Supplementary Online Content

Machline-Carrion MJ, Soares RM, Damiani LP, et al; BRIDGE Cardiovascular Prevention Investigators. Effect of a multifaceted quality improvement intervention on the prescription of evidence-based treatment in patients at high cardiovascular risk in Brazil: the BRIDGE Cardiovascular Prevention cluster randomized clinical trial. *JAMA Cardiol*. Published online April 3, 2019. doi:10.1001/jamacardio.2019.0649

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. The Brazilian health care system

The Brazilian Government provides free public universal healthcare as a constitutional right for all citizens (population of about 200 million). This right represents an important democratization movement in the 1988 constitution. This system is called SUS and it represents one of the largest public health care system in the world. The SUS operates through both public and private participation as it also finances the private sector performing complementary tasks not being taken on by the public sector.

The public healthcare is theoretically able to reach 100% of population, but anyone who can afford, usually opt to have a private insurance healthcare plan. It is estimated that today there are approximately 150 million people that depend exclusively on the public system and 49 million people (or 25%) having private health insurances but that can also access to SUS. Brazil's medical system is to a significant extent decentralized, giving autonomy to states and municipalities

The main strategy for strengthening public primary healthcare is the Family Health Program, introduced by the municipal health secretariats in collaboration with the states and the Ministry of Public Health. The federal government supplies technical support and transfers funding through. Family Health teams are also linked to Primary Care Units or Basic Healthcare units, which usually involves family doctors (generalists), other healthcare professionals and community workers.

Besides primary care, the public system has hospitals of different complexities and medical specialties, where they have specialized outpatient clinics. The same applies to the private (for profit and not for profit) hospitals, also of different complexities and capabilities and which also have specialized outpatient clinics.

Both public and private hospitals can be teaching and non-teaching units. Primary care units can also be teaching or non-teaching units. Teaching units are usually linked to Medical Schools and provide training for undergraduate and graduate medical students and also students from other healthcare areas.

In the BRIDGE CV prevention trial we involved different types of clusters. In this sense, clusters could be outpatient clinics from either public or private hospitals. Clusters could also be teaching or non-teaching units.

eAppendix 2. Eligibility criteria

Eligibility of Clusters and Patients

Consecutive patients with age over 40 years considered to be of high cardiovascular risk (i.e. those with documented coronary artery disease, or documented stroke or transient ischemic attack, or documented peripheral arterial disease) from outpatient clinics from public and private hospitals or primary care clinics (which represent the clusters) from all regions in Brazil.

Patients are considered of high cardiovascular risk if they meet the at least one of the following criteria:

- Any evidence of coronary artery disease as defined by any of the following criteria:
    - History of myocardial infarction,
    - Stable angina
    - Surgical or percutaneous (balloon and/or any type of stent) coronary revascularization procedure
    - Coronary angiography showing at least one stenosis 50% in a major epicardial artery or branch vessel.
- Any evidence of ischemic stroke or transient ischemic attack (TIA) as defined by any of the following criteria:
    - Clinical diagnosis of ischemic stroke or transient ischemic attack (TIA);
    - Computed Tomography or Magnetic Resonance Imaging evidence of previous stroke;
- Peripheral Artery Disease (PAD) defined by previous or actual clinical diagnosis of any of the following criteria:
    - Intermittent claudication;
    - Limb amputation due to arterial cause;
    - Vascular surgery due to atherosclerotic disease;
    - Ankle/arm relation $\leq$0,90 in any leg during rest;
    - Angiographic study or Doppler Ultrasound showing $\geq$70% stenosis in a non- coronary artery.

Patients with atrial fibrillation and/or patients that at the discretion of the attending physician need oral anticoagulants, or patients who do not provide written informed consent are excluded.

eAppendix 3. BRIDGE CV quality improvement intervention

The multifaceted quality improvement intervention includes: reminders, care algorithms, training of a case manager, audit and feedback reports, and educational materials based on current international and national guidelines (Brazilian Society of Cardiology, American College of Cardiology/American Heart Association).

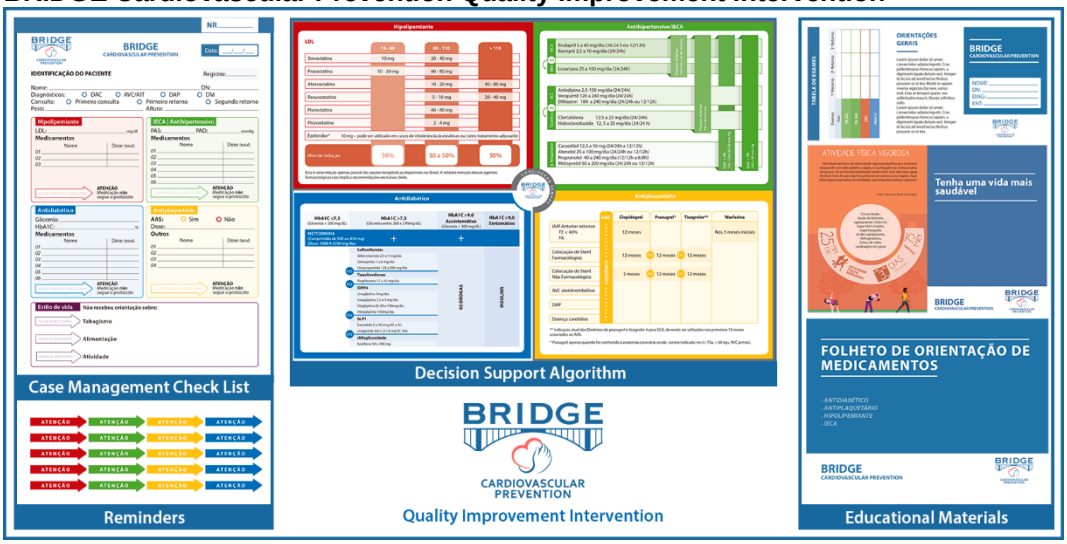
Case Management

Case management is conducted by at least one (1) trained nurse from each cluster. The case manager is responsible for a pre-physician visit patient evaluation. This evaluation always needs to happen the same day and immediately before the physician visit. This evaluation is conducted with a checklist that includes the following items: cardiovascular comorbidities, risk factors (blood pressure, lipid profile, glycemic control, smoking habits) and current medications. This information is organized in four different colored sections pertaining comprehending lipid profile control (red), blood pressure control and antihypertensives usage (green), glycemic control (blue) and antiplatelets indications (yellow). The case manager fills the checklist with the values correspondent to the patient physical exam (e.g., systolic and diastolic blood pressure levels) or laboratory tests (e.g., levels of LDL-cholesterol) as well as medications currently in use by the patient. If the case manager notices abnormalities in any item of the checklist (e.g., LDL-cholesterol levels above target and patient not taking lipid lowering therapy), she will register and highlight that abnormality in the checklist with reminders (colored arrow stickers). The filled checklist is provided to the physician together with the patient medical records. Besides providing the physician with the filled checklist, the case manager needs to prompt the physician verbally immediately before the patient visit. After the physician visit, the case manager checks again if each section of the checklist has been addressed. In case actions are not taken, the physician is prompted again to check if further management decisions are needed. See Figure 2.

Educational Materials and Decision Support

We provide to each physician from clusters randomized to the intervention group a decision support algorithm to be used at each visit. Consistent with the case manager checklist, the information is organized in four different colored sections pertaining comprehending lipid profile control (red), blood pressure control and antihypertensives usage (green), glycemic control (blue) and antiplatelets indications (yellow). The decision support system summarizes in 1-page the key evidence-based recommendations adapted from different guidelines by the trial Steering Committee. See Figure 2.

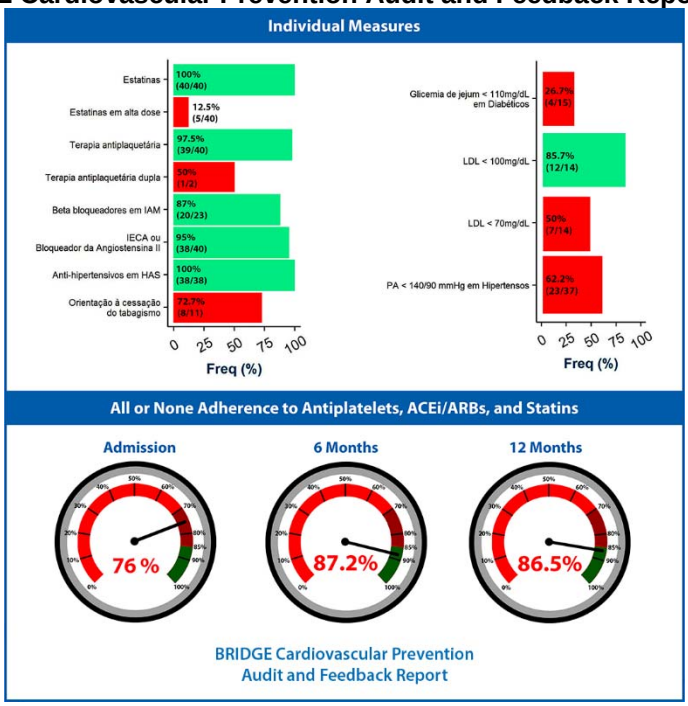
BRIDGE Cardiovascular Prevention Quality Improvement Intervention



Audit and Feedback Reports

Periodical audit and feedback reports on performance are provided to each cluster allocated to the intervention group. This strategy stimulates the teams to seek continuous improvement. Additionally, this report is discussed in periodic web or phone conferences to review the performance measures and set with aspects needed to improve See Figure 3.

BRIDGE Cardiovascular Prevention Audit and Feedback Report



Interactive Training Workshops

Health care providers from clusters randomized to the intervention group (at least a physician who will act as the local leader and a research nurse who will act as case manager) are invited to attend a course and workshop on cardiovascular prevention and also will receive training on how to implement the quality improvement intervention. In addition, all clusters randomized to the intervention receive on-site training visits complemented by web-based and telephone training.

eAppendix 4. Details of the baseline survey

We conducted a baseline survey in participating clusters using the same eligible criteria for patient's inclusion This survey was conducted before randomization to avoid potential systematic errors caused by awareness of allocation to intervention and control groups in clusters that have not participated in the REACT study. We used the same endpoint definition used in the trial. Results from this survey are available in eTable 1.

Berwanger O, Piva e Mattos LA, Martin JF, et al. Evidence-based therapy prescription in high-cardiovascular risk patients: the REACT study. *Arquivos brasileiros de cardiologia.* 2013;100(3):212-220.

eAppendix 5. Statistical methods details

All our analysis took the cluster design into account. In this sense, we performed a regression analysis based on individual-level data. Given that our primary endpoint and most of our secondary endpoints (performance measures) were binary, and given that we had a trial with more than 15 clusters per arm, we performed a logistic regression with random effects adjusted. This logistic regression takes into account between cluster variation. The estimate of the parameter β_i obtained from the logistic regression random effects model yields a cluster-specific estimate of the intervention effect. The exponential of β_i estimates the cluster-specific odds ratio of the outcome of interest (comparing the intervention and control arms). The main analyses were adjusted for baseline performance.

According to Hayes and Moulton, for trials with larger number of clusters (15 or more per arm), the individual-level regression analyses seem to perform reliably, and are likely to be preferred because of their greater convenience when analyzing the effects of individual-level covariates. They are also statistically more efficient that cluster-level methods since they use optimal weights for each cluster in order to minimize the standard errors of parameter estimates. Random effects regression or generalized estimating (GEE) equations with an exchangeable correlation matrix and robust standard errors usually provide very similar results.

Reference: Hayes RJ, Moulton LH. Cluster Randomised Trials (Chapters 10 and 11), 2009 by Taylor & Francis Group, LLC.

eTable 1. Prescription of evidence-based therapies in eligible patients from BRIGDE Cardiovascular Prevention baseline survey and REACT Registry[1]

	BRIDGE-CV Survey (n=275)	REACT (n=1447)	Total (n=1722)
All-or-none: Statin + Antiplatelet Therapy [a] + ACEI or ARB in an "all or none" with no contraindications.	153/259 (59.1)	740/1447 (51.1)	893/1706 (52.3)
Statins	221/259 (85.3)	1032/1447 (71.3)	1253/1706 (73.4)
High dose statins[b]	12/259 (4.6)	0/0 (NaN)	12/259 (4.6)
Antiplatelet Therapy	230/257 (89.5)	1182/1447 (81.7)	1412/1704 (82.9)
Adherence to ACEi or ARB	182/258 (70.5)	1080/1447 (74.6)	1262/1705 (74)
Dual Antiplatelet therapy in patients with recent MI	47/114 (41.2)	169/646 (26.2)	216/760 (28.4)
LDL < 100mg/dL	77/127 (60.6)	413/640 (64.5)	490/767 (63.9)
LDL < 70mg/dL	42/127 (33.1)	160/640 (25)	202/767 (26.3)
BP < 140/90 mmHg in patients with hypertension	146/226 (64.6)	694/1252 (55.4)	840/1478 (56.8)
BP < 120/80 mmHg in patients with hypertension	41/226 (18.1)	184/1252 (14.7)	225/1478 (15.2)
Systolic BP < 120 mmHg in patients with hypertension	55/226 (24.3)	220/1252 (17.6)	275/1478 (18.6)
Fasting glycemia ≤ 110mg/dL in patients with diabetes	23/65 (35.4)	114/360 (31.7)	137/425 (32.2)
Fasting glycemia ≤ 126mg/dL in patients with diabetes	33/65 (50.8)	165/360 (45.8)	198/425 (46.6)
HbA1c ≤ 7.0% in patients with diabetes	22/43 (51.2)	0/0 (NaN)	22/43 (51.2)
Beta blockers in patients with MI	102/118 (86.4)	443/646 (68.6)	545/764 (71.3)
Smoke Cessation Education	69/200 (34.5)	279/474 (58.9)	348/674 (51.6)
Antihypertensive drugs in patients with hypertension[c]	212/226 (93.8)	1181/1252 (94.3)	1393/1478 (94.2)

Abbreviations: ACEi denotes anfiotensin converting enzyme; ARB denotes angiotensin receptor blocker; LDL denotes low-density lipoprotein; BP denotes blood pressure; MI denotes myocardial infarction

[a] We had no data of time since MI from REACT study, therefore, Antiplatelet therapy was considered as only one medication.

[b] High doses defined as: 80mg of Simvastatin, 80mg of Pravastatin, 80mg of Atorvastatin, 40mg of Rosuvastatin, 80mg of Fluvastatin or 4mg of Pitavastatin, [c] Missing information of time since MI.

1. Berwanger O, Piva e Mattos LA, Martin JF, et al. Evidence-based therapy prescription in high-cardiovascular risk patients: the REACT study. *Arquivos brasileiros de cardiologia.* 2013;100(3):212-220.

eTable 2. Overall comparison between baseline characteristics from all included and excluded clusters*

Cluster Baseline Characteristics, n (%)	Excluded (n=3)	Included (n=40)	*P* Value
Clinical Specialty[a]			
Cardiology	2 (66.7)	31 (77.5)	0.56
Neurology	1 (33.3)	3 (7.5)	0.26
Vascular surgery	2 (66.7)	2 (5.0)	0.02
Endocrinology	0 (0)	0 (0)	-
Internal medicine	1 (33.3)	2 (5.0)	0.20
Primary care unit	1 (33.3)	6 (15.0)	0.42
Previous participation in clinical trials	2 (66.7)	32 (80.0)	0.52
Teaching unit	3 (100)	26 (65.0)	0.54
Healthcare sector			
Private	0 (0)	13 (32.5)	0.57
Public	2 (66.7)	20 (50.0)	
Mixed	1 (33.3)	7 (17.5)	
Volume of patients seen in ambulatory per mo, median [IQR]	-	235 [100 - 525]	-
Structured prior protocol for care and management of patients at high cardiovascular risk.	-	18 (45.0)	-

*Analysis should be interpreted with caution due to the very low number of observations in 1 group (3 clusters).
[a] Sum of specialties may be higher than the number of clusters, because a cluster may include more than one specialty.

eTable 3. Adherence to the multifaceted quality improvement intervention

Tools	Admission	6 months follow-up	12 months follow-up
Identification label	565/726 (77.8)	545/720 (75.7)	502/713 (70.4)
Case Manager	702/726 (96.7)	681/720 (94.6)	654/713 (91.7)
Clinical Decision Support Tool	711/726 (97.9)	680/720 (94.4)	658/713 (92.3)
Pre and post consultation sheets	700/726 (96.4)	676/720 (93.9)	652/713 (91.4)
Sharing pre and post cards	694/700 (99.1)	675/676 (99.9)	652/652 (100)
Patient's Card	693/726 (95.5)	671/720 (93.2)	637/713 (89.3)
Brochure with guidelines	700/726 (96.4)	664/720 (92.2)	644/713 (90.3)

eTable 4. Effects of a quality improvement intervention on prescription of evidence-based therapies in eligible patients and risk factors control on admission

End Points	Intervention	Control	Odds Ratio [95% CI]	Valor p	ICC
Adherence to Evidence Based Therapies in admission					
Complete adherence to statins, antiplatelets[a] and ACEi or ARB	492/726 (67.8)	547/893 (61.3)	1.49 [0.86; 2.60]	0.10	0.112
Statins	665/726 (91.6)	750/893 (84)	1.97 [0.81; 4.81]	0.08	0.242
High dose statins[b]	56/726 (7.7)	50/893 (5.6)	2.70 [0.74; 9.86]	0.08	0.364
Antiplatelet Therapy (%)	673/726 (92.7)	782/893 (87.6)	2.30 [2.29; 2.31]	<0.01	0.221
Aspirin (%)	641/718 (89.3)	748/886 (84.4)	1.76 [0.72; 4.28]	0.14	0.243
Clopidogrel (%)	173/726 (23.8)	238/891 (26.7)	0.99 [0.48; 2.02]	0.97	0.18
Ticagrelor (%)	20/724 (2.8)	13/892 (1.5)	2.59 [0.56; 11.93]	0.15	0.338
Prasugrel	3/725 (0.4)	1/893 (0.1)	-	-	-
Adherence to ACEi or ARB	570/723 (78.8)	699/892 (78.4)	1.01 [0.60; 1.68]	0.97	0.087
ACEi	299/723 (41.4)	394/892 (44.2)	1.01 [0.58; 1.76]	0.97	0.115
ARB	287/724 (39.6)	323/893 (36.2)	1.07 [0.61; 1.88]	0.77	0.117
Dual Antiplatelet therapy in patients with recent MI[c]	48/72 (66.7)	109/163 (66.9)	1.92 [0.52; 7.12]	0.26	0.242
Beta blockers in patients with MI	292/370 (78.9)	360/475 (75.8)	1.21 [0.49; 2.98]	0.63	0.231
Smoke Cessation Education	319/640 (49.8)	181/825 (21.9)	4.83 [1.32; 17.67]	<0.01	0.444
Antihypertensive drugs in patients with hypertension[d]	640/662 (96.7)	747/769 (97.1)	0.89 [0.30; 2.70]	0.82	0.227
Risk Factors Control in at admission					
LDL < 100mg/dL	325/476 (68.3)	337/536 (62.9)	1.31 [0.82; 2.08]	0.18	0.052
LDL < 70mg/dL	163/476 (34.2)	166/536 (31)	1.19 [0.82; 1.72]	0.27	0.015
LDL; mean (SD)	89.0 (38.2)	92.4 (37.0)	-4.51 [-10.94; 1.92][e]	0.16	0.026
BP < 140/90 mmHg in patients with hypertension	431/662 (65.1)	458/769 (59.6)	1.23 [0.72; 2.10]	0.38	0.102
BP < 120/80 mmHg in patients with hypertension	120/662 (18.1)	113/769 (14.7)	1.31 [0.78; 2.23]	0.23	0.076
Systolic BP < 120 mmHg in patients with hypertension	129/662 (19.5)	135/769 (17.6)	1.04 [0.62; 1.76]	0.85	0.07
Systolic Blood Pressure in patients with hypertension; mean(SD)	132.4 (20.2)	133.2 (20.7)	-1.53 [-6.67; 1.92][e]	0.55	0.116
Dyastolic Blood Pressure in patients with hypertension; mean(SD)	77.3 (11.1)	80.2 (11.3)	-3.10 [-5.71; -0.49][e]	0.02	0.095

Fasting glycemia ≤ 110mg/dL in patients with diabetes	77/219 (35.2)	73/209 (34.9)	0.98 [0.56; 1.73]	0.94	0
Fasting glycemia ≤ 126mg/dL in patients with diabetes	111/219 (50.7)	104/209 (49.8)	1.04 [0.54; 1.99]	0.89	0.025
HbA1c ≤ 7.0% in patients with diabetes	98/198 (49.5)	87/175 (49.7)	1.55 [0.58; 4.11]	0.29	0.059

Abbreviations: CI denotes confidence interval; ICC denotes intracluster correlation coefficient; ACEi denotes angiotensin converting enzyme inhibitor; ARB denotes angiotensin receptor blocker; MI denotes myocardial infarction.

[a] In patients with MI up to 12 months, double antiplatelet therapy is considered.

[b] High doses defined as: 80mg of Simvastatin, 80mg of Pravastatin, 80mg of Atorvastatin, 40mg of Rosuvastatin, 80mg of Fluvastatin or 4mg of Pitavastatin,

[c] Any combination of listed antiplatelets (Aspirin, Clopidogrel, Ticagrelor and Prasugrel).

[d] Thiazide diuretic, Beta blocker, ACEI, ARB, calcium channel blockers or renin direct inhibitors.

[e] Mean difference and 95% CI estimated by mixed effect regression model using the center as the random intercept and corrected for the baseline survey values as fixed effect

eTable 5. Effects of a quality improvement intervention on prescription of evidence-based therapies in eligible patients, major cardiovascular events, and risk factors control at 6 months follow-up

End Points in 6 months	Intervention	Control	Odds Ratio [95% CI]	P Value	ICC
Adherence to Evidence Based Therapies in 6 months					
Complete adherence to statins, antiplatelets[a] and ACEi or ARB	482/691 (69.8)	498/834 (59.7)	1.82 [0.96; 3.44]	0.03	0.148
Statins	639/691 (92.5)	690/834 (82.7)	2.99 [1.14; 7.85]	0.01	0.273
High dose statins[b]	56/691 (8.1)	57/834 (6.8)	1.88 [0.54; 6.60]	0.24	0.358
Antiplatelet Therapy	646/691 (93.5)	724/834 (86.8)	2.91 [1.23; 6.89]	<0.01	0.199
Aspirin	620/683 (90.8)	689/828 (83.2)	2.26 [1.05; 4.83]	0.01	0.173
Clopidogrel	131/689 (19)	191/833 (22.9)	0.90 [0.41; 2.00]	0.77	0.207
Ticagrelor	12/690 (1.7)	15/834 (1.8)	1.78 [0.28; 11.37]	0.47	0.429
Prasugrel	1/690 (0.1)	2/834 (0.2)	-	-	-
Adherence to ACEi or ARB	545/687 (79.3)	643/834 (77.1)	1.14 [0.72; 1.79]	0.51	0.059
ACEi	269/683 (39.4)	361/834 (43.3)	0.96 [0.55; 1.68]	0.86	0.115
ARB	291/687 (42.4)	290/834 (34.8)	1.28 [0.71; 2.31]	0.33	0.128
Beta blockers in patients with MI	285/365 (78.1)	353/459 (76.9)	1.12 [0.44; 2.84]	0.78	0.245
Smoke Cessation Education	361/713 (50.6)	143/855 (16.7)	11.37 [2.44; 52.92]	<0.01	0.53
Cardiovascular events in 6 months [e]					
MACE [f]	9/726 (1.2)	13/893 (1.5)	0.84 [0.34; 2.05]	0.69	0.115
Cardiovascular mortality	4/726 (0.6)	7/893 (0.8)	0.69 [0.19; 2.47]	0.57	0.151
Stroke	4/726 (0.6)	8/893 (0.9)	0.60 [0.17; 2.11]	0.42	0.159
Myocardial Infarction	3/726 (0.4)	2/893 (0.2)	1.79 [0.30; 10.70]	0.52	0
Total mortality	7/726 (1)	12/893 (1.3)	0.69 [0.27; 1.76]	0.44	0
Risk Factors Control in 6 months					
LDL < 100mg/dL	341/450 (75.8)	266/389 (68.4)	1.27 [0.62; 2.61]	0.44	0.136
LDL < 70mg/dL	186/450 (41.3)	148/389 (38)	1.12 [0.59; 2.14]	0.69	0.116
LDL; mean(SD)	83.8 (35.4)	88.7 (37.1)	-3.80 [-13.31; 5.72][g]	0.42	0.091
BP < 140/90 mmHg in patients with hypertension	420/650 (64.6)	420/735 (57.1)	1.29 [0.81; 2.04]	0.21	0.069

BP < 120/80 mmHg in patients with hypertension	121/650 (18.6)	146/735 (19.9)	0.84 [0.47; 1.49]	0.48	0.101
Systolic Blood Pressure in patients with hypertension; mean(SD)	129.1 (28.1)	128.6 (32.2)	1.31 [-8.17; 10.80][g]	0.78	0.184
Dyastolic Blood Pressure in patients with hypertension; mean(SD)	75.5 (15.3)	76.6 (18.9)	-0.28 [-5.68; 5.11][g]	0.92	0.183
Systolic BP < 120 mmHg in patients with hypertension	138/650 (21.2)	168/735 (22.9)	0.78 [0.45; 1.36]	0.29	0.086
Fasting glycemia ≤ 110mg/dL in patients with diabetes	69/205 (33.7)	68/166 (41)	0.73 [0.37; 1.45]	0.28	0.017
Fasting glycemia ≤ 126mg/dL in patients with diabetes	108/205 (52.7)	86/166 (51.8)	1.08 [0.58; 2.01]	0.76	0
HbA1c ≤ 7.0% in patients with diabetes	98/189 (51.9)	65/143 (45.5)	1.37 [0.53; 3.57]	0.43	0.033

Abbreviations: CI denotes confidence interval; ICC denotes intracluster correlation coefficient; ACEi denotes angiotensin converting enzyme inhibitor; ARB denotes angiotensin receptor blocker; MI denotes myocardial infarction; MACE: Major Adverse Cardiac Events

[a] In patients with MI up to 12 months, double antiplatelet therapy is considered.

[b] High doses defined as: 80mg of Simvastatin, 80mg of Pravastatin, 80mg of Atorvastatin, 40mg of Rosuvastatin, 80mg of Fluvastatin or 4mg of Pitavastatin,

[c] Any combination of listed antiplatelets (Aspirin, Clopidogrel, Ticagrelor and Prasugrel).

[d] Thiazide diuretic, Beta blocker, ACEI, ARB, calcium channel blockers or renin direct inhibitors.

[e] Cardiovascular events in 12 months presented as Hazard Ratios estimates from unadjusted Frailty Cox proportional hazard models with random effect by center.

[f] Combined occurrence of a first cardiovascular event (cardiovascular mortality, non-fatal acute myocardial infarction and non-fatal stroke).

[g] Mean difference and 95% CI estimated by mixed effect linear regression model using the center as the random intercept and corrected for the baseline survey values as fixed effect

eTable 6. Post hoc sensitivity analysis for the primary outcome considering multiple imputations

End Points in 6 months	Intervention	Control	Odds Ratio [95% CI]	P Value
Sensitivity Analysis 1 – Multiple Imputation				
Primary Outcome	73.6%	58.6%	2.16 [1.19; 3.94]	.01
Sensitivity Analysis 2 – Adjusted Analysis				
Primary Outcome	73.5%	58.7%	2.30 [1.01; 5.36]	.01

Abbreviations: CI denotes confidence interval

* Adjusted for baseline characteristics (adjusted for patient age, unit profile (hospital outpatient clinic or primary care center), unit status (teaching unit versus non-teaching unit), general versus specialized unit was performed.