

ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Addenda

The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)

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2.1 Epidemiology

- Savonitto S, Ardissino D, Granger CB, Morando G, Prando MD, Mafrici A, Cavallini C, Melandri G, Thompson TD, Vahanian A, Ohman EM, Califf RM, Van de Werf F, Topol EJ. Prognostic value of the admission electrocardiogram in acute coronary syndromes. *JAMA* 1999;**281**:707–713.

3.1 Clinical presentation

- Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000;**36**:959–969.
- Braunwald E. Unstable angina. A classification. *Circulation* 1989;**80**:410–414.

- Hamm CW, Braunwald E. A classification of unstable angina revisited. *Circulation* 2000;**102**:118–122.
- Eggers KM, Oldgren J, Nordenskjold A, Lindahl B. Diagnostic value of serial measurement of cardiac markers in patients with chest pain: limited value of adding myoglobin to troponin I for exclusion of myocardial infarction. *Am Heart J* 2004;**148**:574–581.
- van Miltenburg-van Zijl AJ, Simoons ML, Veerhoek RJ, Bossuyt PM. Incidence and follow-up of Braunwald subgroups in unstable angina pectoris. *J Am Coll Cardiol* 1995;**25**:1286–1292.

3.2 Diagnostic tools

- Avanzas P, Arroyo-Espiguero R, Cosin-Sales J, Aldama G, Pizzi C, Quiles J, Kaski JC. Markers of inflammation and multiple complex stenoses (pancoronary plaque vulnerability) in patients with non-ST segment elevation acute coronary syndromes. *Heart* 2004;**90**:847–852.
- Bertrand ME, LaBlanche JM, Tilmant PY, Thieuleux FA, Delforge MR, Carre AG, Asseman P, Berzin B, Libersa C, Laurent JM. Frequency of provoked coronary arterial spasm in 1089 consecutive patients undergoing coronary arteriography. *Circulation* 1982;**65**:1299–1306.
- Bholasingh R, Cornel JH, Kamp O, van Straalen JP, Sanders GT, Tijssen JG, Umans VA, Visser CA, de Winter RJ. Prognostic value of predischARGE dobutamine stress echocardiography in chest pain patients with a negative cardiac troponin T. *J Am Coll Cardiol* 2003;**41**:596–602.
- Cannon CP, McCabe CH, Stone PH, Rogers WJ, Schactman M, Thompson BW, Pearce DJ, Diver DJ, Kells C, Feldman T, Williams M, Gibson RS, Kronenberg MW, Ganz LI, Anderson HV, Braunwald E. The electrocardiogram predicts one-year outcome of patients with unstable angina and non-Q wave myocardial infarction: results of the TIMI III Registry ECG Ancillary Study. Thrombolysis in Myocardial Ischemia. *J Am Coll Cardiol* 1997;**30**:133–140.
- Giannitsis E, Becker M, Kurz K, Hess G, Zdunek D, Katus HA. High-sensitivity cardiac troponin T for early prediction of evolving non-ST-segment elevation myocardial infarction in patients with suspected acute coronary syndrome and negative troponin results on admission. *Clin Chem* 2010;**56**:642–650.
- Hasdai D, Lev EI, Behar S, Boyko V, Danchin N, Vahanian A, Battler A. Acute coronary syndromes in patients with pre-existing moderate to severe valvular disease of the heart: lessons from the Euro-Heart Survey of acute coronary syndromes. *Eur Heart J* 2003;**24**:623–629.
- Hoffmann U, Nagurney JT, Moselewski F, Pena A, Ferencik M, Chae CU, Cury RC, Butler J, Abbara S, Brown DF, Manini A, Nichols JH, Achenbach S, Brady TJ. Coronary multidetector computed tomography in the assessment of patients with acute chest pain. *Circulation* 2006;**114**:2251–2260.
- Ingkanisorn WP, Kwong RY, Bohme NS, Geller NL, Rhoads KL, Dyke CK, Paterson DI, Syed MA, Aletras AH, Arai AE. Prognosis of negative adenosine stress magnetic resonance in patients presenting to an emergency department with chest pain. *J Am Coll Cardiol* 2006;**47**:1427–1432.
- Kontos MC, Jesse RL, Schmidt KL, Ornato JP, Tatum JL. Value of acute rest sestamibi perfusion imaging for evaluation of patients admitted to the emergency department with chest pain. *J Am Coll Cardiol* 1997;**30**:976–982.
- Melanson SE, Morrow DA, Jarolim P. Earlier detection of myocardial injury in a preliminary evaluation using a new troponin I assay with improved sensitivity. *Am J Clin Pathol* 2007;**128**:282–286.
- Möllmann H, Nef HM, Kostin S, Dragu A, Maack C, Weber M, Troidl C, Rolf A, Elsasser A, Bohm M, Brantner R, Hamm CW, Holubarsch CJ. Ischemia triggers BNP expression in the human myocardium independent from mechanical stress. *Int J Cardiol* 2010;**143**:289–297.
- Nef HM, Möllmann H, Elsasser A. Tako-tsubo cardiomyopathy (apical ballooning). *Heart* 2007;**93**:1309–1315.
- Ntalianis A, Sels JW, Davidavicius G, Tanaka N, Muller O, Trana C, Barbato E, Hamilos M, Mangiacapra F, Heyndrickx GR, Wijns W, Pijls NH, De Bruyne B. Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. *JACC Cardiovasc Interv* 2010;**3**:1274–1281.
- Rioufol G, Gilard M, Finet G, Ginon I, Boschat J, Andre-Fouet X. Evolution of spontaneous atherosclerotic plaque rupture with medical therapy: long-term follow-up with intravascular ultrasound. *Circulation* 2004;**110**:2875–2880.
- Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med* 2004;**351**:2611–2618.
- Sylven C, Lindahl S, Hellkvist K, Nyquist O, Rasmanis G. Excellent reliability of nurse-based bedside diagnosis of acute myocardial infarction by rapid dry-strip creatine kinase MB, myoglobin, and troponin T. *Am Heart J* 1998;**135**:677–683.
- Takakuwa KM, Halpern EJ. Evaluation of a ‘triple rule-out’ coronary CT angiography protocol: use of 64-Section CT in low-to-moderate risk emergency department patients suspected of having acute coronary syndrome. *Radiology* 2008;**248**:438–446.
- White HD. Higher sensitivity troponin levels in the community: what do they mean and how will the diagnosis of myocardial infarction be made? *Am Heart J* 2010;**159**:933–936.

4.1 Clinical risk assessment

- Boersma E, Pieper KS, Steyerberg EW, Wilcox RG, Chang WC, Lee KL, Akkerhuis KM, Harrington RA, Deckers JW, Armstrong PW, Lincoff AM, Califf RM, Topol EJ, Simoons ML. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. *Circulation* 2000;**101**:2557–2567.
- Kurz DJ, Bernstein A, Hunt K, Radovanovic D, Erne P, Siudak Z, Bertel O. Simple point-of-care risk stratification in acute coronary syndromes: the AMIS model. *Heart* 2009;**95**:662–668.
- Singh M, Reeder GS, Jacobsen SJ, Weston S, Killian J, Roger VL. Scores for post myocardial infarction risk stratification in the community. *Circulation* 2002;**106**:2309–2314.

4.2 Electrocardiogram indicators

- Gottlieb SO, Weisfeldt ML, Ouyang P, Mellits ED, Gerstenblith G. Silent ischemia as a marker for early unfavorable outcomes in patients with unstable angina. *N Engl J Med* 1986;**314**:1214–1219.
- Hyde TA, French JK, Wong CK, Straznicky IT, Whitlock RM, White HD. Four-year survival of patients with acute coronary syndromes without ST-segment elevation and prognostic significance of 0.5-mm ST-segment depression. *Am J Cardiol* 1999;**84**:379–385.
- Jernberg T, Lindahl B, Wallentin L. The combination of a continuous 12-lead ECG and troponin T; a valuable tool for risk stratification during the first 6 hours in patients with chest pain and a non-diagnostic ECG. *Eur Heart J* 2000;**21**:1464–1472.
- Nyman I, Areskog M, Areskog NH, Swahn E, Wallentin L. Very early risk stratification by electrocardiogram at rest in men with suspected unstable coronary heart disease. The RISC Study Group. *J Intern Med*. 1993;**234**:293–301.
- Patel DJ, Holdright DR, Knight CJ, Mulcahy D, Thakrar B, Wright C, Sparrow J, Wicks M, Hubbard W, Thomas R, Sutton GC, Hendry G, Purcell H, Fox K. Early continuous ST segment monitoring in unstable angina: prognostic value additional to the clinical characteristics and the admission electrocardiogram. *Heart* 1996;**75**:222–228.
- de Zwaan C, Bar FW, Janssen JH, Cheriex EC, Dassen WR, Brugada P, Penn OC, Wellens HJ. Angiographic and clinical characteristics of patients with unstable angina showing an ECG pattern indicating critical narrowing of the proximal LAD coronary artery. *Am Heart J* 1989;**117**:657–665.

4.3 Biomarkers

- Aronson D, Suleiman M, Agmon Y, Suleiman A, Blich M, Kapelevich M, Beyar R, Markiewicz W, Hammerman H. Changes in haemoglobin levels during hospital course and long-term outcome after acute myocardial infarction. *Eur Heart J* 2007;**28**:1289–1296.
- Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, Neumann FJ, Robertson DH, DeLucca PT, DiBattiste PM, Gibson CM, Braunwald E. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;**344**:1879–1887.
- Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;**16**:31–41.
- Coll E, Botey A, Alvarez L, Poch E, Quinto L, Saurina A, Vera M, Piera C, Darnell A. Serum cystatin C as a new marker for non-invasive estimation of glomerular filtration rate and as a marker for early renal impairment. *Am J Kidney Dis* 2000;**36**:29–34.
- de Lemos JA, Morrow DA, Bentley JH, Omland T, Sabatine MS, McCabe CH, Hall C, Cannon CP, Braunwald E. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N Engl J Med* 2001;**345**:1014–1021.
- de Winter RJ, Koch KT, van Straalen JP, Heyde G, Bax M, Schotborgh CE, Mulder KJ, Sanders GT, Fischer J, Tijssen JG, Piek JJ.

C-reactive protein and coronary events following percutaneous coronary angioplasty. *Am J Med* 2003;**115**:85–90.

- Hamm CW, Heeschen C, Goldmann B, Vahanian A, Adgey J, Miguel CM, Rutsch W, Berger J, Kootstra J, Simoons ML. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) Study Investigators. *N Engl J Med* 1999;**340**:1623–1629.
- Heeschen C, Hamm CW, Goldmann B, Deu A, Langenbrink L, White HD. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. PRISM Study Investigators. Platelet Receptor Inhibition in Ischemic Syndrome Management. *Lancet* 1999;**354**:1757–1762.
- Heeschen C, Hamm CW, Mitrovic V, Lantelme NH, White HD. N-terminal pro-B-type natriuretic peptide levels for dynamic risk stratification of patients with acute coronary syndromes. *Circulation* 2004;**110**:3206–3212.
- Jernberg T, Stridsberg M, Venge P, Lindahl B. N-terminal pro brain natriuretic peptide on admission for early risk stratification of patients with chest pain and no ST-segment elevation. *J Am Coll Cardiol* 2002;**40**:437–445.
- Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;**130**:461–470.
- Lindahl B, Diderholm E, Lagerqvist B, Venge P, Wallentin L. Mechanisms behind the prognostic value of troponin T in unstable coronary artery disease: a FRISC II substudy. *J Am Coll Cardiol* 2001;**38**:979–986.
- James SK, Lindahl B, Siegbahn A, Stridsberg M, Venge P, Armstrong P, Barnathan ES, Califf R, Topol EJ, Simoons ML, Wallentin L. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: a Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV substudy. *Circulation* 2003;**108**:275–281.
- James SK, Lindback J, Tilly J, Siegbahn A, Venge P, Armstrong P, Califf R, Simoons ML, Wallentin L, Lindahl B. Troponin-T and N-terminal pro-B-type natriuretic peptide predict mortality benefit from coronary revascularization in acute coronary syndromes: a GUSTO-IV substudy. *J Am Coll Cardiol* 2006;**48**:1146–1154.
- Kurek T, Lenarczyk R, Kowalczyk J, Swiatkowski A, Kowalski O, Stabryla-Deska J, Honisz G, Lekston A, Kalarus Z, Kukulski T. Effect of anemia in high-risk groups of patients with acute myocardial infarction treated with percutaneous coronary intervention. *Am J Cardiol* 2010;**105**:611–618.
- Masoudi FA, Plomondon ME, Magid DJ, Sales A, Rumsfeld JS. Renal insufficiency and mortality from acute coronary syndromes. *Am Heart J* 2004;**147**:623–629.
- Mueller C, Laule-Kilian K, Schindler C, Klima T, Frana B, Rodriguez D, Scholer A, Christ M, Perruchoud AP. Cost-effectiveness of B-type natriuretic peptide testing in patients with acute dyspnea. *Arch Intern Med* 2006;**166**:1081–1087.
- Shlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman AB, Siscovick DS, Stehman-Breen C. Cystatin C and the risk of death

and cardiovascular events among elderly persons. *N Engl J Med* 2005;**352**:2049–2060.

- Taglieri N, Fernandez-Berges DJ, Koenig W, Consuegra-Sanchez L, Fernandez JM, Robles NR, Sanchez PL, Beiras AC, Orbe PM, Kaski JC. Plasma cystatin C for prediction of 1-year cardiac events in Mediterranean patients with non-ST elevation acute coronary syndrome. *Atherosclerosis* 2010;**209**:300–305.
- Weber JA, van Zanten AP. Interferences in current methods for measurements of creatinine. *Clin Chem* 1991;**37**:695–700.
- Weber M, Kleine C, Keil E, Rau M, Berkowitsch A, Elsaesser A, Mitrovic V, Hamm C. Release pattern of N-terminal pro B-type natriuretic peptide (NT-proBNP) in acute coronary syndromes. *Clin Res Cardiol* 2006;**95**:270–280.
- Wong JA, Goodman SG, Yan RT, Wald R, Bagnall AJ, Welsh RC, Wong GC, Kornder J, Eagle KA, Steg PG, Yan AT. Temporal management patterns and outcomes of non-ST elevation acute coronary syndromes in patients with kidney dysfunction. *Eur Heart J* 2009;**30**:549–557.

4.4 Risk scores

- Khan SQ, Narayan H, Ng KH, Dhillon OS, Kelly D, Quinn P, Squire IB, Davies JE, Ng LL. N-terminal pro-B-type natriuretic peptide complements the GRACE risk score in predicting early and late mortality following acute coronary syndrome. *Clin Sci (Lond)* 2009;**117**:31–39.
- Macrae AR, Kavsak PA, Lustig V, Bhargava R, Vandersluis R, Palomaki GE, Yerna MJ, Jaffe AS. Assessing the requirement for the 6-hour interval between specimens in the American Heart Association Classification of Myocardial Infarction in Epidemiology and Clinical Research Studies. *Clin Chem* 2006;**52**:812–818.

5.1 Anti-ischaemic agents

- Chaitman BR. Ranolazine for the treatment of chronic angina and potential use in other cardiovascular conditions. *Circulation* 2006;**113**:2462–2472.
- DePace NL, Herling IM, Kotler MN, Hakki AH, Spielman SR, Segal BL. Intravenous nitroglycerin for rest angina. Potential pathophysiologic mechanisms of action. *Arch Intern Med* 1982;**142**:1806–1809.
- Gibson RS, Young PM, Boden WE, Schechtman K, Roberts R. Prognostic significance and beneficial effect of diltiazem on the incidence of early recurrent ischemia after non-Q-wave myocardial infarction: results from the Multicenter Diltiazem Reinfarction Study. *Am J Cardiol* 1987;**60**:203–209.
- Held PH, Yusuf S, Furberg CD. Calcium channel blockers in acute myocardial infarction and unstable angina: an overview. *BMJ* 1989;**299**:1187–1192.
- Jespersen CM. The effect of verapamil on major events in patients with impaired cardiac function recovering from acute myocardial infarction. The Danish Study Group on Verapamil in Myocardial Infarction. *Eur Heart J* 1993;**14**:540–545.
- Kaplan K, Davison R, Parker M, Przybylek J, Teagarden JR, Lesch M. Intravenous nitroglycerin for the treatment of angina at rest

unresponsive to standard nitrate therapy. *Am J Cardiol* 1983;**51**:694–698.

- Mega JL, Hochman JS, Scirica BM, Murphy SA, Sloan S, McCabe CH, Merlini P, Morrow DA. Clinical features and outcomes of women with unstable ischemic heart disease: observations from metabolic efficiency with ranolazine for less ischemia in non-ST-elevation acute coronary syndromes-thrombolysis in myocardial infarction 36 (MERLIN-TIMI 36). *Circulation* 2010;**121**:1809–1817.
- Morrow DA, Scirica BM, Sabatine MS, de Lemos JA, Murphy SA, Jarolim P, Theroux P, Bode C, Braunwald E. B-type natriuretic peptide and the effect of ranolazine in patients with non-ST-segment elevation acute coronary syndromes: observations from the MERLIN-TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary-Thrombolysis In Myocardial Infarction 36) trial. *J Am Coll Cardiol* 2010;**55**:1189–1196.
- Norris RM, Clarke ED, Sammel NL, Smith WM, Williams B. Protective effect of propranolol in threatened myocardial infarction. *Lancet* 1978;**2**:907–909.
- Psaty BM, Heckbert SR, Koepsell TD, Siscovick DS, Raghunathan TE, Weiss NS, Rosendaal FR, Lemaitre RN, Smith NL, Wahl PW, Wagner EH, Furberg CD. The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA* 1995;**274**:620–625.
- Roubin GS, Harris PJ, Eckhardt I, Hensley W, Kelly DT. Intravenous nitroglycerine in refractory unstable angina pectoris. *Aust N Z J Med* 1982;**12**:598–602.
- Smith NL, Reiber GE, Psaty BM, Heckbert SR, Siscovick DS, Ritchie JL, Every NR, Koepsell TD. Health outcomes associated with beta-blocker and diltiazem treatment of unstable angina. *J Am Coll Cardiol* 1998;**32**:1305–1311.
- Theroux P, Taeymans Y, Morissette D, Bosch X, Pelletier GB, Waters DD. A randomized study comparing propranolol and diltiazem in the treatment of unstable angina. *J Am Coll Cardiol* 1985;**5**:717–722.
- Yusuf S, Sleight P, Rossi P, Ramsdale D, Peto R, Furze L, Sterry H, Pearson M, Motwani R, Parish S, Gray R, Bennett D, Bray C. Reduction in infarct size, arrhythmias and chest pain by early intravenous beta blockade in suspected acute myocardial infarction. *Circulation* 1983;**67**:132–141.
- Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. II. Unstable angina, heart failure, primary prevention with aspirin, and risk factor modification. *JAMA* 1988;**260**:2259–2263.

5.2 Antiplatelet agents

- Albaladejo P, Marret E, Piriou V, Samama CM. Perioperative management of antiplatelet agents in patients with coronary stents: recommendations of a French Task Force. *Br J Anaesth* 2006;**97**:580–582.
- Aleil B, Jacquemin L, De Poli F, Zaehring M, Collet J-P, Montalescot G, Cazenave J-P, Dickele M-C, Monassier J-P, Gachet C. Clopidogrel 150 mg/day to overcome low responsiveness in patients undergoing elective percutaneous coronary

- intervention: results from the VASP-02 (Vasodilator-Stimulated Phosphoprotein-02) randomized study. *JACC: Cardiovasc Interv* 2008;**1**:631–638.
- Antiplatelet Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:71–86.
 - Berkowitz SD, Harrington RA, Rund MM, Tchong JE. Acute profound thrombocytopenia after c7E3 Fab (abciximab) therapy. *Circulation* 1997;**95**:809–813.
 - Bonello L, Paganelli F, Arpin-Bornet M, Auquier P, Sampol J, Dignat-George F, Barragan P, Camoin-Jau L. Vasodilator-stimulated phosphoprotein phosphorylation analysis prior to percutaneous coronary intervention for exclusion of postprocedural major adverse cardiovascular events. *J Thromb Haemost* 2007;**5**:1630–1636.
 - Bouman HJ, Schomig E, van Werkum JW, Velder J, Hackeng CM, Hirschhauser C, Waldmann C, Schmalz HG, ten Berg JM, Taubert D. Paraoxonase-1 is a major determinant of clopidogrel efficacy. *Nat Med* 2011;**17**:110–116.
 - Cuisset T, Frere C, Quilici J, Gaborit B, Castelli C, Poyet R, Bali L, Morange P-E, Alessi M-C, Bonnet J-L. Predictive values of post-treatment adenosine diphosphate-induced aggregation and vasodilator-stimulated phosphoprotein index for stent thrombosis after acute coronary syndrome in clopidogrel-treated patients. *Am J Cardiol* 2009;**104**:1078–1082.
 - Ebrahimi R, Dyke C, Mehran R, Manoukian SV, Feit F, Cox DA, Gersh BJ, Ohman EM, White HD, Moses JW, Ware JH, Lincoff AM, Stone GW. Outcomes following pre-operative clopidogrel administration in patients with acute coronary syndromes undergoing coronary artery bypass surgery: the ACUITY (Acute Catheterization and Urgent Intervention Triage strategy) Trial. *J Am Coll Cardiol* 2009;**53**:1965–1972.
 - Farid N, Payne C, Small D, Winters K, Ernest CS 2nr, Brandt J, Darstein C, Jakubowski J, Salazar D. Cytochrome P450 3A inhibition by ketoconazole affects prasugrel and clopidogrel pharmacokinetics and pharmacodynamics differently. *Clin Pharmacol Ther* 2007;**81**:735–741.
 - Gollapudi RR, Teirstein PS, Stevenson D, Simon R. Aspirin sensitivity: implications for patients with coronary artery disease. *JAMA* 2004;**292**:3017–3023.
 - Hochholzer W, Trenk D, Bestehorn H-P, Fischer B, Valina C, Ferenc M, Gick M, Caputo A, Buttner H, Neumann F-J. Impact of the degree of peri-interventional platelet inhibition after loading with clopidogrel on early clinical outcome of elective coronary stent placement. *J Am Coll Cardiol* 2006;**48**:1742–1750.
 - Judge HM, Patil SB, Buckland RJ, Jakubowski JA, Storey RF. Potentiation of clopidogrel active metabolite formation by rifampicin leads to greater P2Y₁₂ receptor blockade and inhibition of platelet aggregation following clopidogrel. *J Thromb Haemost* 2010;**8**:1820–1827.
 - Lajus S, Clofent-Sanchez G, Jais C, Coste P, Nurden P, Nurden AT. Thrombocytopenia after abciximab use results from different mechanisms. *Thromb Haemost* 2010;**103**:651–661.
 - Lau WC, Gurbel PA, Watkins PB, Neer CJ, Hopp AS, Carville DGM, Guyer KE, Tait AR, Bates ER. Contribution of hepatic cytochrome P450 3A4 metabolic activity to the phenomenon of clopidogrel resistance. *Circulation* 2004;**109**:166–171.
 - Mega JL, Close SL, Wiviott SD, Shen L, Walker JR, Simon T, Antman EM, Braunwald E, Sabatine MS. Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis. *Lancet* 2010;**376**:1312–1319.
 - Möllmann H, Nef HM, Hamm CW, Elsasser A. How to manage patients with need for antiplatelet therapy in the setting of (un-)planned surgery. *Clin Res Cardiol* 2009;**98**:8–15.
 - Moliterno DJ, Topol EJ. A direct comparison of tirofiban and abciximab during percutaneous coronary revascularization and stent placement: rationale and design of the TARGET study. *Am Heart J* 2000;**140**:722–726.
 - Muller I, Seyfarth M, Rudiger S, Wolf B, Pogatsa-Murray G, Schomig A, Gawaz M. Effect of a high loading dose of clopidogrel on platelet function in patients undergoing coronary stent placement. *Heart* 2001;**85**:92–93.
 - Ramanuja S, Breall J, Kalaria V. Approach to 'aspirin allergy' in cardiovascular patients. *Circulation* 2004;**110**:e1–e4.
 - Schrör K, Weber A. Comparative pharmacology of GP IIb/IIIa antagonists. *J Thromb Thrombolysis*. 2003;**15**:71–80.
 - Sibbing D, Braun S, Morath T, Mehilli J, Vogt W, Schömig A, Kastrati A, von Beckerath N. Platelet reactivity after clopidogrel treatment assessed with point-of-care analysis and early drug-eluting stent thrombosis. *J Am Coll Cardiol* 2009;**53**:849–856.
 - Unger EF. Weighing benefits and risks—the FDA's review of prasugrel. *N Engl J Med* 2009;**361**:942–945.
 - von Tiehl KF, Price MJ, Valencia R, Ludington KJ, Teirstein PS, Simon RA. Clopidogrel desensitization after drug-eluting stent placement. *J Am Coll Cardiol* 2007;**50**:2039–2043.
 - White HD, Ohman EM, Lincoff AM, Bertrand ME, Colombo A, McLaurin BT, Cox DA, Pocock SJ, Ware JA, Manoukian SV, Lansky AJ, Mehran R, Moses JW, Stone GW. Safety and efficacy of bivalirudin with and without glycoprotein IIb/IIIa inhibitors in patients with acute coronary syndromes undergoing percutaneous coronary intervention: 1-year results from the ACUITY (Acute Catheterization and Urgent Intervention Triage strategy) Trial. *J Am Coll Cardiol* 2008;**52**:807–814.

5.3 Anticoagulants

- Collins R, MacMahon S, Flather M, Baigent C, Remvig L, Mortensen S, Appleby P, Godwin J, Yusuf S, Peto R. Clinical effects of anticoagulant therapy in suspected acute myocardial infarction: systematic overview of randomised trials. *BMJ* 1996;**313**:652–659.
- Comparison of two treatment durations (6 days and 14 days) of a low molecular weight heparin with a 6-day treatment of unfractionated heparin in the initial management of unstable angina or non-Q wave myocardial infarction: FRAX.I.S. (FRAXiparine in Ischaemic Syndrome). *Eur Heart J* 1999;**20**:1553–1562.
- Hirsh J, Guyatt G, Albers GW, Harrington R, Schunemann HJ, American College of Chest Physicians. Antithrombotic and thrombolytic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;**133**(6 Suppl):110S–112S.

- James S, Armstrong P, Califf R, Husted S, Kontny F, Nieminen M, Pfisterer M, Simoons ML, Wallentin L. Safety and efficacy of abciximab combined with dalteparin in treatment of acute coronary syndromes. *Eur Heart J* 2002;**23**:1538–1545.
- Klein W, Buchwald A, Hillis SE, Monrad S, Sanz G, Turpie AG, van der Meer J, Olaisson E, Undeland S, Ludwig K. Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease. Fragmin in unstable coronary artery disease study (FRIC). *Circulation* 1997;**96**:61–68.
- Lincoff AM, Bittl JA, Harrington RA, Feit F, Kleiman NS, Jackman JD, Sarembock IJ, Cohen DJ, Spriggs D, Ebrahimi R, Keren G, Carr J, Cohen EA, Betriu A, Desmet W, Kereiakes DJ, Rutsch W, Wilcox RG, De Feyter PJ, Vahanian A, Topol EJ. REPLACE-2 Investigators. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA* 2003;**289**:853–863.
- Mehta SR, Granger CB, Eikelboom JW, Bassand JP, Wallentin L, Faxon DP, Peters RJ, Budaj A, Afzal R, Chrolavicius S, Fox KA, Yusuf S. Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: results from the OASIS-5 trial. *J Am Coll Cardiol* 2007;**50**:1742–1751.
- Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. *JAMA* 1996;**276**:811–815.
- Petersen JL, Mahaffey KW, Hasselblad V, Antman EM, Cohen M, Goodman SG, Langer A, Blazing MA, Le-Moigne-Amrani A, de Lemos JA, Nessel CC, Harrington RA, Ferguson JJ, Braunwald E, Califf RM. Efficacy and bleeding complications among patients randomized to enoxaparin or unfractionated heparin for antithrombin therapy in non-ST-segment elevation acute coronary syndromes: a systematic overview. *JAMA* 2004;**292**:89–96.
- Petitou M, Duchaussoy P, Herbert JM, Duc G, El Hajji M, Branellec JF, Donat F, Necciari J, Cariou R, Bouthier J, Garrigou E. The synthetic pentasaccharide fondaparinux: first in the class of antithrombotic agents that selectively inhibit coagulation factor Xa. *Semin Thromb Hemost* 2002;**28**:393–402.
- Rosenberg RD, Aird WC. Vascular-bed-specific hemostasis and hypercoagulable states. *N Engl J Med* 1999;**340**:1555–1564.
- Turpie AG. Fondaparinux: a factor Xa inhibitor for antithrombotic therapy. *Expert Opin Pharmacother* 2004;**5**:1373–1384.
- Wessler S, Yin ET. On the antithrombotic action of heparin. *Thromb Diath Haemorrh* 1974;**32**:71–78.
- Yin ET, Wessler S, Stoll PJ. Biological properties of the naturally occurring plasma inhibitor to activated factor X. *J Biol Chem* 1971;**246**:3703–3711.
- de Winter RJ, Windhausen F, Cornel JH, Dunselman PH, Janus CL, Bendermacher PE, Michels HR, Sanders GT, Tijssen JG, Verheugt FW. Early invasive versus selectively invasive management for acute coronary syndromes. *N Engl J Med* 2005;**353**:1095–1104.
- Neumann FJ, Kastrati A, Pogatsa-Murray G, Mehilli J, Bollwein H, Bestehorn HP, Schmitt C, Seyfarth M, Dirschinger J, Schomig A. Evaluation of prolonged antithrombotic pretreatment ('cooling-off' strategy) before intervention in patients with unstable coronary syndromes: a randomized controlled trial. *JAMA* 2003;**290**:1593–1599.
- O'Donoghue M, Boden WE, Braunwald E, Cannon CP, Clayton TC, de Winter RJ, Fox KA, Lagerqvist B, McCullough PA, Murphy SA, Spacek R, Swahn E, Wallentin L, Windhausen F, Sabatine MS. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. *JAMA* 2008;**300**:71–80.
- Sorajja P, Gersh BJ, Cox DA, McLaughlin MG, Zimetbaum P, Costantini C, Stuckey T, Tchong JE, Mehran R, Lansky AJ, Grines CL, Stone GW. Impact of delay to angioplasty in patients with acute coronary syndromes undergoing invasive management: analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage strategy) trial. *J Am Coll Cardiol* 2010;**55**:1416–1424.

5.5 Special populations and conditions

- Alter DA, Manuel DG, Gunraj N, Anderson G, Naylor CD, Laupacis A. Age, risk–benefit trade-offs, and the projected effects of evidence-based therapies. *Am J Med* 2004;**116**:540–545.
- Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, Schwab SJ, Goodkin DA. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998;**339**:584–590.
- Buettner HJ, Mueller C, Gick M, Ferenc M, Allgeier J, Comberg T, Werner KD, Schindler C, Neumann FJ. The impact of obesity on mortality in UA/non-ST-segment elevation myocardial infarction. *Eur Heart J* 2007;**28**:1694–1701.
- Bugiardini R. Normal coronary arteries: clinical implications and further classification. *Herz* 2005;**30**:3–7.
- Bugiardini R, Manfrini O, De Ferrari GM. Unanswered questions for management of acute coronary syndrome: risk stratification of patients with minimal disease or normal findings on coronary angiography. *Arch Intern Med* 2006;**166**:1391–1395.
- Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001;**357**:1385–1390.
- Deedwania P, Kosiborod M, Barrett E, Ceriello A, Isley W, Mazzone T, Raskin P. Hyperglycemia and acute coronary syndrome: a scientific statement from the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation* 2008;**117**:1610–1619.
- Dickstein K, Vardas PE, Auricchio A, Daubert JC, Linde C, McMurray J, Ponikowski P, Priori SG, Sutton R, van Veldhuisen DJ, Vahanian A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs

5.4 Coronary revascularization

- Cannon CP. Revascularisation for everyone? *Eur Heart J* 2004;**25**:1471–1472.

- R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas P, Widimsky P, Anker SD, Blanc JJ, Gasparini M, Hoes AW, Israel CW, Kalarus Z, Merkely B, Swedberg K, Camm AJ. 2010 Focused Update of ESC Guidelines on device therapy in heart failure: an update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC guidelines for cardiac and resynchronization therapy. Developed with the special contribution of the Heart Failure Association and the European Heart Rhythm Association. *Eur Heart J* 2010;**31**:2677–2687.
- Ghali JK, Anand IS, Abraham WT, Fonarow GC, Greenberg B, Krum H, Massie BM, Wasserman SM, Trotman ML, Sun Y, Knusel B, Armstrong P. Randomized double-blind trial of darbepoetin alfa in patients with symptomatic heart failure and anemia. *Circulation* 2008;**117**:526–535.
 - Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med* 1987;**316**:1371–1375.
 - Hasdai D, Behar S, Wallentin L, Danchin N, Gitt AK, Boersma E, Fioretti PM, Simoons ML, Battler A. A prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and the Mediterranean basin; the Euro Heart Survey of Acute Coronary Syndromes (Euro Heart Survey ACS). *Eur Heart J* 2002;**23**:1190–1201.
 - Heer T, Gitt AK, Juenger C, Schiele R, Wienbergen H, Towae F, Gottwitz M, Zahn R, Zeymer U, Senges J. Gender differences in acute non-ST-segment elevation myocardial infarction. *Am J Cardiol* 2006;**98**:160–166.
 - Hemmelgarn BR, Southern D, Culleton BF, Mitchell LB, Knudtson ML, Ghali WA. Survival after coronary revascularization among patients with kidney disease. *Circulation* 2004;**110**:1890–1895.
 - Lyseng-Williamson KA, Keating GM. Ferric carboxymaltose: a review of its use in iron-deficiency anaemia. *Drugs* 2009;**69**:739–756.
 - Maeder M, Klein M, Fehr T, Rickli H. Contrast nephropathy: review focusing on prevention. *J Am Coll Cardiol* 2004;**44**:1763–1771.
 - Marso SP, Amin AP, House JA, Kennedy KF, Spertus JA, Rao SV, Cohen DJ, Messenger JC, Rumsfeld JS. Association between use of bleeding avoidance strategies and risk of periprocedural bleeding among patients undergoing percutaneous coronary intervention. *JAMA* 2010;**303**:2156–2164.
 - Mollmann H, Elsasser A, Nef H, Schneider S, Nienaber CA, Richardt G, Weber M, Kelm M, Levenson B, Bonzel T, Tebbe U, Sabin G, Pfannebecker T, Senges J, Hamm CW. Treatment of in-stent restenosis with sirolimus-eluting-stents: results from the prospective German Cypher stent registry. *Clin Res Cardiol* 2008;**97**:432–440.
 - Moscucci M, Fox KA, Cannon CP, Klein W, Lopez-Sendon J, Montalescot G, White K, Goldberg RJ. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J* 2003;**24**:1815–1823.
 - Mueller C, Neumann FJ, Roskamm H, Buser P, Hodgson JM, Peruchoud AP, Buettner HJ. Women do have an improved long-term outcome after non-ST-elevation acute coronary syndromes treated very early and predominantly with percutaneous coronary intervention: a prospective study in 1,450 consecutive patients. *J Am Coll Cardiol* 2002;**40**:245–250.
 - Nikolsky E, Mehran R, Dangas G, Fahy M, Na Y, Pocock SJ, Lincoff AM, Stone GW. Development and validation of a prognostic risk score for major bleeding in patients undergoing percutaneous coronary intervention via the femoral approach. *Eur Heart J* 2007;**28**:1936–1945.
 - O'Connell KA, Wood JJ, Wise RP, Lozier JN, Braun MM. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA* 2006;**295**:293–298.
 - Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurlley S, Kleiman J, Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;**348**:1309–1321.
 - Prinzmetal M, Kennamer R, Merliss R, Wada T, Bor N. Angina pectoris. I. A variant form of angina pectoris; preliminary report. *Am J Med* 1959;**27**:375–388.
 - Prizel KR, Hutchins GM, Bulkley BH. Coronary artery embolism and myocardial infarction. *Ann Intern Med* 1978;**88**:155–161.
 - Roe MT, Harrington RA, Prosper DM, Pieper KS, Bhatt DL, Lincoff AM, Simoons ML, Akkerhuis M, Ohman EM, Kitt MM, Vahanian A, Ruzyllo W, Karsch K, Califf RM, Topol EJ. Clinical and therapeutic profile of patients presenting with acute coronary syndromes who do not have significant coronary artery disease. The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) Trial Investigators. *Circulation* 2000;**102**:1101–1106.
 - Roffi M, Chew DP, Mukherjee D, Bhatt DL, White JA, Heesch C, Hamm CW, Moliterno DJ, Califf RM, White HD, Kleiman NS, Theroux P, Topol EJ. Platelet glycoprotein IIb/IIIa inhibitors reduce mortality in diabetic patients with non-ST-segment-elevation acute coronary syndromes. *Circulation* 2001;**104**:2767–2771.
 - Samama CM, Djoudi R, Lecompte T, Nathan-Denizot N, Schved JF. Perioperative platelet transfusion: recommendations of the Agence Francaise de Securite Sanitaire des Produits de Sante (AFSSaPS) 2003. *Can J Anaesth* 2005;**52**:30–37.
 - Schiele F, Vuilleminot A, Kramarz P, Kieffer Y, Anguenot T, Bernard Y, Bassand JP. Use of recombinant hirudin as antithrombotic treatment in patients with heparin-induced thrombocytopenia. *Am J Hematol* 1995;**50**:20–25.
 - Strippoli GF, Navaneethan SD, Craig JC. Haemoglobin and haematocrit targets for the anaemia of chronic kidney disease. *Cochrane Database Syst Rev* 2006;**4**:CD003967.
 - Wong CK, Newby LK, Bhapker MV, Aylward PE, Pfisterer M, Alexander KP, Armstrong PW, Hochman JS, Van de Werf F, Califf RM, White HD. Use of evidence-based medicine for acute coronary syndromes in the elderly and very elderly: insights from the Sibrafin vs aspirin to Yield Maximum Protection from ischemic Heart events postacute cOroNary sYndromes trials. *Am Heart J* 2007;**154**:313–321.

Addendum 2. Table

Goals of secondary prevention after an ACS/NSTEMI

Risk Factor	Goal	Intervention
Smoking	Smoking cessation. No exposure to environmental tobacco (i.e. passive smoking).	<ul style="list-style-type: none"> Record smoking status at every visit. Advise to quit smoking and to avoid environmental tobacco smoke. Develop a plan for smoking cessation. Consider special programmes, pharmacotherapy (i.e. nicotine replacement, bupropion) Ask about smoking status in every patient. Assess the degree of addiction and readiness to quit smoking. Advise unequivocally to quit smoking. Assist with smoking cessation strategy including behavioural counselling, nicotine replacement therapy and pharmacological intervention.
Hypertension	<140/90 mm Hg <130/90 mm Hg in patients with diabetes and chronic renal disease	<ul style="list-style-type: none"> Lifestyle modification with increased physical activity, sodium reduction, healthy diet, alcohol moderation, low-fat dairy products Blood pressure-lowering drugs if blood pressure \geq140/90 mm Hg. Blood pressure medication, preferably with β blocker and/or ACE inhibitors/ ARBs. Antihypertensive treatment is justified in patients with CVD and blood pressure 130–139/85–89 mm Hg.
Hyperlipidaemia	LDL-C <70 mg/dL when feasible	<ul style="list-style-type: none"> Statin therapy with target LDL-C levels <1.8 mmol/L (<70 mg/dL) initiated early after admission is recommended.
Physical Inactivity	Regular aerobic exercise >30 min per day on most days of the week	<ul style="list-style-type: none"> Assess the risk with a physical activity history and/or an exercise test to guide prescription. Encourage 30–60 min of moderate-intensity aerobic activity on most, preferably all, days of the week, supplemented by an increase in daily lifestyle activities. Encourage resistance training 2 days per week. Advise medically supervised programmes for high-risk patients (e.g. recent acute coronary syndrome or revascularization, heart failure) 30 min of moderately vigorous exercise on most days of the week.
Overweight/obesity	Weight reduction BMI 18.5–24.9 Waist circumference: men <94 cm women <80 cm.	<ul style="list-style-type: none"> Assess BMI and/or waist circumference on each visit and consistently encourage weight maintenance/reduction through an appropriate balance of physical activity, caloric intake, and formal behavioural programmes to maintain/achieve a BMI between 18.5 and 24.9. If waist circumference is >80cm in women and >94 cm in men initiate lifestyle changes and consider treatment for metabolic syndrome as indicated. Weight reduction if BMI \geq25, especially if BMI \geq30 No further weight gain if waist circumference 80–88 cm in women and 94–102 cm in men Advise weight loss if waist circumference >88 cm in women and >102 cm in men.
Diabetes	HbA1c <7% HbA1c <6.5% fasting glucose <6 mg/dL post-prandial <7.5 mg/dL	<ul style="list-style-type: none"> Initiate lifestyle and pharmacotherapy to achieve near-normal HbA1c levels. Begin vigorous modification of other risk factors. Instruct patients to perform regular self-monitoring of blood glucose levels. Emphasis on lifestyle counselling and weight reduction Aggressive risk management: blood pressure <130/80 mm Hg, total cholesterol <175 mg/dL (<155 mg/dL if feasible), LDL cholesterol <100 mg/dL (<80 mg/dL if feasible).
Nutrition	Healthy diet	<ul style="list-style-type: none"> Wide variety of food Energy intake adjusted to avoid overweight Encourage fruits, vegetables, wholegrain cereals, bread, and fish (especially oily), lean meat, low-fat dairy products. Replace saturated fats with monosaturated and polyunsaturated fats (vegetable and marine) Hypertensive subjects should reduce salt intake.

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; ARB = angiotensin receptor blocker; BMI = body mass index; CVD = cardiovascular disease; HbA_{1c}, glycated haemoglobin; LDL-C = low-density lipoprotein cholesterol; NSTEMI = non-ST-segment elevation myocardial infarction.