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Impactful Clinical Trials of 2012: What Clinicians Need to Know

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ABSTRACT

The results of clinical trials serve to inform cardiovascular (CV) practice. In 2012, a number of clinical trials were reported that have an immediate effect on patient management. We highlight the results of key trials in several areas: interventional cardiology, acute coronary syndromes (ACS), and pharmacologic therapy. The FREEDOM trial, which demonstrated a significant benefit on hard outcomes of coronary artery bypass grafting vs multivessel percutaneous coronary intervention (PCI) in patients with diabetes, answered a long-debated question. The MADIT-RIT trial demonstrated an impressive reduction in inappropriate shocks and mortality in stable implantable cardioverter defibrillator (ICD) patients by altering ICD programming variables. In ACS, prolonged dual antiplatelet therapy (DAPT) with acetylsalicylic acid (ASA) and prasugrel in medically managed patients was not superior to ASA plus clopidogrel, and ongoing trials will assess if there are benefits to use of DAPT beyond 1 year. The WOEST trial compared warfarin plus DAPT vs warfarin plus ASA alone in PCI patients who had an indication for ongoing anticoagulation. Not surprisingly, the major bleeding rate was lower with double compared

RÉSUMÉ

Les résultats d'essais cliniques servent à renseigner la pratique en soins cardiovasculaires (CV). En 2012, un certain nombre d'essais cliniques ont démontré que avoir un effet immédiat sur la gestion des patients. Nous soulignons les résultats de nombreux essais principaux dans les domaines suivants : la cardiologie interventionnelle, les syndromes coronariens aigus (SCA) et le traitement pharmacologique. L'essai FREEDOM, qui a démontré un avantage significatif sur les résultats réels du pontage aortocoronarien par rapport à l'intervention coronarienne percutanée (ICP) multivaisseaux chez les patients ayant le diabète, répond à une question longuement débattue. L'essai MADIT-RIT a démontré une réduction impressionnante des chocs inappropriés et de la mortalité en modifiant les variables de programmation du défibrillateur automatique implantable (DAI) chez les patients qui ont un DAI et qui sont stables. En ce qui concerne le SCA, la prolongation de la bithérapie antiplaquettaire (BTAP) à l'acide acétylsalicylique (AAS) et au prasugrel chez les patients médicalement pris en charge n'a pas été supérieure à celle à l'AAS et au clopidogrel, et les essais en cours détermineront s'il existe des avantages à utiliser

Randomized clinical trials serve to inform clinical practice, and nowhere is this more evident than in cardiovascular (CV) medicine. Summarizing the most significant advancements for the year is not a simple task, so we have focused on trials most likely to have immediate impact on the CV specialist (Fig. 1).

Intervention and Device Studies

In determining who is the most appropriate patient for revascularization and which modality to use, 2 studies, **F**ractional Flow Reserve vs **A**ngiography for **M**ultivessel **E**valuation **2** (FAME-2) and the **F**uture **Re**vascularization **E**valuation in Patients With **D**iabetes Mellitus: **O**ptimal Management of **M**ultivessel Disease (FREEDOM) trial, provide guidance. In FAME-2, patients with stable coronary artery disease (CAD) who were appropriate candidates for PCI with a fractional flow reserve (FFR) of < 0.80 were randomized to PCI with optimal medical therapy (OMT) vs OMT alone. Previous studies have demonstrated that an FFR < 0.8 correlates with hemodynamically significant coronary stenoses. FAME-2 was terminated early (mean follow-up of 214 days vs 2 years) as PCI with OMT was superior (4.3% vs 12.7%, $P < 0.001$), with the composite end point driven by reduction in urgent revascularization. Considering the lack of reduction in death or myocardial infarction (MI), the early termination of FAME-2 has generated controversy. Furthermore, the long-term value of FFR-guided management remains unknown.

In FREEDOM, a highly selected diabetic population with multivessel CAD was randomized to either multivessel PCI or

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with triple therapy. However, major CV events were unexpectedly lower with double therapy as well, a finding that warrants confirmation in larger studies. One of the most exciting developments in 2012 was with PCSK9 inhibitors, injectable monoclonal antibodies, that were shown to lower low-density lipoprotein cholesterol by 40%-70% above the effects of maximal dose statin therapy. We now await the results of large outcome trials with this promising class of drugs.

la BTAP au-delà de 1 an. L'étude WOEST a comparé la warfarine plus BTAP par rapport à la warfarine plus AAS seul chez les patients ayant subi une ICP et chez qui une anticoagulation constante a été indiquée. Il n'est pas étonnant que les taux d'hémorragie importants aient été plus faibles chez les patients traités par la bithérapie que chez ceux traités par la trithérapie. Aussi, les événements CV majeurs ont été de manière inattendue plus faibles chez les patients traités par la bithérapie, une conclusion qui mérite d'être confirmée par des études de plus grande envergure. L'un des développements des plus passionnants en 2012 a probablement été celui des inhibiteurs de la PCSK9, des anticorps monoclonaux injectables, qui ont démontré abaisser le cholestérol à lipoprotéines de faible densité de 40 % à 70 % au-delà des effets du traitement par statines à dose maximale. Nous attendons maintenant les essais d'envergure sur les résultats de cette classe prometteuse de médicaments.

coronary artery bypass grafting (CABG). Over a median follow-up of 3.8 years, CABG was superior to PCI for the combined end point of death, nonfatal stroke, and nonfatal MI (26.6% vs 18.7%; $P = 0.005$). All-cause mortality and MI were independently and significantly decreased, with benefit in all major subgroups. Importantly, the benefit of CABG over PCI was independent of **Syn**ergy Between Percutaneous Coronary Intervention With **Tax**us and Cardiac Surgery (SYNTAX) score (a reflection of CAD extent and severity). There was however, a modest but significant increase in early stroke with CABG, which must factor into clinical decision-making. CABG was also superior in the subset of patients with 2-vessel disease, generating considerable controversy and requiring further study. Despite best attempts, selection bias in recruiting participants into studies like FREEDOM cannot be avoided. It is possible that lower-risk patients with anatomy more suitable for PCI were not enrolled. However, given the evidence thus far, CABG seems to be the preferred approach for most patients with diabetes and significant multivessel disease.

The **C**ardiovascular **P**atient **O**utcomes **R**esearch **T**eam (C-PORT E) trial evaluated 18,867 patients undergoing elective PCI at centres without on-site cardiac surgery, confirming the safety of this approach. All-cause mortality at 6 weeks was similar (0.9% vs 1.0%; $P = 0.004$ for non-inferiority) between centres with and without on-site surgery, and emergency CABG trended higher at surgical centres 0.1% vs 0.2%; $P = 0.05$.

Implantable cardioverter defibrillators (ICDs) are the mainstay for the prevention of sudden death. Inappropriate shocks however are common, uncomfortable, and associated with high morbidity and mortality. The **M**ulticenter **A**utomatic **D**efibrillator **I**mplantation **T**rial-**R**educe **I**nappropriate **T**herapy (MADIT-RIT) study randomized ICD patients to 3 different ventricular tachycardia detection settings—higher rate, longer delay, or conventional setting. Time to first occurrence of inappropriate shock was reduced by both interventions (4% vs 5% vs 20%, respectively; $P < 0.001$). Impressively, all-cause mortality was reduced (3.2% vs 4.3% vs 6.6%) by the higher rate and longer delay settings. Thus, simple changes in ICD programming parameters can yield important clinical benefit for this high risk population.

Acute Coronary Syndromes

The last year was challenging for acute coronary syndromes (ACS) research. Though more potent antiplatelet therapy in ACS with ticagrelor or prasugrel is superior to clopidogrel, it remains unknown whether dual antiplatelet therapy (DAPT) provides benefit beyond one year after ACS. The **T**a**r**geted Platelet **I**nhibition to C**l**arify the **O**ptimal Strate**g**y to Medicall**y** Manage **A**cute **C**oronary **S**yndromes (TRILOGY ACS) study evaluated medically managed patients for long-term DAPT comparing prasugrel with clopidogrel. Over 30-month follow-up, no significant difference emerged in the primary composite outcome of death, MI, or stroke between the 2 groups (13.9% vs 16%; $P = 0.21$), although an unexplained trend in favour of prasugrel emerged after 1 year. Major bleeding rates were similar. For now, DAPT beyond 1 year remains unproven, though may be reasonable in patients with drug-eluting stents or with previous MI, if bleeding risk is acceptably low. Two ongoing studies will shed further light. Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin (PEGASUS-TIMI 54) compares acetylsalicylic acid (ASA) plus ticagrelor with ASA alone in patients with vascular disease or multiple risk factors who are at least 1 year post-ACS. **D**ual **A**nti**p**latelet **T**rial (DAPT) compares dual vs monotherapy in PCI patients beyond 1 year.

There has been hope that raising high-density lipoprotein (HDL) may reduce CV events. The dal-OUTCOMES study compared the cholesterol ester transfer protein (CETP) inhibitor dalcetrapib to placebo in patients with recent ACS, all of whom received optimal statin therapy. Dal-OUTCOMES was terminated early for futility. Despite a 30% HDL increase after a median follow up of 31 months, there was no significant difference in the primary composite end point (8.3% vs 8.0%; $P = 0.52$). Notably, systolic blood pressure was increased with dalcetrapib by 0.6 mm Hg ($P < 0.0001$), similar to results with an earlier CETP inhibitor, torcetrapib. Combined with the announcement that the **H**eart **P**rotection **S**tudy **2**: **T**reatment of **H**DL to **R**educe the **I**ncidence of **V**ascular **E**vents (HPS2-THRIVE) study evaluating niaspan/laropiprant also showed no benefit, the HDL-raising hypothesis has been severely challenged in 2012.

Key Clinical Trials of 2012			
Study Primary Author	**Reference**	**Patients, N**	**Intervention Tested**
FAME-2 De Bruyne B, et al	N Engl J Med 2012;367:991-1001	447	FFR guided PCI and OMT vs OMT alone in stable CAD
FREEDOM Farkouh ME, et al	N Engl J Med 2012;367:2375-2384	1900	Multivessel revascularization strategy in diabetics
C-PORT Aversano T, et al	N Engl J Med 2012;367:1792-1802	18,867	Stand alone elective PCI
MADIT-RIT Moss AJ, et al	N Engl J Med 2012;367:2275-2283	1500	ICD programming strategy for inappropriate shocks
TRILOGY ACS Roe MT, et al	N Engl J Med 2012;367:1297-1309	7243	Prasugrel vs clopidogrel in medically managed ACS
dal-Outoomes Schwartz GG, et al	N Engl J Med 2012;367:2089-2099	15,871	Dalcetrapib in ACS
WOEST Dewilde W, et al	Lancet 2013;381:1107-15	573	DAPT in OAC requiring patients undergoing PCI
Einstein-PE investigators	N Engl J Med 2012;366:1287-1297	4833	Rivaroxaban in symptomatic pulmonary embolism
ALTITUDE Parving HH, et al	N Engl J Med 2012;367:2204-2213	8561	Dual RAAS blockade with aliskiren in diabetics
PHS II Sesso HD, et al	JAMA 2012;308:1751-1760	14,641	Vitamin C and Vitamin E for primary prevention
The ORIGIN Investigators	N Engl J Med 2012;367:309-318	12,536	n-3 fatty acids in high cardiovascular risk patients
Giugliano RP, et al	Lancet 2012;380:2007-17	629	PCSK9 inhibitors in combination with statins
Roth EM, et al	N Engl J Med 2012;367:1891-1900	92	PCSK9 inhibitors with atorvastatin in primary hypercholesterolemia

Figure 1. Key clinical trials of 2012. ACS, acute coronary syndromes; ALTITUDE, Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints; CAD, coronary artery disease; C-PORT, Cardiovascular Patient Outcomes Research Team; DAPT, dual antiplatelet therapy; EINSTEIN-PE, EINSTEIN-Pulmonary Embolism trial; FAME-2, Fractional Flow Reserve vs Angiography for Multivessel Evaluation 2; FFR, fractional flow reserve; FREEDOM, Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease; ICD, implantable cardioverter defibrillator; MADIT-RIT, Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy; OAC, oral anticoagulant therapy; OMT, optimal medical therapy; ORIGIN, Outcome Reduction With Initial Glargine Intervention; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin/kexin 9; PHS II, Physicians' Health Study II; RAAS, renin-angiotensin-aldosterone system; TRILOGY ACS, Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes; WOEST, What Is the Optimal Antiplatelet and Anticoagulation Therapy in Patients With Oral Anticoagulation and Coronary Stenting.

Oral Anticoagulant Therapy

Clinicians dread combining oral anticoagulant therapy (OAC) with DAPT because of the increased major bleeding risk. The **W**hat Is the **O**ptimal Antiplat**e**let and Anticoagulation Therapy in Patients With Oral Anticoagulation and Coronary **S**ten**t**ing (WOEST) study randomized patients requiring OAC undergoing PCI to OAC plus DAPT vs OAC plus ASA alone. The primary end point was major bleeding. Over 1 year triple therapy resulted in significantly greater bleeding (44.9% vs 19.5%; $P < 0.001$) and a higher rate of death, MI, stroke, and stent thrombosis (17.7% vs 11.3%; $P = 0.025$). However, WOEST was not powered to assess efficacy per se. The reduced efficacy of triple therapy is counterintuitive and requires confirmation in larger studies, but it seems reasonable to consider dual vs triple therapy in patients at high risk for major bleeding.

For symptomatic acute pulmonary embolism, the EINSTEIN-Pulmonary Embolism (EINSTEI-PE) study evaluated the Factor Xa inhibitor rivaroxaban. Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg daily was noninferior to early enoxaparin bridged to a vitamin K antagonist for recurrent venous thromboembolism (2.1% vs 1.8%; $P = 0.003$) over 1-year follow-up. Major bleeding was reduced with rivaroxaban (1.1% vs 2.2%; $P = 0.003$), making this a simpler, safer option for patients with acute pulmonary embolism.

Pharmacological Failures

While dual renin-angiotensin-aldosterone system (RAAS) blockade with an angiotensin-converting enzyme inhibitor and angiotensin receptor blocker has generally proved disappointing in CV disease, a renin inhibitor might offer unique benefits.

This hypothesis was tested in the **Al**iskiren **T**rial **i**n **T**ype 2 Diabetes **U**sing Car**d**io-Renal **E**ndpoints (ALTITUDE) study of diabetic patients with renal dysfunction or CV disease. Patients were randomized to dual blockade with aliskiren vs an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker alone. ALTITUDE was terminated early due to increased adverse events with aliskiren ($P = 0.12$), with no benefit on clinical outcome, and trends in the wrong direction. Combined with a recent meta-analysis,[1] ALTITUDE suggests that dual RAAS blockade is best avoided in patients with high-risk diabetes. Many patients take vitamins and supplements in hopes of CV benefits. The **P**hysicians' **H**ealth **S**tudy **II** (PHS II) study randomized healthy men to vitamin E (400 IU) and C (500 mg), followed for more than 10 years. There was no benefit with either vitamin on major CV events ($P = 0.86$, and 0.91, respectively) or cancer.

The **O**utcome **R**eduction With **I**nitial **G**largine **In**tervention (ORIGIN) trial randomized patients with recent onset diabetes or prediabetes in combination with CV disease to 1 g of ethyl esters of n-3 fatty acids vs placebo. Over a median follow-up of 6.2 years, no significant difference in major vascular events was noted (16.5% vs 16.3%; $P = 0.81$). In contrast to previous positive trials of fish oil supplements, more than 50% of these patients were receiving statin therapy. In summary, there does not appear to be a role for fish oil supplementation for CV disease prevention in high-risk patients.

A Look to the Future

Our national lipid guidelines were updated this year[2] and reinforced the benefits of powerful low-density lipoprotein (LDL) reduction, especially in high-risk patients. However, some patients are unable to reach LDL targets or develop statin intolerance. This past year saw phase 2 trials of injectable fully humanized monoclonal antibodies against proprotein convertase subtilisin/kexin 9 (PCSK9), a chaperone of LDL receptor destruction. PCSK9 inhibition is associated with LDL reduction. Using every 2 or 4 week injections, LDL was reduced by 40%-70% on top of maximal dose statins. Short-term side effects were minimal and mainly injection site reactions. We await ongoing long-term studies for this promising therapeutic class.

Summary

The clinical trial class of 2012 offers valuable guidance as we collectively strive to improve CV outcomes for our patients. All trials however have limitations with respect to patient selection, trial design, and end points measured. We encourage you to review the full articles of these important trials (Fig. 1).

Disclosures

The authors have no conflicts of interest to disclose.

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