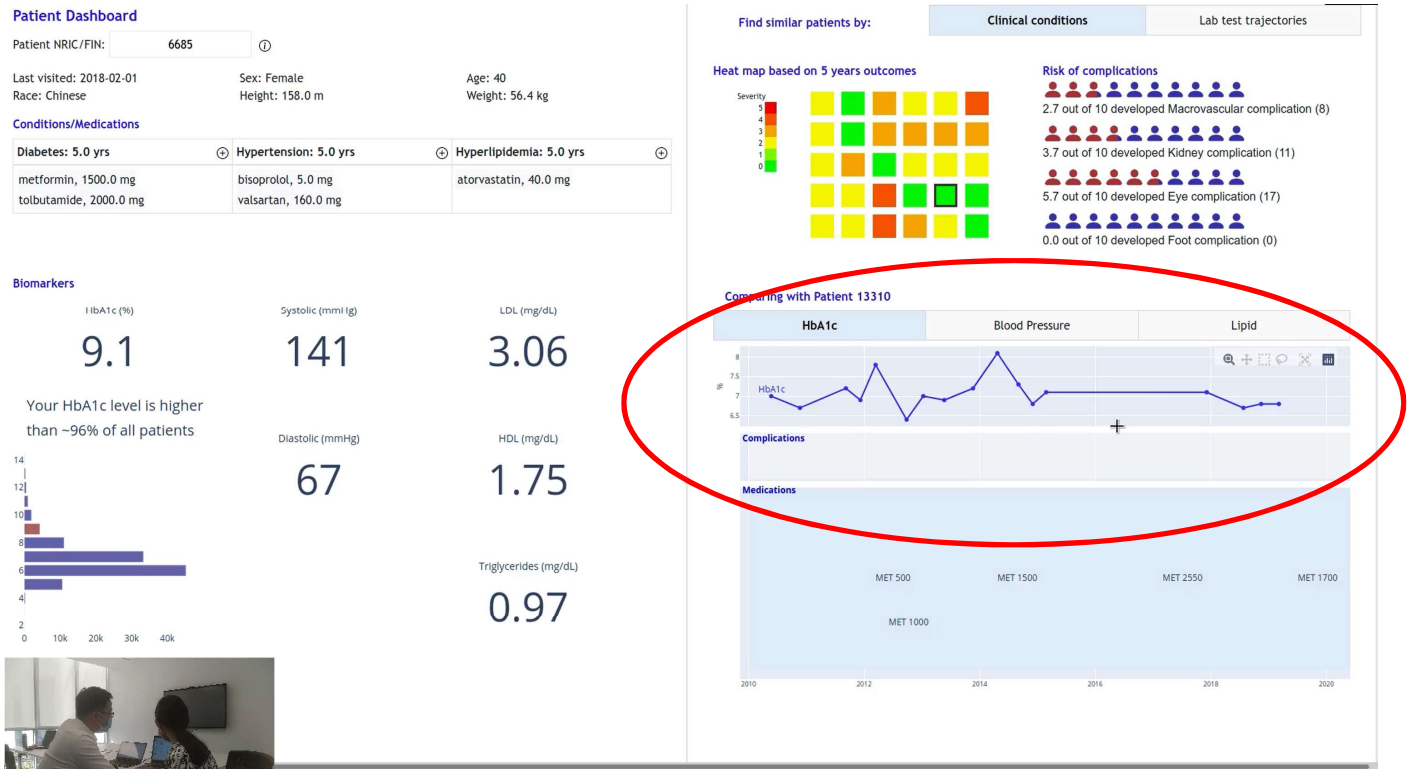
Personalized narratives (negative)



Aid patients with illness prognostication through narratives

JARVIS$_{DHL}$ Primary Care Decision Support Tool

Personalized narratives (positive)



Aid patients with illness prognostication through narratives

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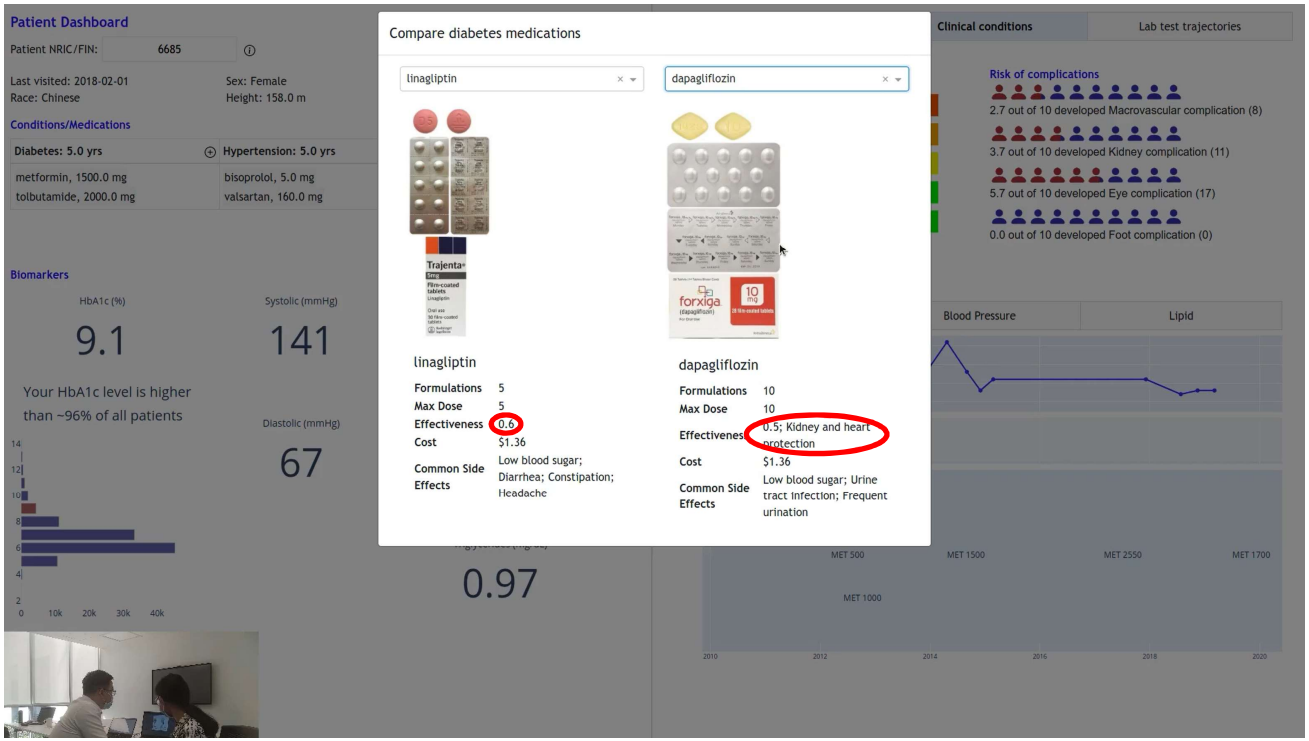
JARVIS$_{DHL}$ Primary Care Decision Support Tool

Treatment effectiveness for shared decision-making



More information to facilitate shared decision-making for improved patient ownership of treatment choices

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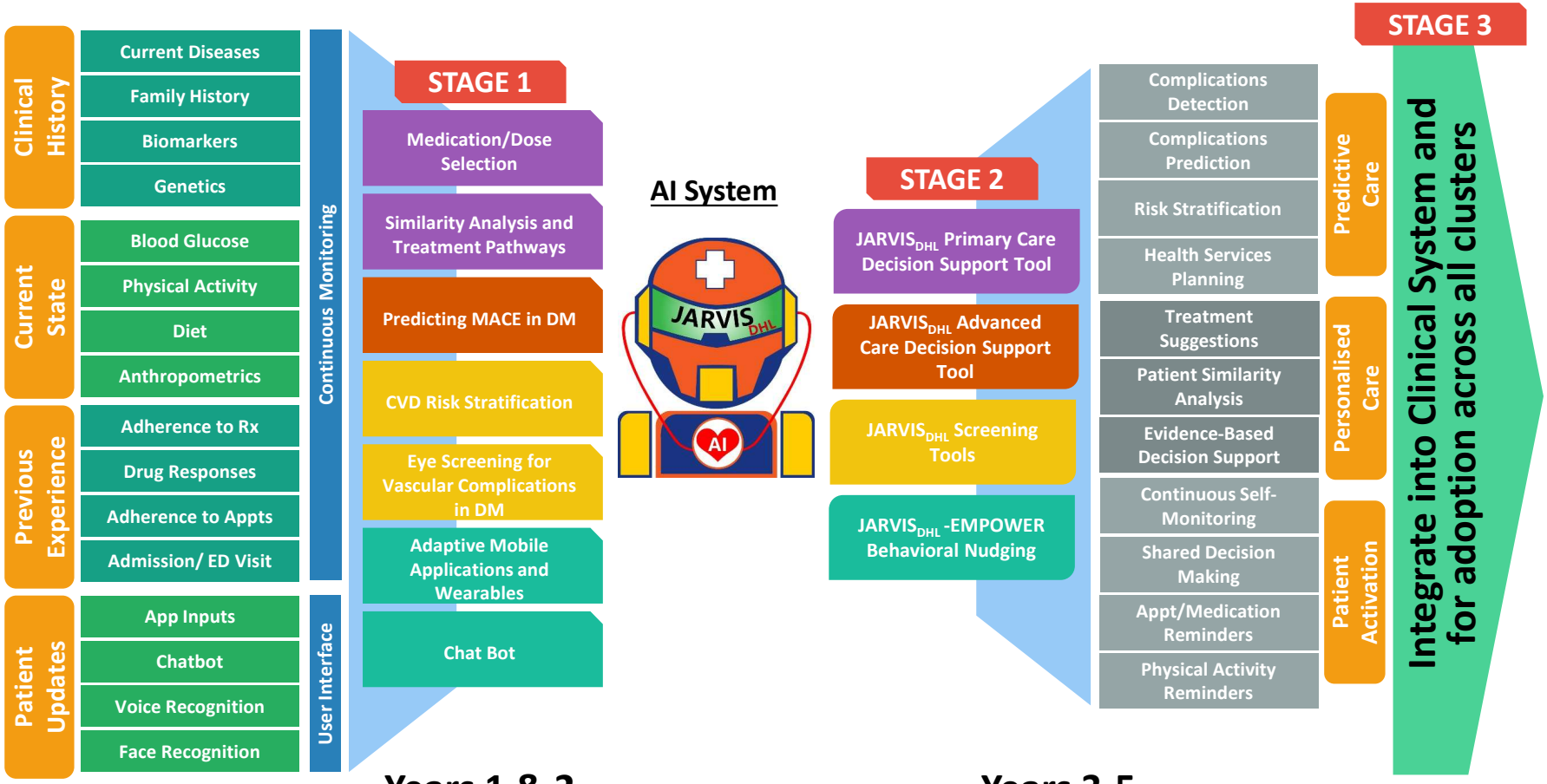
JARVIS$_{DHL}$ Roadmap



Years 1 & 2 (Development)

Years 3-5 (Validation and Implementation)

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Summary of Implementation Plan

	Primary Care Decision Support Tool	Advanced Care Decision Support Tool	Screening Tools	EMPOWER Behavioral Nudges
Test Site	SingHealth Polyclinics	Diabetes and Metabolism Centre (DMC)	NHCS DMC Retina Clinic	SingHealth Polyclinics and Diabetes Centre from SGH, CGH, SKH and NHCS
Test Population	Patients with DHL aged 21 years and older attending Family Physician Clinics	Patients with T2DM	Patients undergoing cardiac CT at NHCS and asymptomatic high risk diabetic patients seen at DMC retina clinics.	Patients with DHL
Intervention	Primary Care Decision Support Tool to support clinical consultations and for shared-decision making	MACE Counselling Tool	• CVD risk score • SIVA-DLS • Retina-DLS	• Shared decision making consultation and clinical follow- up • EMPOWER app • Smartwatch
Control		Usual Care		
Study Design	Open-label Cluster Randomized Controlled Trial	Unblinded Randomized Controlled Trial	Prospective Cohort matched with propensity score matched historical control	2-arm (1:1), Pragmatic, Randomized Controlled Trial
Performance Metric		Based on RE-AIM Framework		

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  - Mr Narayanan Ragavendran

- **NUS**
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  - Prof Lee Mong Li
  - Prof Ng See Kiong
  - Ms Tan Wei Ying
  - Ms Gao Qiao
  - Mr Ronald Wihal Oei

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